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Jackie Tsang

COVID-19

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All articles have been internally and externally peer-reviewed. Authors with potential conflicts of interest have been identified where applicable.

Front cover illustration by Jackie Tsang

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Introduction to 98th volume of the University of Toronto Medical Journal Issue on COVID-19

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The outbreak of COVID-19 caused by a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan City, Hubei Province, China in December 2019 quickly turned into a global pandemic. On January 30, 2020 the World Health Organization declared the outbreak a Public Health Emergency of International Concern. Subsequently, a number of public health measures were instituted by governments to slow the spread of the virus and decrease the burden on health care systems and economies. Despite significant efforts, a year after the outbreak (as of December 31, 2020), 83,113,878 laboratory-confirmed cases of COVID-19 and 1,811,128 deaths have been reported globally. For the past year, the entire world united to achieve a common goal - to reduce the burden of the pandemic on our society. Although the rapid research advancements and collaborations have led to production and approval of vaccines at a record pace, the battle with COVID-19 is ongoing and a number of barriers still need to be overcome.

For our issue on COVID-19, UTMJ invited national and international leaders to reflect on on-going challenges and lessons learned during the world's response and journey during this pandemic. Dr. Chloe Atkins, Associate Professor in the Department of Political Science at the University of Toronto, and her Postdoctoral Fellow, Dr. Andrea Whiteley, in their commentary, discuss the disproportionate impact the COVID-19 pandemic has had on the vulnerable populations. They urge us to take social determinants of health into account to better equip our society to weather crises, such as the current global pandemic. During the COVID-19 pandemic, a number of injustices received little attention and one of them has been the use of solitary confinement by the U.S. Immigration and Customs Enforcement (ICE) agency in an attempt to slow the spread of COVID-19 in their detention centres. Dr. Wesley Boyd, Associate Professor of Psychiatry and a faculty at the Center for Bioethics at the Harvard Medical School, alongside Dr. Samara Fox, Resident Physician at Beth Israel Deaconess Medical Center, and Ellen Gallagher, former policy adviser at the Department of Homeland Security's Office of Civil Rights and Civil Liberties who first blew the whistle on ICE's use of solitary confinement, cast a light on the medical ethics of this largely undiscussed issue. Finally, Dr. Sadath Sayeed, Assistant Professor of Global Health and Social Medicine at Harvard Medical School, and Dr. Lauren Taylor, Postdoctoral Fellow at NYU Grossman School of Medicine, evaluate the guidance offered by bioethics to address critical care resources during the pandemic. They discuss the potential reasons why bioethics may be poorly equipped to confront the scale of institutional dismantling that might be required to address root causes of social injustice in the United States.

In addition to the invited commentaries, UTMJ had the privilege to interview a number of highly respected leaders in the fields of healthcare advocacy, preventative medicine, and education. Interviewees shared their insights into leadership strategies and the impact COVID-19 pandemic has had on our society. Dr. Jeff Kwong, the Program Leader of the Populations and Public Health Program at ICES, a Scientist at the Public Health Ontario, and a Professor at the University of Toronto, shared his insights into the impact of COVID-19 on health care, public health measures and vaccination. Dr. Andreas Schleicher, the Director for Education and Skills at the Organisations for Economic Co-Operation and Development (OECD), discussed with our team the impact COVID-19 has had on education, educational policies and practices worldwide. Dr. Brian Goldman, a well-known emergency room physician at Mount Sinai Hospital, Toronto, a vivid healthcare advocate and voice for Canadians from coast-to-coast, reflected on his dual role as a physician and a prominent healthcare informer for the Candian public. He is the host of two popular CBC radio shows, White Coat, Black Art, and The Dose, which have been strong platforms for sharing stories of our fellow Canadians during the pandemic and providing news related to the pandemic in an accessible way. Another interviewee was Dr. John Yip, a highly regarded leader in ophthalmology and community health with a number of roles, including CEO of Kensington Health in Toronto and Vice President of Corporate Services for Health Quality Ontario in the past. With his interview, he inspires and urges to redefine leadership during the COVID-19 pandemic. Finally, the UTMJ also interviewed Nancy Schlichting, retired CEO of Henry Ford Health System (HFHS), who pivoted HFHS out of its free-fall through her unconventional leadership and a drive for innovation. She was honored as one of the 100 Most Influential People in Healthcare by Modern Healthcare magazine, as well as named to the Top 25 Women in Healthcare.

The UTMJ takes pride in supporting manuscript submission by trainees all over the world. In this issue, Jack G. Underschultz from the Faculty of Medicine and Dentistry, University of Alberta received the first prize trainee submission award. His paper, entitled "What Drives Resistance to Public Health Measures in Canada's COVID-19 Pandemic? An Online Survey of Canadians' Knowledge, Attitudes, and Practices," may help inform public health policy and individual behaviour.

This is the first issue of the University of Toronto Medical Journal's 98th volume. We would like to sincerely thank our dedicated editorial team for all the hard work that went into preparing this issue, and their continued efforts in upcoming issues. We are grateful for the patrons and faculty that continue to support the University of Toronto Medical Journal and the authors that have allowed us to showcase their important work and provided insight into the rapidly evolving advancements made during COVID-19 pandemic. We hope that you find this issue informative and thought-provoking.

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2020-2021 UTMJ Editorial Team

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Award Winning Manuscripts

The *University of Toronto Medical Journal* (*UTMJ*) was established in 1923 and is Canada's oldest student-run medical journal. We strive to uphold the *UTMJ*'s legacy of excellence by publishing interesting and timely research articles for our esteemed readers. Trainees continue to be important contributors to many of the research articles published by the *UTMJ*. We recognize the value in student-led research and are proud to serve as an outlet for this work. The *UTMJ* has established three awards to acknowledge outstanding submissions from trainees in each of our issues. We would like to congratulate the following award winners for the current issue on COVID-19:

First Prize

What drives resistance to public health measures in Canada's COVID-19 pandemic? An online survey of Canadians' knowledge, attitudes, and practices

Jack G. Underschultz, Paul Barber, Daniel Richard, Tracey Hillier

Second Prize

Polypharmacy in the age of COVID-19: medication management during a pandemic

Filip Potempski, Krish Bilimoria

Third Prize

The history of neuro-oncologic surgery

Jack Lam

These awards would not be possible without the continued support of the University of Toronto Medical Society and generous donations from our readers. Please consider supporting the UTMJ so that we can further our efforts to promote student research, publish impactful articles and grow our readership. UTMJ would like to thank the following patrons for their support:

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Vulnerability, social triage and the COVID-19 pandemic

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Abstract

If we are concerned about managing pandemics better, we need to secure and ameliorate the lives of all vulnerable people, including those with disabilities, people of colour, immigrants, seniors, and low-income essential workers who have been disproportionately affected by the coronavirus disease 2019 (COVID-19) pandemic. Before the pandemic even started, these groups had been "triaged" away from care by their social and economic circumstances, where structural features of their lives made them more susceptible to the physical dangers of COVID-19. This commentary article argues that the social determinants of health (SDOH) must be taken into account to create better living and working conditions for our most vulnerable citizens. By adopting a macroscopic perspective that re-examines cultural biases, safety regulations, labour laws, building codes, urban-planning and socio-economic policies, our society will be better equipped to weather global pandemics or other crises in the future.

Introduction

The first wave of the new coronavirus has exposed our biases towards vulnerable people and has brought to light our shortcomings in how we accommodate people who appear to be different. Increased vulnerability during this pandemic arises not only from innate physical characteristics, such as a weakened immune system, obesity, and heart disease, but also from policy decisions and social behaviours that alienate certain individuals from the rest of the population and have made them psychologically, physically, socially and economically susceptible to this virus. Disabled populations have borne a significant burden not only from the disease but also from the public health and socioeconomic responses to the pandemic. Additionally, the elderly population suffered terribly from the coronavirus disease in many countries including Canada;[1] seniors died at home as well as in long term care facilities, often isolated and alone. Racial and ethnic minorities, and those with lower incomes, have experienced noticeably higher infection and mortality rates due to the coronavirus disease 2019 (COVID-19).[2,3] These individuals tended to be part of the "essential" workforce, which not only cared for the ill, but also picked vegetables and fruit, cleaned public and private spaces, transported goods and re-stocked retail shelves. Across many differing jurisdictions, these workers fell prey to the coronavirus in highly disproportionate numbers.[4] While triage protocols were drafted or implemented in response to the extraordinary demands of COVID-19 on health care systems – recall the "who gets a ventilator debate" at the beginning of the global pandemic – we argue that pre-existing social, physical and economic conditions had already largely triaged many people away from care by creating contexts in which viral transmission could thrive and kill. The COVID-19 pandemic teaches us once again that everyone's health, but most particularly that of the physically vulnerable and socio-economically disadvantaged, depends upon more than just medicine, it depends on social factors.

Social Determinants of Health (SDOH)

Experts have shown that access to housing, green space, playgrounds, safe neighbourhoods, transportation, well-functioning schools, fresh food, and employment improves overall health.[5] Although many recognize and try to address these SDOH, acting on this knowledge proves to be difficult.[6] Many communities do not have adequate capacity to address these determinants to undertake ameliorative social policies. Moreover, addressing SDOH requires coordination between a variety of sectors with separate funding streams, where investments in one siloed sector may accrue savings in an adjacent one, and so data collection and calculating the impacts of investment is difficult. For example, a government agency which funds social housing will not likely propose or assess any benchmarks with regard to the physical or mental health of residents, and so it remains unaware of the health impacts that its bricks and mortar projects might engender.

The Invisibility And Ubiquity of Persons with Disabilities

In the disability community, despite advances in the legal recognition of disabled persons' rights, inadequate consideration and funding of their needs exacerbates an already impoverished climate of social inaction.[7] For example, government programs may focus on social housing for people with disabilities, but neglect to address the problem of stigmatization of the disability community.[8] Establishing the SDOH for "people with disabilities" is also highly complex because of varying categorizations of this population: a blind person's needs may be very different than a person who has lost a limb, or a person with depression, or type 1 diabetes. These

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differences also enter into ethical debates when it comes to triage policies, where people with disabilities are categorized according to an able-bodied definition of quality of life. In Ontario, for example, a draft COVID-19 triage protocol statement, the "Clinical Triage Protocol for Major Surge in COVID Pandemic", came under fire when the document was leaked to the public.[9] Over 200 disability organizations signed an open letter outlining concerns about its contents. The document was revised but has not been repealed despite a human rights challenge at the Ontario Human Rights Commission.[10,11] In Canada, people with disabilities also spoke out when the Canada Emergency Relief Benefit (CERB) for people out of work due to the pandemic, was determined to be almost twice what people with disabilities receive from the government and are expected to live on.[12]

Considering that the Centre for Disease Control (CDC) in the United States estimates that 26% of adults have some kind of disability, it is perhaps not surprising that people with disabilities have been adversely affected by the pandemic given the accessibility challenges facing this large group.[13] CDC data also shows that one in three adults with a disability does not have a regular health care provider, or has an unmet health care need because of the cost of care.[13] This systemic issue of access to health care has undoubtedly played into how people with disabilities have weathered the first six months of the coronavirus pandemic. While Canada has universal health coverage, its system nonetheless displays bias against disabled persons. Essential items, such as wheelchairs, crutches, ventilators, hearing aids, and medications are not covered by the federal program. Provinces have partial funding for these items, but these efforts remain largely focused on the indigent.

Moreover, during the first wave, public health data did not track the rates of infection among the disabled or chronically ill.[14] For example, the Ontario government released ongoing public health statistical updates which did not actively track disabled patients and did not include group homes where many disabled people reside because they are overseen by a different ministry. While experts identified the disabled as vulnerable to COVID-19, no effort was undertaken to assess the morbidity and mortality within this population and whether specific strategies might reduce infection rates. Disabled persons remained invisible within the early pandemic even as their personal support workers (PSWs) withdrew or fell ill. Access to food, household items and PPE became more difficult, and communication was impaired by the need to mask and/or by a lack of access to technology and the internet.

The problem of access to the physical environment is another systemic challenge not only for people with disabilities, but also for seniors or others with episodic mobility challenges. Despite awareness of universal design, building codes remain inconsiderate of people's fluctuating needs. Changes in housing construction would result in fewer admissions to long term care facilities – a tangible instance of how social policy influences the delivery of health care. One outcome of the global pandemic has been the realization that accommodations matter – overcrowded congregate settings kill. When the vast majority of citizens experienced working from home, the inadequacy of home offices, kitchen tables, and living room couches as working environments became evident. Not only people with disabilities, but everyone needs ergonomic home-and workspaces.

The renowned disabled academic Rosemarie Garland-Thomson writes: "No other social identity category is as porous and unstable. In fact, most of us will live on both sides of the volatile line between disabled and nondisabled".[15] We all experience morbidity at varying stages in our lives, some of our impairments may be temporary, some may be congenital, some may be permanent, and some may gradually emerge in the diminishment of old age. In sum, we all have a vested interest in getting things right for the disabled because ultimately, they are us and we are them.

Systemic Inadequacies of Care for the Elderly

The virus also lays bare the fact that the most vulnerable in our society, the elderly, are failed by "the system." Worldwide, whether the elderly reside in facilities or at home in multigenerational households, COVID-19 was far more lethal to them compared to the rest of the population. The Atlantic Monthly states that over 40% of American deaths have occurred in nursing homes.[16] Olga Khazan writes: "In just one New Jersey nursing home, at least 53 residents died after the sick were housed with the healthy and staffers had little more than rudimentary face shields for protection".[16] As of the end of the summer, California, New York, New Jersey, Massachusetts and Pennsylvania had the highest death rates in these facilities, exceeding 3,300 individually. Florida, Illinois, Texas, Maryland and Connecticut followed close behind.[17] In 15 states, over half the deaths had occurred in this population.[18] In Italy, the reported average age of deceased patients is 81.[19] As of the end of May, Swedish seniors, aged 70 and above, experienced over 50% of COVID-19 related deaths in that country.[20] In Canada, the provinces of Ontario and Quebec reported over 40% of COVID-19 cases in persons over 60. Nursing home residents accounted for over 80% of deaths in Canada during the first wave – one of the worst in the world.[1]

Many countries lack coordinated plans which integrate elder care with their broader health care systems. An Austrian report states that it had problems with PPE in its institutions because no one had thought to prepare the sector for the new coronavirus.[21] When the Canadian Armed forces were deployed to assist in the COVID-19 outbreaks in several long term care homes in Ontario and Quebec, they reported that "numerous forms of unhygienic and dangerous behaviour" were contributing to the spread of infection.[22] If public health and building codes required proper infection control and design, it would mean that vulnerable individuals would not have to share bedrooms and be exposed to infectious pathogens. While it is true that advanced age, chronic illness, and disability create a high degree of innate frailty, Canadians can no longer ignore that these individuals are also sick and dying because they live in over-crowded, under-funded environments.

This coronavirus health crisis in long term care in Canada is also causing a mental health crisis for seniors for have endured social isolation from family, friends, and each other for several months. Further lockdowns are likely when a second wave of the virus develops. Provincial governments initially approached the pandemic solely from a medical perspective, imposing aggressive restrictions to control viral spread. In the midst of a dire labour shortage, family members and PSWs were banned from entering senior homes. In some facilities, no extra personal items of any kind were allowed into the building including food items made or bought by families, flowers, or clothing, and all in-house social activities were stopped. In Ontario, long term care administrators were told that acute care

hospitals would not accept transfers from seniors' residences, even if patients were critically ill. These strategies, consequently put a massive strain on an already understaffed sector, resulting in more staff absences or turn around, and cognitive decline of seniors who lack social interaction and mental stimulation.[23] Lack of staff to care for residents resulted in many elderly dying from dehydration and even malnutrition in some cases.[24] Family advocates reacted strongly to these policies, and pressured provincial governments to come up with better alternatives to what many felt to be inhumane restrictions. Jianyang Fan, a regular contributor to The New Yorker recently published a piece about her anguished attempts to have her mother's PSWs reinstated at a nursing home where her mother lay completely immobile and ventilator-dependent with ALS. Those in charge of long term care seemed to respond rigidly to the threats of the first wave of COVID-19, failing to take into account the severe mental health toll on an already stressed and cognitively fragile population, nor modifying visitation rules as scientific knowledge and capacities evolved and as it became clear families and friends were prepared to undergo rigorous testing and isolation in order to care for loved ones.

The early stages of the pandemic exposed nursing homes' and other congregate settings' pervasively feeble architecture, inadequate funding and chronic labour incapacity. British Columbia's Senior's Advocate, Isobel Mackenzie, and the British Columbia government are conducting a survey of seniors in British Columbia to understand the deeper impact the pandemic has had on seniors and their families.[26] Another advocate in Alberta, Dr. Lorian Hardcastle, writes, "The only thing that could further exacerbate the devastation in the long-term care sector is if governments fail to seize this opportunity to make long-overdue changes".[27]

Low-income Essential Workers as the New Precariat

The high infection rates among low paid labourers such as cleaners, garbage collectors, grocery checkout workers, public transit workers, meat processing plant workers, and low-level health care workers are also explained by systemic inadequacies. Immigrants tend to occupy these roles in many industrialized countries. In Sweden, émigré Syrian and Iraqi communities experienced much higher rates of infection and mortality. In the UK and the US, people of colour (Hispanics, Blacks and South Asians) are dying in disproportionate numbers. They have a 70% greater chance of dying of the coronavirus than Whites.[28]

These alarming statistics demand social analysis and point to how systemic employment issues have exacerbated the spread of the virus. For example, many low-level workers continue to labour in high risk workplaces because their low wages and lack of benefits keep them too impoverished to search for alternatives. They often live in crowded circumstances and use public transport, raising their potential to catch and transmit the virus. In Alberta, the largest outbreak occurred in a meat-packing plant staffed by refugees and recent immigrants who butchered in an overcrowded premise. Multiple family members worked for the same employer and workers car-pooled and shared households in order to save money. In Ontario, migratory agricultural workers bore a heavy burden of disease as they were housed in run-down, congregate settings with little or no privacy and inadequate sanitation. Further, government mandating higher wages for caring and other forms of high risk unskilled labour would result in less exposure and risk to COVID-19 by being able to work in a single setting and being able to afford proper housing and transportation. One lesson that must be learned from this pandemic is that a safe workplace is an essential SDOH.

For the care they provide to the elderly and the disabled, PSWs – again often composed of overqualified immigrants and refugees – are undervalued, overworked labourers. As of November 1, 2020, staff composed 29% of long-term care COVID-19 cases in Ontario.[29] Negligible pay rates meant that many health care aides worked at multiple facilities to earn a living wage. This led to the spread of infection between multiple care sites. Moreover, in Ontario, infected PSWs were asked to work in care homes because extreme staff shortages meant that patients were dehydrated and lying in their own waste. Additionally, due to privatization of nursing homes, both Quebec and Ontario governments struggled to enforce administrative oversight of these facilities.

This class of worker in Western industrialized countries has been identified as the new "precariat" – or precarious proletariat – meaning a person working under uncertain and even dangerous conditions.[30] Given that those who care for the aged and disabled are at the bottom of the social and health-care hierarchy, little consideration is paid to this sector in good times, and almost no attention was paid to it in pandemic planning. This results in weak regulatory oversight, poor management, lack of staff training, and ongoing shortages of PPE, thereby contributing to increased infection rates in these vulnerable groups and facilitating viral spread to the larger community.

One unanticipated outcome of the COVID-19 pandemic has been the untold effects on a workforce suddenly forced to change business practices. For example, while employers have often rejected virtual work as an accommodation for its disabled employees, forcing people to take disability leave instead, it is now the primary form of labour during the pandemic. Just as families of disabled and chronically ill individuals who have been forced out of the workforce become more financially fragile and more likely to need state subsidy, the COVID-19 pandemic is laying waste to whole industries and fleets of laid-off workers are becoming more economically vulnerable. Workers who still have jobs may be wishing they and their employers had invested in accommodations earlier for working from home, never planning for a time when they too might be in a position of vulnerability and uncertainty.

Conclusion

By refusing to integrate marginal individuals, we needlessly fail them, and we fail ourselves. This social triage, where issues facing vulnerable populations have not been designated as a priority, has resulted in devastating pockets of COVID-19 outbreaks among disadvantaged segments of society. In hindsight, our response to the COVID-19 pandemic reveals systemic inadequacies that ignore the eventuality that we will all experience disease, disability, and vulnerability at some time in our lives. The pandemic shows how seemingly unrelated and distant policy decisions result in increased rates of infection and deaths in specific populations. Social conditions play an enormous role in pandemics. If we more consciously adjusted our attitudes, behaviours, environments, and policies to truly integrate our human vulnerabilities into all aspects of our lives we would have a far more resilient society, more capable

of responding to crises and emergencies and also likely to produce greater overall well-being. COVID-19 highlights our inherent frailties. Instead of ignoring them, we should embrace them, thereby making us a more capable and strong society.

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Declaration of Author's Competing Interests

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Torture in the name of health: ICE is using solitary confinement to curb the spread of COVID

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From the first moments of his campaign, Donald Trump set his sights on immigrants and asylum seekers. As everyone knows, Trump campaigned on the promise to drastically reduce the flow of immigrants entering the United States. Once he took office, Trump, the Department of Homeland Security, and his immigration policy architect Stephen Miller, unleashed a torrent of anti-immigrant policies. These included repeated bans on immigrants entering the US from certain predominantly Moslem countries, separating children from their families, forcing asylum seekers to enter the US at only specific points of entry while forcing them to remain in Mexico during the process, and most recently, halting all immigration at the southern border, purportedly due to public health concerns regarding COVID-19.

Although these and many other practices by the Trump administration have received a lot of press and vociferous backlash, there are many other injustices perpetrated by the executive branch that have received relatively little attention. Among them is the fact that individuals in U.S. Immigration and Customs Enforcement (ICE) custody are regularly placed in solitary confinement (often termed "administrative or disciplinary segregation") for extended periods of time. One of the authors (E.G.) has reviewed hundreds of ICE "segregation reports" as well as medical and disciplinary case records while working for the Department of Homeland Security and sought to expose this practice.[1] Segregation reports showed that ICE has been inappropriately using solitary confinement for the "medical isolation" of individuals who are sick with various ailments, including cancer, tuberculosis, mumps, HIV, and mental illness.[2,3] In addition, two of the authors (S.F. and W. B.) have performed scores of forensic psychological evaluations of asylum seekers, some of whom were in ICE detention and some of whom who had been held in solitary confinement for extended periods of time, and have seen and documented the harmful psychological effects of being held in solitary.

Once the pandemic hit, it was only a matter of time before COVID-19 spread through prisons and, indeed, COVID-19 has spread through detention centers across the country.[4] As of mid-November, eight people had died from COVID-19 while in ICE custody and 7,202 had tested positive for the virus.[5] ICE has released hundreds of individuals who have been identified by courts or the agency itself as high risk for severe illness or death due to COVID-19. However, there are still over 20,000 individuals in detention, any of whom could die or become severely ill if they contracted COVID-19. The majority of those in detention have not committed any crimes and pose little or no risk to the general public. Instead of releasing them, ICE has made it clear that it views solitary confinement as an appropriate public health response to the pandemic.[6] ICE also claims that all those in medical isolation have access to amenities such as recreation and telephones, and that because of this access medical isolation is distinct from solitary confinement.[7] However, individuals placed in segregation units for medical isolation report having as little as one hour per day allowed outside of their single cell. Former UN Special Rapporteur on Torture Juan Méndez defined solitary confinement as isolation from others (not including guards) for 22 hours a day or more.[8] Oscar Perez Aguirre recounted in a sworn court document that he contracted COVID-19 while in ICE custody and required hospitalization.[9] When he was discharged from the hospital, he was placed into "the Hole," another term for segregation or solitary confinement. His cell was "filthy and freezing" and he was so sick he couldn't stand. Another ICE detainee, Ruben Mencias Soto, reported being forced to remain in a bare cinderblock room alone, for 23 hours every day, after his hospitalization for COVID-19.[10]

Before we begin to discuss the ethical issues around ICE's use of solitary confinement for those who have or are suspected of having COVID-19, we want to examine the dire health consequences of solitary confinement for the individual. Almost thirty five years ago, psychiatrist Stuart Grassian evaluated individuals held in solitary confinement and found the same symptoms in many of them, including: hypersensitivity to external stimuli; affective disturbances, such as anxiety and panic attacks; difficulties with thinking, memory and concentration; obsessive compulsive behaviors, perceptual disturbances such as hallucinations and derealization experiences; paranoia; and problems with impulse control.[11] These symptoms are consistent with neurological and psychiatric illness and can emerge de novo in individuals without a pre-existing mental illness as well as worsen symptoms in those with pre-existing psychiatric conditions. These symptoms often – but not always – decrease in severity after release from solitary.

Other researchers have reached similar conclusions about the harmful effects of solitary confinement and medical literature has corroborated these findings. Social psychologist Craig Haney interviewed individuals incarcerated in Pelican Bay State prison and found that 63% of men kept in solitary confinement said

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they consistently felt on the verge of an "impending breakdown," compared to 4% of the other individuals in maximum-security prisons.[12] He reported that 73% of people in solitary confinement felt chronically depressed, compared to 48% for other inmates. Additionally, Haney found that the harmful effects of isolation could last years after release, given that many individuals felt emotionally numb and continued to experience anxiety and depression long after their release from solitary. Not surprisingly, many who had spent time in solitary confinement in Pelican Bay had difficulty integrating into society and preferred to remain in confined spaces even after incarceration.

And it does not take long for these symptoms to emerge. Forced isolation for as little as five days is correlated with increased risk of PTSD and suicide.[13-15] In Texas, for example, suicides rates for those in solitary confinement are five times higher than those of the general prison community. Consider the case of Choung Woong Ahn, who was detained at the Mesa Verde ICE facility in California and was placed in COVID-19 medical isolation on May 15. Two days later, Woong Ahn died by suicide.[16] Carlos Hernandez Corbacho, who spent a little over one week in an ICE segregation unit for COVID-19 isolation, put it succinctly: "In the end, what they did was psychologically torture me."[17]

Not only is placing individuals in solitary confinement for extended periods tantamount to torture, solitary confinement and unit lockdowns are insufficient for preventing disease transmission. Using segregation units to isolate those who are ill also discourages those with symptoms from coming forward. Epidemiologists have predicted that without sufficient public health measures, at least 72% of those held in immigration detention could become infected.[18] And to compound the harms, many of those who are sick and placed in solitary confinement are going to receive inadequate medical care.

Given these conditions, numerous professionals including the Department of Homeland Security's own medical experts and one former head of ICE, have called for the large-scale release of those in detention.[19,20] To date, only a small fraction of those being held in detention have been released. Part of the resistance to releasing individuals is that many ICE detention facilities are for-profit and as such are loathe to shed beds and lose revenue.

Using solitary confinement for civil detention – especially for those seeking asylum, which is fully legal according to US and international law – is inhumane and unethical. In 2011, the U.N. Special Rapporteur on Torture and Other Cruel, Inhuman or Degrading Treatment or Punishment condemned the use of solitary confinement except in exceptional circumstances and argued to ban the practice completely for people with mental illnesses and for juveniles.[21] Multiple organizations agree with this position, including the American Academy of Child and Adolescent Psychiatry and the American Medical Association, which both oppose the use of solitary confinement in juveniles.[22,23]

Current ICE policies and practices pertaining to the use of solitary confinement raise ethical concerns. First, as many people know, the four foundational principles of bioethics are autonomy, justice, beneficence, and nonmaleficence. Although there are a number of critiques of these principles – many of which we believe have merit – these principles nonetheless offer a reasonable framework for an initial analysis of the ethical issues at play here.

We will begin with the principle of autonomy, or respect for persons. Autonomy is described in the Belmont Report and other subsequent treatises on bioethics as the freedom to act on one's own judgment without obstruction, unless one's actions are clearly detrimental to others.[24] One might argue that due to their incarceration, those detained in ICE custody have forfeited any right to exercise their own autonomy. But the broader question in the case of detained immigrants is whether their detention is justifiable in the first place. After all, immigration violations are civil and not criminal offenses, so a priori incarceration is a harsh punishment except, perhaps, for those immigrants who have committed serious crimes.[25] Furthermore, many immigrants are not afforded basic due process rights, including having a bond hearing within a reasonable length of time after being detained, often waiting years without an actual court hearing.[26,27] Compounding matters ethically is the fact that so many ICE detention facilities are for-profit, such that these facilities have financial incentives to keep as many individuals in detention as possible.[28] Given this significant conflict of interest it is indeed difficult to justify the deprivation of the basic right to autonomy for those immigrants who have committed civil offenses and pose no risk of harm to others.

Yet another basic ethical principle that ICE violates in its standard operating procedure is that of beneficence, a bioethical principle which entails making an active effort to secure the well-being of others.[29] ICE and other supporters of the use of segregation units for medical isolation may argue that they are doing good by promoting health – after all who could argue against attempting to prevent the spread of a potentially deadly infection? This argument, however, can be more closely examined using two popular moral philosophical frameworks. Deontological ethicists such as Kant are commonly understood to believe that some actions (such as murder) are always morally indefensible, regardless of the circumstances or the ultimate outcomes of those actions. Torture, like murder, is an act which most deontological ethicists would find either morally or legally unacceptable in any situation.[30] In the case of Kantians in particular, solitary confinement violates the categorical imperative, both because we can safely assume that we would not accept it if everyone suspected of a COVID-19 infection were placed in solitary confinement to prevent the spread of the disease, and because placing people in solitary confinement treats those individuals as means rather than ends.[31] By contrast, solitary confinement might well be justified in certain utilitarian frameworks given that that whatever the harms to the individual, the benefits to society at large might far outweigh them.[32] That being said, considering the fact that those kept in segregation units can still transmit COVID-19 via the detainment facility ventilation system or guards, that at-home quarantining would be more effective and would drastically reduce psychological harms to inmates, and that allowing thousands of non-violent civil offenders to quarantine at home would be much less costly to society, it is unlikely in the present scenario that we are "maximizing utility."[33]

Given the above, the arguments to promote nonmaleficence are readily apparent. Solitary confinement is widely considered torture internationally, so preventing its practice will obviously prevent harm. And this fact leads directly to an argument on behalf of justice. Justice is a broadly conceived and agreed upon ethical standard about what is fair and just. If international standards and accords agree that solitary confinement is tantamount to torture, then placing individuals in solitary is unjust and obviously

harmful. As such, the use of solitary confinement flies in the face of any bioethical principle.

The upshot is that placing detained immigrants in segregation units, regardless of the motivation, is incredibly cruel, is tantamount to torture, and contrary to international medical ethical principles. The use of solitary confinement in ICE facilities was on the rise before the pandemic, and since COVID-19 its use has only continued to grow.[34,35] Such practice is unconscionable and antithetical to the values the U.S. has previously purported to represent.

Historically, the U.S. was seen as a beacon of light for immigrants seeking a better life. Given the Trump administration's abdication of its ethical responsibilities, that light appears to have gone off. Let's hope we can get the power back on soon.

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A Pandemic induced reckoning: bioethics and justice

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Bioethics Responds to the Pandemic

The COVID-19 pandemic has forced previously unimaginable moral dilemmas to the forefront of American consciousness. Health care providers faced the question of how to allocate medical resources in the event that the health care system was overrun with patients, which was thought to be a near inevitable scenario at the peak of the outbreak in New York City. Practitioners and policymakers grappled with an overwhelming sense of resource scarcity, which was subsequently replicated in communities across the country. Even as the worry over a lack of ventilators and ICU beds has receded in many (but not all) parts of the U.S., health professionals continue with unfamiliar and unsettling practices, such as reusing personal protective equipment and negotiating how to provide compassionate patient care while minimizing the risk of infection transmission to themselves and others.

Ethical challenges at the clinical bedside are not all that the pandemic has laid bare in the United States. Deeper questions about basic human values, for example, what is fair and just, have revealed themselves. We are struggling with the question of what we owe one another - both as individuals and as members of families, communities, and society. Bioethics, a broadly-conceived discipline for methodical and reason-based inquiry into ideas at the intersection of human well-being, health and morality, appears to be well suited to provide needed expertise in guiding our approach forward. As a pragmatic endeavor, bioethics often seeks to reconcile tensions between competing human values in the context of medicine, public health, and society, sometimes through the instillation of process-focused solutions.

In this commentary, we aim to raise questions about the capacity of mainstream bioethics to respond to complex problems involving the circumstances of justice that the pandemic has highlighted in the United States. We use circumstances of justice to describe the background conditions influencing "how to distribute the benefits and burdens of social cooperation as well as the rights and duties persons should have in the basic institutions of society."[1] Our interest in this provocation stems from our own immersive experiences within the field of bioethics, and as such, reflects a self-criticism as much as it does an evaluation of others.

We begin with a brief account of the highest profile guidance offered by bioethicists to address the critical care resources rationing concern in the Spring of 2020. We review critics' responses to this guidance, which argued that the frameworks neglected to consider long-standing structural injustices in their initial modeling. Although these critiques were levied specifically in response to COVID-19 guidelines, similar arguments have been made about the field of bioethics as a whole. We explore several reasons why the field of bioethics may be poorly-equipped to confront the scale of institutional dismantling that might be required to address root causes of social injustice in the United States. Finally, we suggest some interesting implications for bioethics if it seeks to seriously reckon with questions of justice.

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A Neglected Principle

In response to the COVID-19 crisis, prominent bioethicists put forth in the most widely read medical journals in the United States two frameworks for the ethical allocation of critical care resources under conditions of scarcity. On March 20, Emanuel and colleagues published in the New England Journal of Medicine and on March 27, White and Lo published in JAMA.[2,3] Both proposals advocated for a standardized approach incorporating multiple moral values. Both also called for prioritizing the principle of "maximizing benefits," understood as saving the most lives with explicit inclusion of years of life lived as an additional measure of fairness.[2,3] Both claimed a "consensus" among experts that in a public health crisis, "responsible stewardship" of scarce resources demanded this kind of prioritization scheme.[2,3] The ethical appeal in their position is intuitive: under conditions where all people cannot be saved, it seems plenty sensible to save as many lives as possible. If each human life has equal value, the absolute numbers saved surely ought to count. However, we note here that a maximizing benefits approach is a contestable moral assertion, not an ethical given just because of "consensus" among certain kinds of experts.[4] In July 2020, Annas commented:

> *[V]irtually all commentary on resource allocation in crises, like COVID-19, assume without analysis that utilitarianism rules in a pandemic. But a pandemic, as horrific as it is, does not automatically alter the ethics of the medical profession by adopting utilitarianism as its code.*[5]

The Emanuel article specified other values – "treat people equally" and "giving priority to the worst off" – as essential principles to consider.[2] The authors' treatment of these potent moral claims, however, was shallow. The framework did not substantively engage with the social determinants of health and disease that inescapably inform how we understand words like "equally" and "worst off." Reliance on such a sterilized notion of fairness created the conditions for a swift and devastating critique from numerous angles, including the following from Schmidt:

> *[B]ackground conditions should matter in how we assess who should be put on a ventilator. But they don't. Instead, the 'save the most lives' guidance assigns patients points from one to eight, taking into*

account a person's physiology and life expectancy….Life expectancy across geographic, income and racial groups can vary by up to 30 years. For example, inner-city residents of Chicago, who are more likely to be black, can expect to live to 60 years. Those in suburban areas, who are typically white, live to 90. In the model guidance, the 56-year-old inner-city black patient could receive two penalty points – whereas a 60-year-old white suburban patient would receive none.[6]

Appealing to criteria such as one's present or projected physiological state or life expectancy is seductively "objective." It leaves the impression of fairness by allowing us to compare apples to apples, or in the case of medical facts, data points to data points. These numbers bear no trace of the often unjustifiable reasons why and how they have come to manifest in living, breathing human beings. The "isms" that shape so much of how and why the numbers appear – racism, sexism, ageism, ableism and others – are made conveniently invisible. In the words of another sharp critic:

Using heuristics for "survivability" thus infects with bias our seemingly objective clinical criteria, and allows existing health disparities to worsen, creating a vicious circle. Doing that worsens life prospects for the most disadvantaged in society, in the name of saving the most lives.[7]

Justice is a canonical principle in contemporary American bioethics but it was only once mentioned in one of these two headline-grabbing allocation frameworks. It was not mentioned in the other article at all. After complaints were publicly levied, one set of authors quickly amended their guidance by adding an explicit ethical goal of "diminishing the negative effect of social inequalities that lessen some patients' long-term life expectancy" to their priority of "saving lives" and "saving life-years."[3] They further reconstructed their scoring system to remove long-term survival expectancy from the prioritization calculus.[3] These changes are commendable. Nevertheless, it is worth considering whether the initial neglect to factor in the circumstances of justice, the social context and background conditions, represents an endemic myopia within the discipline of bioethics.

We are not the first to voice a concern that mainstream bioethical discourse, particularly in the U.S., has neglected to engage with the far-reaching social and institutional demands of justice.[8-10] Prior critiques have put forward the following, incisive observation: the field of bioethics regards itself as a pragmatic discipline, suited to offer implementable solutions to problems that arise within a given set of background structures and conditions; the field is not primarily organized, nor are most of its experts expertly positioned, to provide answers to more fundamental questions about the rightness or wrongness of the political, economic, and/or social organization of our society. Francis elaborates on this presumption:

Many of the issues in applied ethics fields deal with relationships between professionals and their clients….what is important is that these issues about individuals and their relationships are treated first, rather than being situated within a framework of justice.[8]

The elevation of this style of methodological inquiry in settings like the United States enables value conflicts in the health care field to be examined with a convenient presumption of relative social and institutional stability. When bioethicists are called upon to help explain or resolve a novel concern (for example, what we should do about the newfound ability to edit the human genome), we generally do not begin with an interrogation of the fairness of the American health care system as whole – nor is that conventionally expected.

Why is Justice Neglected?

In what follows, we aim to build on others' concerns regarding why the field of bioethics might struggle to address the circumstances of justice, both in the context of a pandemic and in general. In our brief discussion, we hope to sketch a provocative picture for further reflection. For the American bioethics community to earnestly confront the reality of health care injustice, it requires a willingness to go to places that we suspect might be personally and professionally uncomfortable for many of us.

First, it should not be controversial to suggest that the substance of professional level training (and expertise) in American bioethics is not centered around asking and answering questions about the circumstances of justice. Rather, many, if not most recognized leaders and educators in the field have built their credentials and careers by providing useful insight into ethical dilemmas arising at the clinical bedside, or within the context of human subject research, or in addressing the implications of new medical and scientific technologies. Many are first clinicians by professional training, and later ethicists by intellectual curiosity. Curricula in graduate level programs for bioethics largely reflect this specific kind of focus and expertise.[11] This emphasis also flows naturally from the fact that the enterprise of American bioethics now understands itself in no small part as a consultative service to long-established institutions such as hospitals, medical schools, managed care organizations, and industry.

Questions that probe whether the "conditions in which people are born, grow, live, work, and age are responsible for most of the unjust, preventable, and systemic differences in outcomes among groups" are simply not regarded as primary.[12] If our job was to do "ethics in the context of unjust institutions and conduct," the boundaries of our moral inquiry would be blurred.[8] For instance, if the root causes of an individual's health challenges are a by-product of matters entirely out of her control (where she was born, her skin color, her access to decent schooling, exposure to violence, clean water, and fresh foods), does that mean our recommendations must include a condemnation of the political, economic, and social forces that so circumscribe her autonomy? More daunting still, does it oblige us to put forth a workable plan for remedying these societal ills? Clearly, it simplifies any ethical analysis to assume that the justness of background conditions is not in question, or at least not a question we need to primarily concern ourselves with.

Second, the few bioethicists in the U.S. (often with PhDs in philosophy) that have deeply reflected for more than a college semester about the social, institutional, and political demands of justice are not required to understand the problem in a uniform manner. They, just like full-time political theorists, moral philosophers, and politicians, are not obligated to agree on the specific content of the demands of justice in our society. Surely some bioethicists are more libertarian or conservative in their orientation just as some are surely more egalitarian or liberal; some might defend a mostly private, market-based set of organizational principles for structuring health care delivery in the U.S. because they value individual property rights over equal access rights. Others might ethically defend a single-payer government run system. Without agreement on what justice requires, it can be difficult to maintain a robust focus on it within the field.

Third, even if there was broad agreement across the bioethics community about the social and institutional demands of justice in remedying health disparities and their moral priority, any proposed solution would necessarily require a robust commitment to activism as a major component of the enterprise. For us, it is hard to imagine any serious, pragmatic engagement with justice that does not involve inherently political arguments and positions. The hard work of installing fairness and equity in the American health care system cannot effectively be accomplished by directing most of our energies to teaching in a classroom, speaking at academic conferences, and authoring peer-reviewed articles in technical journals.

The ethical indefensibility of the peculiarly American approach to health care was captured in a feature article on the pandemic in the New York Times on July 1, 2020 titled: "Why Surviving the Virus Might Come Down to Which Hospital Admits You":

> *In Queens, the borough with the most coronavirus cases and the fewest hospital beds per capita, hundreds of patients languished in understaffed wards, often unwatched by nurses or doctors. Some died after removing oxygen masks to go to the bathroom. In hospitals in impoverished neighborhoods around the boroughs, some critically ill patients were put on ventilator machines lacking key settings, and others pleaded for experimental drugs, only to be told that there were none available. It was another story at the private medical centers in Manhattan, which have billions of dollars in endowments and cater largely to wealthy people with insurance. Patients there got access to heart-lung bypass machines and specialized drugs like remdesivir, even as those in the city's community hospitals were denied more basic treatments like continuous dialysis.*[13]

Many obvious sources of health care injustice in the United States can be boiled down to our continued acceptance of a decentralized, market-based and profit-centered approach to health care delivery. As the economists Case and Deaton argue, "The American health care industry is not good at promoting health, but it excels at taking money from all of us for its benefit. It is an engine of inequality."[14] Taking justice seriously would require us to take a vocal stand on the failings of the current organization of American health care. It requires more of us in the political realm, including a willingness to speak out on issues in the deliberative bodies of government, not to mention the boardrooms of many of our home institutions. The dispassionate and apolitical cover often granted to academics would no longer suffice.

Fourth, career bioethicists may face personal disincentives to address issues of social and economic justice head-on in settings like the United States. Our roles as intellectuals and academics support us in constructing narrow boundaries around our foci and eschew the need to speak out about how "injustice anywhere" poses a threat to justice everywhere. When the structural status quo has worked for us, it undeniably makes it harder to call out flaws from which we have benefited. The more we are recognized and applauded under established terms, the harder we might find it to believe that we are complicit in a rigged set of structures and hierarchies that reinforce rather than rectify social injustice. We might also become susceptible to another insidious narrative about the special privileges we have earned on account of our talents and hard work. As Michael Sandel remarks:

> *Meritocracies also produce morally unattractive attitudes among those who make it to the top. The more we believe that our success is our own doing, the less likely we are to feel indebted to, and therefore obligated to, our fellow citizens. The relentless emphasis on rising and striving encourages the winners to inhale too deeply of their success, and to look down on those who lack meritocratic credentials.*[15]

We have no reason to believe that bioethicists, by virtue of their interest in human morality, are immune to this kind of unattractive thinking.

Fifth, at least in the United States, bioethics has to date been overwhelmingly dominated by people who identify as white, hold advanced educational degrees, and work in positions of relative privilege – at colleges and universities, think tanks, and health care delivery organizations. While it would be flatly wrong to assume that people in these positions have no personal experience of injustice, it stands to reason that people who are not actively experiencing the proverbial short end of the justice stick in their daily working lives are less likely to (a) feel they have the lived experience to talk about the effects of injustice or (b) want to confront the realities of what tackling injustice would require of them. We want to be clear here that we think people in positions of privilege are capable of taking justice seriously, but they may be less likely to prioritize concerns about social injustice than people whose on-going life experience gives them primary "data" with which to care and act.

Sixth and finally, we suggest that the circumstances of justice might also be neglected by bioethicists because serious explorations of the topic raise uncomfortable questions about our own integrity. We have experienced this discomfort first hand and discussed some of the ways in which teaching a course on global health ethics has challenged us as self-identified proponents of a health equity agenda.[16] To publicly acknowledge the rampant unfairness of so many structures and systems that confront health outcomes exposes those of us in positions of relative power and privilege to charges of hypocrisy. One lives with the worry that a student, or perhaps a colleague, will one day adapt a phrase from GA Cohen and ask: "if you're so interested in justice, how come you work for a private academic medical center with a tremendous endowment, that operates with massive profit margin, and that markets a concierge service for well-heeled patients?"

Implications for the Field

We share others' concern that COVID-19 will be remembered as a moment in which the field of bioethics failed to provide moral clarity about how American society ought to reconcile competing values in the context of human health and welfare.[9] Nevertheless, we also appreciate that prominent academic bioethics programs, think tanks, and individual scholars are taking steps to integrate the circumstances of justice more sincerely into their work. In the past few months, the two of us have received a litany of invitations to seminars, forums, and special journal issues with the word justice in the title. It is clear that many people in leadership positions are making an effort to "lean in" to the challenge. In what follows, we offer some out-of-the-box cautionary notes about how we might strengthen these efforts.

If one thinks of the field of bioethics as an informal kind of organization in which people loosely coordinate their efforts to accomplish a set of goals, there may be insights to borrow from management science. For many years, leading management scholars have recognized that it is difficult for organizations, especially organizations with revered expertise in a particular domain, to learn how to do new things.[17] This is particularly true when the new thing

will fundamentally challenge the old way things were done. Think of a newspaper trying to make the leap from a paper publication to an online publication, or an entertainment company trying to switch from mail-order DVDs to a subscription streaming service. Researchers have shown that the best way for an organization to be great at both yesterday and tomorrow's business is to create a sharp distinction between them within the organization and, to the extent possible, keep interaction amongst the people working on yesterday and tomorrow at a minimum. The key insight is that if the "old guard" and the innovators interact too extensively – even by sitting in the same building, some would say – the former will pollute the latter and the organization will fail to change. Real change will not occur, and business will mostly go on as usual.[18]

The implications of such thinking for the field of bioethics, or any field attempting to do something radically new, are quite interesting. If bioethics is serious about addressing justice in ways it has not before, we see two potential imperatives. The first is that the field, and the organizations within it, may want to take seriously the need to identify new intellectual capital in people with very different lived experiences from beyond traditional academic pedigrees and/or clinical training. People from outside the academy altogether, including those from civil rights movements and religious communities, may bring especially bold perspectives on justice. In extending a welcome to such thinker-activists, bioethics may want to heed our earlier cautionary notes about what kind of people may be most motivated to address systemic injustices. The second is that once these new human resources are identified, the "old guard" of bioethics should be very careful not to become a drag on these people's ideas. This poses something of a problem for an academic field that relies so heavily on mentorship as a means of advancing careers. Nevertheless, the management insight described above suggests that even if bioethics were to recruit a new crop of young thinker-activists into its midst, it should be careful about pairing these young people with mentors who tell them, either explicitly or implicitly, that their ideas are too radical, politically untenable, or more mundanely, unpublishable.

Even if a new batch of thinker-activists are brought into the mainstream fold of bioethics, the field faces a major problem that is worth emphasizing here. The problem is that many of the institutions which house and support the work of bioethics are embedded in a larger set of organizational hierarchies that must themselves be ethically interrogated. Most leaders in anything considered "mainstream" have achieved their status by demonstrating some fealty to these hierarchies. They have played, by and large, by the conventional rules. But now, we are asking these leaders to not only recognize, but encourage potential subversion of the values that these hierarchies reflect. We admit we are unsure this is even possible, let alone welcome, but it does seem warranted.

A Concluding Note on Humility

The COVID-19 pandemic has brought mainstream American bioethics to a momentous inflection point, as it has with virtually all social institutions. Early on, many predicted that COVID-19 would come to be a "great equalizer" and exact an equal health toll on people regardless of their standing. Instead, the disease has shown itself to be a great exposer. Clearly, it has exposed the injustices that had previously been buried in plain sight. It has also exposed the deficiencies of many of the United States' political institutions and health systems, and, we have argued, the deficiencies of bioethics. Rather than running from the shame of our unpreparedness, the two of us are trying to understand how we got here and determine how we can do better. James Baldwin wrote that "Not everything that is faced can be changed, but nothing can be changed until it is faced." This essay serves as our effort to begin to face the relationship between bioethics and justice more squarely.

We are, frankly, unsure whether the field can credibly back away from the problem of justice, as we have described it, and continue to focus on narrower questions and concerns with an assumption of social stability. There is virtue in recognizing one's limits and staying in one's chosen lane. However, if this is the path that is consciously chosen by the field moving forward, it seems impossible to reconcile the same with a foundational disciplinary commitment to justice. We think bioethics might, for moral inspiration, look to other organizations that are attempting to radically refashion themselves in the United States. Bold initiatives to address racial injustice within the theater community are one example, where long-standing leaders in many companies are stepping down to make room for new voices.[17] We are sure others exist. The common thread for any justice-first organizational effort is for the current leadership to approach the problem with a sincere willingness to take career-threatening risks, and to question loyalty to organizational ways of working that mostly keeps things the same. It requires people with power and privilege, perhaps most of all, to exercise humility.

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The hailing heroes myth: raising awareness of stigma experienced by healthcare workers during COVID-19

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Introduction

When the COVID-19 pandemic first began unfolding, an unprecedented outpouring of solidarity, gratitude, and appreciation for healthcare workers (HCWs) was felt around the world. In light of public health restrictions, communities found unique and innovative ways to celebrate HCWs for their efforts in responding to COVID-19. Balconies and streets filled with nightly applause and cheers. Sidewalks were covered with chalk messages thanking them for being heroes. Planes carried out fly-pasts across various cities. Online concerts to honor front-line workers broadcasted widely.

Despite these acts of appreciation, HCWs have faced numerous challenges as the pandemic has progressed. HCWs have become targets of stigma, prejudice, discrimination, and violence. In reality, people participating in such activities of praise are not any less likely to hold harsh and stigmatizing beliefs about the threat HCWs pose.[1] HCWs have also experienced shortages of personal protective equipment (PPE), increased workload, lack of adequate compensation, and difficulty with striking a balance between their professional and personal responsibilities.[2-5] Under the guise of heroism, HCWs have faced violations of their rights: the right to just and favorable working conditions, the right to health, and the right to be free from discrimination and violence. The purpose of this commentary is to raise awareness of the stigma that HCWs have experienced during COVID-19 by providing an overview of the manifestations of stigma, its impacts and drivers, and potential strategies that can be applied to reduce stigma.

Stigma and HCWs

Globally, the stigmatization against HCWs has taken many forms. In this commentary, stigma is defined as the coexistence of "labelling, stereotyping, separating, status loss, and discrimination in a power situation that allows these processes to unfold."[6] HCWs are defined as all nurses, doctors, volunteers, and technicians in healthcare facilities.[7] Given the potential proximity to COVID-19 patients in a hospital setting, HCWs have been perceived by others as "dirty", infected, and contagious by family members, friends, and the general public.[8-10] Family members and friends have reacted negatively after learning that they were working in a hospital at the start of the outbreak.[8] Many avoided interacting with them, joked about them being infected on social media, or perceived them as carriers of contagion.[8-10] For instance, after an outbreak began on a cruise ship in Japan, HCWs who provided care on-site were referred to as "germs".[11] In a recent study in Canada and the United States, 42% of survey respondents indicated that they do not want to be around HCWs who treat COVID-19 patients, while 39% of respondents believed that HCWs who work in hospitals are likely to have COVID-19.[1]

HCWs have faced substantial social ostracism from their communities. In a wide range of countries, HCWs have become victims of acts of verbal and physical violence as illustrated by the following examples. In India, two female doctors were filmed being stoned by a mob after they screened a patient suspected of having COVID-19.[12] Media coverage also revealed incidents of HCWs in India being spat on while carrying out their duties and even receiving threats of sexual violence.[13] In Mexico, the Ministry of Interior recorded at least 47 acts of aggression towards HCWs as of April 28, including chlorine and eggs being thrown at nurses on the street.[14] From March 19 to May 8, the Mexican National Council to Prevent Discrimination received over 250 complaints from HCWs concerning discrimination due to COVID-19.[14] In the Philippines, a nurse was doused in bleach by a group of men who believed he had COVID-19 due to working at the hospital.[13] In Pakistan, doctors were arrested for protesting the lack of PPE required to care for COVID-19 patients.[15] HCWs have also been denied access to various essential services, making an already straining situation more difficult.[13] Across Pakistan, Japan, Mexico, and India, HCWs have reported being evicted from their homes due to fear of them being infected.[13,16,17] Similarly, they have been refused access to public transportation, shops, and grocery stores.[18] In Canada and the United States, 29% of survey respondents felt that HCWs should have restricted freedoms and 28% of respondents felt that HCWs should not go out in public.[1]

It is crucial to recognize that the stigma associated with COVID-19 is not neutral across critical factors such as race and gender. For HCWs of Chinese descent and those perceived as Chinese, the stigma associated with their occupation is compounded with a surge in anti-Chinese stigma. Between March 16-18, 2020, President Donald Trump referred to coronavirus as

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the "Chinese virus" in a series of tweets, which linked race to the virus and insinuated that Chinese communities are responsible for originating and spreading COVID-19.[19] After Donald Trump's tweets, there was nearly a 10-fold increase in the use of phrases such as "Chinese virus" and "China virus" on Twitter across the United States.[20] The World Health Organization (WHO) recommends not naming new human infectious diseases based on geographic locations as it can have negative social and economic impacts as well as foster distrust of public health.[21] Such instances of racism and discrimination are embedded within the historical perceptions of Chinese communities being "perpetual foreigners" who are "sickly" and "disease-ridden".[22,23] HCWs of other Asian ethnicities, including Korean and Filipino, have also experienced racism, including racial slurs (e.g. "go back to China"), physical assault (e.g. being spit on), and patients refusing care from HCWs perceived to be Asian.[24] Ironically, although HCWs have been on the frontlines saving lives, many Asian HCWs continue to be blamed for the onset of the pandemic.[24]

The experiences of stigma are believed to be stronger for HCWs who are more proximal to patients and heavily involved in patient care, such as nurses, who have reported more adverse stigma-related psychological impacts.[8,25] In Canada, women represent over 90% of nurses, which suggests that women may be experiencing stigma at higher rates.[26-28] Women also often carry the burden of caring for their loved ones, have higher participation rates in housework and childcare than men, and are making difficult decisions about childcare in response to school closures.[26] Women are coping with COVID-19 without crucial safety nets, while simultaneously being on the frontlines and putting care at the center of their work.

Impact of Stigma on HCWs

Stigmatization has widespread and profound negative impacts. Physicians and other HCWs experience higher levels of stress than the general population, and during a pandemic, this stress is heightened.[29] HCWs have developed symptoms of PTSD, depression, and substance-use disorders during previous pandemics and outbreaks, such as SARS, MERS, H1N1 influenza, and Ebola.[25,30] Frequently, pandemic-related stress stems from an increased workload and fear of infection.[31] Stigma-based discrimination and prejudice can increase the mental burden on HCWs. In particular, it can increase feelings of social rejection and isolation which can lead to anxiety and depression.[32] For instance, the first COVID-19-related death in Japan was related to mental health, when a government worker who was responsible for returning citizens from Wuhan died by suicide.[11]

In addition to the mental health challenges, HCWs also experience an increase in the prevalence of physical symptoms, such as headaches, sore throat, lethargy, and insomnia.[3,33] When compounded, these physical symptoms can further exacerbate pandemic-related mental health problems and vice versa.[3,33] The stigmatization during COVID-19 is also positively related to burnout and fatigue.[3] Discrimination due to stigma can also lead to poor physical health, greater risk of cardiovascular disease, and hypertension.[34,35]

Impact of Stigma on Healthcare and Communities

The hostility HCWs have experienced is, in many ways, characterized as an attack on healthcare as a system. The World Health Organization defines an attack on healthcare as "any verbal or physical act of violence, obstruction or threat that interferes with the availability, access and delivery of such services."[36] Stigma and discrimination impact HCWs' decision-making, efficiency, and ability to manage the crisis effectively.[16] It can also de-motivate HCWs from their roles and responsibilities and can contribute to staff shortages, as many HCWs may not feel safe coming to work.[17,36] This lack of motivation has direct implications on the quality of care that patients receive and can disrupt the availability and smooth delivery of essential health services in hospitals.[36]

Inconsistent public health messaging combined with the spread of misinformation on social media has led to uncertainty and fear regarding the origins and methods of transmission of COVID-19, as well as respective treatments and preventative measures.[37] The combined effect of misinformation and fear has resulted in a growing mistrust towards HCWs and public health officials. HCWs and their families are being increasingly seen as a risk to communities rather than a solution to this public health emergency.[36] There have been various reports of HCWs' children being bullied, socially excluded, and denied admission to nursery schools because of fear that HCWs will spread COVID-19 to others.[11,31] For example, in Canada, a nurse's daughter was excluded from a neighborhood playdate because many feared that she had COVID-19.[38] This stigma towards HCWs and their families increases public fear and distrust, which can be detrimental to public health efforts, as seen with vaccine hesitancy.

Drivers of Stigma

To understand the increase in stigmatizing beliefs against HCWs, it is important to understand that fear is one of the common drivers of stigma.[39] This relationship is best described by the "COVID stress syndrome" which is characterized by: (a) fear of infection and/or coming into contact with carriers of the virus; (b) worry about personal finances and other socioeconomic costs; (c) xenophobic beliefs that immigrants and other minority groups are carriers of the virus; (d) traumatic stress symptoms associated with direct or indirect exposure to COVID-19 and; (e) compulsive checking and reassurance seeking.[40] A network analysis of these five factors reveals that at the core of this syndrome is fear of infection, thus explaining the increase in stigma and discrimination against HCWs during the pandemic.[40] Furthermore, the analysis reveals an interconnectedness between xenophobia and the fear of infection, which elucidates the layered stigma HCWs of Asian descent have been facing, as previously mentioned.

Strategies to Combat Stigma

Given the scientifically limited and rapidly evolving nature of COVID-19, the spread of misinformation and fear is inevitable. To address this, several guidelines have been released by different entities, including the WHO, Centers for Disease Control and Prevention, UNICEF, and The Centre for Addiction and Mental Health, amongst others.[41-44] These guidelines show similar characteristics in stigma definition, its impact, and how to reduce stigma in healthcare facilities including: learning about the disease of interest and/or

related stigma, encouraging relationship-building with populations that face stigma, and promoting wellness in stigma-afflicted groups.[45] However, to our knowledge, evidence on community uptake of and adherence to such guidelines is limited.

While guidelines provide valuable information, it is necessary to evaluate their efficacy in reducing stigma.[17,45] The heterogeneity of interventions and the lack of standardized measures makes assessing their efficacy in different healthcare settings challenging.[45] In addition, many of the proposed interventions fail to target root drivers of stigma and often take retroactive steps to addressing its impacts.

To address this, we recommend that researchers and decision-making bodies utilize a translational research (TR) framework, which is centered on understanding the uptake of guidelines and interventions that address stigma by community end-users. The TR framework(s), although often adapted, is an iterative process which involves: identifying a problem, contextualizing existing or synthesized knowledge, developing interventions to address the problem, and evaluating the long-term effectiveness of interventions.[46] Within Canada, one of the most widely recognized TR frameworks is the Knowledge-to-Action Cycle.[46] The use of this framework is valuable to HCWs and the general community as it encourages researchers to identify root causes of problems, to tailor interventions to local contexts, and to evaluate their efficacy for sustainable use.

In the context of COVID-19, adopting the TR framework could begin with identifying existing guidelines and interventions designed to reduce stigma towards HWCs published by public health and associated entities. This approach can be followed by community-wide assessments that analyze stigmas, biases, and knowledge that community members hold in relation to HCWs and COVID-19. It could also explore potential barriers and facilitators to the implementation of current guidelines and interventions. In collaboration with community members, the findings could then be utilized to iteratively improve current efforts or to develop new interventions that address the root causes of stigma. In turn, stakeholders can return to the community to assess the intervention's effectiveness in increasing knowledge, reducing fear, and ultimately stigma.

Conclusion

As the COVID-19 pandemic unfolds in real-time, HCWs continue to face substantial stigma, prejudice, discrimination, and violence. Stigma has profound physical and mental health impacts not only on HCWs, but on their families, the patients they serve, and the broader healthcare system. While various guidelines to combat stigma against HCWs currently exist, to our knowledge, evidence on community uptake, adherence, and efficacy is limited. Moving forward, it is suggested that researchers and decision-making bodies utilize a translational research approach to address the stigma HCWs have and continue to face due to COVID-19. While communities are encouraged to continue hailing HCWs as heroes, more needs to be done to ensure that they are structurally protected and cared for during COVID-19 and future pandemics.

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Are app-based platforms safe for communicating patient health Information?

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We live in a post-digital world where photos, videos, and messages can be transmitted instantaneously with the click of a button. From our clinical experiences, many Canadian physicians are still reliant on pagers, fax machines, telephone calls, and hand-written notes for health-related communication. Today, there are a plethora of alternative communications platforms in the form of mobile device applications (Apps). These App-based platforms include WhatsApp (www.whatsapp.com), PageMe (www.pagemeapp.com), Hypercare (www.hypercare.com), ShareSmart (www.sharesmart.ca), Telmediq (www.telmediq.com), and PetalMD (www.petalmd.com), each with unique strengths and weaknesses. Physicians already routinely use WhatsApp and equivalent platforms in their clinical practice in many jurisdictions within Ireland, USA, and the UK among others.[1-3] Here, we argue that an updated telecommunication policy incorporating the use of App-based communications platforms is needed.

In Canada, each provincial and territorial governing body is responsible for overseeing and enforcing access and privacy laws with unique information security safeguard standards (Table 1). In Ontario, the Personal Health Information Protection Act (PHIPA) and Information and Privacy Commissioner (IPC) set

Table 1. Provincial and territorial governing bodies responsible for overseeing and enforcing access and privacy laws

Province/Territory	Governing body responsible for overseeing and enforcing access and privacy laws	Privacy law relating to health records	Website link to privacy law
Alberta	Office of the Information and Privacy Commissioner of Alberta	Health Information Act	http://www.qp.alberta.ca/documents/Acts/H05.pdf
British Columbia	Office of the Information and Privacy Commissioner for British Columbia	E-Health (Personal Health Information Access and Protection of Privacy) Act	http://www.bclaws.ca/EPLibraries/bclaws_new/document/ID/freeside/00_08038_01
Manitoba	Office of the Ombudsman	The Personal Health Information Act	http://web2.gov.mb.ca/laws/statutes/ccsm/p033-5e.php
New Brunswick	Office of the Integrity Commissioner for New Brunswick	Personal Health Information Privacy and Access Act	http://laws.gnb.ca/en/showfulldoc/cs/P-7.05//20190819
Newfoundland and Labrador	Office of the Information and Privacy Commissioner Newfoundland and Labrador	Personal Health Information Act	https://www.assembly.nl.ca/legislation/sr/statutes/p07-01.htm
Northwest Territories	Office of the Information and Privacy Commissioner Northwest Territories	Health Information Act	https://atipp-nt.ca/wp-content/uploads/2016/03/Health-Information-Act.pdf
Nova Scotia	Office of the Information and Privacy Commissioner Nova Scotia	Personal Health Information Act	https://nslegislature.ca/legc/bills/61st_2nd/3rd_read/b089.htm
Nunavut	Office of the Information and Privacy Commissioner of Nunavut	Consolidation of Access to Information and Protection of Privacy Act	https://atipp-nu.ca/wp-content/uploads/2018/04/consolidation-of-access-to-informationand-protection-of-privacy-act.pdf
Ontario	Information and Privacy Commissioner of Ontario	Personal Health Information Protection Act	https://www.ontario.ca/laws/statute/04p03
Prince Edward Island	Information and Privacy Commissioner of Prince Edward Island	Freedom of Information and Protection of Privacy Act	https://www.canlii.org/en/pe/laws/stat/rspei-1988-c-f-15.01/latest/rspei-1988-c-f-15.01.pdf
Quebec	Commission d'accès à l'information du Québec	Act Respecting the Protection of Personal Information in the Private Sector	http://legisquebec.gouv.qc.ca/en/pdf/cs/P-39.1.pdf
Saskatchewan	Office of the Saskatchewan Information and Privacy Commissioner	The Health Information Protection Act	https://pubsaskdev.blob.core.windows.net/pubsask-prod/8623/H0-021.pdf
Yukon	Yukon Information and Privacy Commissioner	Health Information Privacy and Management Act	http://www.gov.yk.ca/legislation/acts/hipm_c.pdf

Abbreviations and acronyms:
CMPA - Canadian Medical Protective Association
IPC - Information and Privacy Commissioner
NHS - National Health System
PHI - Personal health information
PHIPA - Personal Health Information Protection Act
VPN - Virtual private network

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Table 2. WhatsApp application-specific precautions on Apple and Android products with the potential to maximize privacy safeguards

1. Block WhatsApp from downloading media onto mobile device albums This feature allows users to prevent the automatic download of media products, such as pictures of patients' medical presentations. Consequently, all media shared through WhatsApp conversations remains restricted to the secure platform. Users must fulfill all three sets of steps under Apple or both sets of steps under Android
2. Enable screen lock Although WhatsApp does not currently allow password locks on the application, screen lock is an equivalent feature on iPhones. When combined with the "Immediately" option, screen lock will require users to unlock the application using the same biometric (Face ID or Touch ID) they use to unlock their phone. After several attempts users will be able to input the security code used to unlock their iPhone. This feature keeps the conversations on the application secure even if the phone is lost or stolen or if someone outside the circle of care takes the custodian's unlocked iPhone. Although Android does not currently offer screen lock options, it is recommended to download and use a third-party locking application on WhatsApp. This is the equivalent to the iPhone screen lock feature.
3. Disable iCloud and Google Drive backups WhatsApp automatically creates unencrypted backups unless this feature is disabled. Disabling unencrypted cloud backups is the safest thing step that can be done to ensure unencrypted copies of PHI are not created.
4. Enable two-factor authentication Two-factor authentication, also known as two-step verification, adds an additional periodic passcode to a user's WhatsApp. The secure six-digit PIN is requested when logging onto WhatsApp using a different device thereby decreasing chances of someone accessing a user's account without their consent. This feature also periodically requests the PIN after opening WhatsApp. The six-digit PIN cannot be shared with anyone.
5. Continuously check for and update WhatsApp application Updating WhatsApp ensures the application is up-to-date and contains patches for potential vulnerabilities. These updates are released as the company finds security weaknesses, such as following cyberattacks. Regularly checking and updating the application keeps users' conversations safe from security breaches.
6. Disable message previews This feature protects patient privacy since users receive message notifications. The contents of the conversation are not shown. Users must open the WhatsApp conversation to view the message.
7. Set password lock All mobile devices must have a password lock that only the user knows. Passcode must be required immediately upon turning on the device from sleep mode. Smartphone password locks should not be a simple pattern, consecutive numbers, or repetitions of the same digit. Longer number combinations are more secure than shorter combinations. The safest password locks are those that include special characters, numbers, and capital and lower-case letters.
8. Use the official WhatsApp desktop application rather than WhatsApp Web Although WhatsApp Web offers several more features than the official WhatsApp desktop application, it can easily be manipulated and thus has bigger security threats. The official WhatsApp desktop application is safer to use if looking to use WhatsApp on a laptop.
9. Double-check the conversation's end-to-end encryption Although unnecessary, verifying that the end-to-end encryption works is a quick way to provide peace of mind that the privacy safeguards are working in that conversation.
10. Enable security notifications This feature allows for a notification to be sent when a security code changes. Security codes change when a new phone or laptop accesses an existing chat such as when one of the conversation participants switches their WhatsApp to a new phone. Always double-check the conversation's end-to-end encryption following a change in the security code.
11. Beware of phishing scams The most common phishing scams originate from unfamiliar phone numbers and discuss a premium version of WhatsApp (WhatsApp Gold) or the user account's expiring. There are no premium versions of the application and WhatsApp will always be free of charge. Users should contact WhatsApp for more information about suspicious messages.
12. Protect your privacy on WhatsApp This option prevents non-contacts from being able to learn information about users. This also prevents other people from being able to reverse image search a user's profile photo to learn more information about the custodian. It is best to keep "Read Receipts" enabled (i.e. "on") to facilitate other custodians knowing if their messages have been read.
13. Audit group conversation membership Users should regularly audit the participants of a group chat, particularly if the user is the group chat admin, to check for unauthorized members such as people not within the circle of care.

forth requirements for administrative, physical, and technical safeguards, including encryption, to keep personal health information (PHI) secure on mobile devices.[4,5] However, the onus is on healthcare practitioners, hospitals, and community health facilities to determine whether a given communication platform is compliant, safe, and secure.[6] As such, there is much discordance across the country with regards to which messaging platforms are secure for the transmission of PHI.

Through consulting with Information Technology Departments of several Canadian hospitals, we found that most groups favoured the so called 'trusted' modalities – fax machines, hospital pagers, and encrypted email servers – for communication between and amongst physicians and trainees. Many institutions currently discourage or ban App-based communication platforms due to privacy concerns. Their concerns include the lack of control over who can access conversations, as well as the fear that companies could mine or sell sensitive PHI. However, such concerns surrounding the confidentiality of PHI using these platforms may stem in part from our lack of understanding of how these applications store and transmit information.[7] Significant security and privacy gaps are often overlooked and downplayed when comparing traditional communication technologies to new platforms. For example, fax machines allow healthcare providers to share patient information with one another as many electronic health record systems are not interoperable. Although fax machines may be difficult for outside users to hack electronically, sensitive PHI can be mistakenly sent to the wrong fax number or faxes could be picked up by unintended persons, thereby breaching patient privacy. Likewise, hospital pagers may transmit critical messages, particularly in acute emergencies, but are nonetheless time-consuming, unencrypted, and easily intercepted.[8] Furthermore, pagers lengthen consult and referral wait times; this disrupts the flow of communication within circles of care since users are often unaware of the content or urgency of pages and whether the other party has received the message. Although encrypted email servers, such as eHealth Ontario's ONE Mail, may provide expedited communication, they require secure transmission and cooperation between sender and receiver to be safe. Only emails sent from one clinician's ONE Mail account to another ONE Mail user are secure. Moreover, sensitive emails can be unintentionally, albeit permanently, sent to an incorrect recipient.

We are currently addressing health-related communication in a 21st-century technological world with 20th century tools. Today, safe communication alternatives that adhere to provincial and

Table 3. Steps on Apple and Android products to enact WhatsApp application-specific precautions

Precaution	Steps on Apple & Android Products
Block WhatsApp from downloading media onto mobile device albums	1. Apple: WhatsApp>Settings>Data and Storage Usage>Media auto-download>Never>Tap onto each of these four to disable auto-downloads: photos; audio; videos; documents. 2. Apple: Settings>WhatsApp>Photos>Never. 3. Apple: WhatsApp>Tap on conversation>Tap on group/member name in the chat window>Save to Camera Roll>Never. 1. Android: WhatsApp>Settings>Data and Storage Usage>Media auto-download>Disable auto-downloads>Tap onto each of these three to disable auto-downloads: when using cellular data; when connected on Wi-Fi; when roaming. 2. Android: WhatsApp>Tap on conversation>Tap on group/member name in the chat window>Media visibility>No.
Enable screen lock	Apple: WhatsApp>Settings>Privacy>Screen Lock>Require Face ID/Touch ID>Immediately. Android: Download and use a third-party locking application.
Disable iCloud and Google Drive backups	Apple: WhatsApp>Settings>Chats>Chat Backup>Auto Backup>Off. Android: WhatsApp>Menu>Settings>Chats>Chat Backup>Backup to Google Drive>Never.
Enable two-factor authentication	Apple: WhatsApp>Settings>Chats>Chat Backup>Auto Backup>Off. Android: WhatsApp>Menu>Settings>Chats>Chat Backup>Backup to Google Drive>Never.
Continuously check for and update WhatsApp application	Apple: Appstore>Updates>WhatsApp>Update (if WhatsApp is already updated the button will say "Open" otherwise it will say "update"). Android: Google Play Store>Menu icon (top-left corner)>My Apps & Games>WhatsApp>Update (WhatsApp will only appear on the list of apps to be updated only if an update is available).
Disable message previews	Apple: WhatsApp>Settings>Notifications>Show Preview. Flip the toggle to white (i.e. "off"). Android: Settings>Apps>WhatsApp>Notifications>Message Notifications>On the lock screen>Hide sensitive notification content.
Set password lock	Apple: Settings>Touch ID/Face ID & Passcode>Passcode. On the Touch ID/Face ID & Passcode page: Require Passcode>Immediately. Android: Settings>Security>Screen lock.
Use the official WhatsApp desktop application rather than WhatsApp Web	Apple & Android: Visit whatsapp.com/download and click on the "supported versions" that is appropriate for your laptop.
Double-check the conversation's end-to-end encryption	Apple & Android: Start conversation in WhatsApp>Tap contact's name in chat window>Encryption>QR code and 40-digit security code. Manually verify if the 40-digit security code is the same for all users in the conversation either in person or using a different messenger application (i.e. not WhatsApp). Alternatively, ask the contact to scan your QR code using the WhatsApp application or you scan their QR code using the "Scan Code" button.
Enable security notifications	Apple & Android: WhatsApp>Settings>Account>Security>Show security notifications. Flip the toggle to green (i.e. "on").
Beware of phishing scams	Apple & Android: Do not open the message if it is from an unfamiliar number. Delete the suspected message.
Protect your privacy on WhatsApp	Apple & Android: WhatsApp>Settings>Account>Privacy. For maximum efficiency and security set Profile Photo and About to "Nobody" and Last Seen and Status to "My Contacts".
Audit group conversation membership	Apple & Android: WhatsApp>Tap on conversation>Tap on the group chat name in chat window>View the participants to check for unauthorized members within the group. To delete unauthorized members the group admin must: WhatsApp>Tap on conversation>Tap on the group chat name in chat window>Tap on unauthorized participant (under "Participants" section)>Remove from Group.

territorial privacy laws exist and should be considered as adjuncts to our traditional communication armamentarium. WhatsApp is one such example. WhatsApp is currently the most commonly used messaging application worldwide, with over 1.5 billion accounts and 500 million daily users.[9,10] Clinicians can send medical photos to colleagues, see the moment their messages are opened, and instantly receive real-time feedback, all at no charge. It should therefore come as no surprise that our informal multi-hospital survey of 50 Canadian residents and clinicians found the use of WhatsApp to communicate PHI despite the platform often being prohibited by hospitals. When used securely, WhatsApp can potentially support patient care by facilitating rapid communication, encouraging interprofessional collaboration, and flattening hierarchies by allowing junior trainees to propose management plans and ask questions critical for their learning.[11] WhatsApp also has a potential role in helping coordinate healthcare teams with tasks such as managing acute medical crises, including trauma cases, to ongoing public health concerns, such as coordinating care during the COVID-19 pandemic. Delivery notifications and read receipts, including the exact time a message was read, offer accountability in communication.[12] WhatsApp therefore allows for accountable, efficient, and instantaneous interdisciplinary communication that would otherwise be difficult or even impossible through fax machines, pagers, and encrypted emails.

WhatsApp incorporates security features that allow users to enable in-app precautionary features to maximize privacy safeguards to levels compliant with province- and territory-specific health record privacy laws.[13] It employs default end-to-end encryption based on Signal Protocol with advanced encryption standard key lengths of 256-bits, which exceed the 128-bit minimum currently set by the PHIPA and IPC.[4,14] These security algorithms are designed to prevent anyone, inside and outside the company, from creating master keys to decrypt and read conversations, or mine and sell PHI. The application also allows users 4096 seconds (68 minutes, 16 seconds) to permanently delete sensitive messages that were unintentionally sent to individuals outside the circle of care.[15] Despite being targeted by large-scale security breaches in the past, WhatsApp ultimately offers stronger barriers against hacking and interception of PHI than our current hospital communication platforms. Properly following specific security precautions can help further maximize WhatsApp's compliance with current provincial and territorial regulations (Table 2 and Table 3) and keep PHI safe.[13,16-19] Canadian app-based platforms specially created for medical use, including PageMe, Hypercare, ShareSmart, Telmediq, and PetalMD, provide potentially even safer alternatives. Unlike WhatsApp, these app-based platforms can only be used by healthcare workers in clinical settings. This helps prevent medical messages being sent to non-healthcare professionals. Regardless of the encrypted communication platform chosen, safety of PHI should remain front and center. This can be done using encrypted mobile devices and a virtual private network (VPN) when using unsecured Wi-Fi networks. As with any tool, these platforms

should be incorporated into clinical practice with appropriate user training for safe application use. The Canadian Medical Protective Association (CMPA) does not have an official position on this issue, but advises clinicians using App-based platforms to follow provincial and territorial privacy standards indicating that electronic exchanges are explicit forms of communication and must therefore be included in the patient's medical record.

It is our position that a blanket ban on the use of all app-based communication platforms risks their off-label use, which places patient's privacy in far greater danger compared to finding ways to integrate this technology into clinical settings safely. A recent US study found 'inconvenience' as the most significant self-reported barrier to compliance with communication policy, with 58% of residents having violated regulatory standards by sending PHI through unencrypted text messages.[20] Another survey reported 30-50% of medical professionals are already routinely using messaging applications in their clinical practice.[2] Given the impact of COVID-19, the United States Department of Health and Human Services recently liberalized privacy law compliance guidelines allowing the use of encrypted app-based platforms, such as WhatsApp, iMessage, and Zoom, for telehealth purposes.[21] It is important to acknowledge that our widespread reliance on telemedicine during the COVID-19 pandemic, both in Canada and the United States, will likely continue long after social distancing measures subside. Therefore, our professional societies must understand the strengths and weaknesses of each platform and provide guidance to safe usage of communication platforms so that we can safely embrace and benefit from the newest innovations, while simultaneously upholding patient privacy.

The current speed of advances in app-based communication technology is remarkable. We call on our provincial regulatory bodies and professional medical societies to continually reassess and offer guidance to healthcare professionals on the safe use of app-based communication platforms for medical purposes as part of a technological vision for the future. In the United Kingdom, the National Health System (NHS) has already made great strides towards a fully digitized NHS, a critical part of their Technological Vision and NHS Long Term Plan.[22,23] To this end, the NHS is phasing out the use of fax machines and hospital pagers for non-emergency medical communications by 2020 and 2021, respectively, with a transition to their in-house messaging application.[24,25] We need a multidisciplinary working group of experts and stakeholders – health professionals, technological specialists, patient advocates, lawyers, ethicists, and others – to outline a Canadian telecommunication vision for the future with patient privacy and security front and center. Such a group could continuously monitor cybersecurity advancements and test new applications against up-to-date security standards to provide healthcare custodians with a verified list of secure communication apps and instructions on safe usage. Overall, finding ways to safely integrate app-based platforms into clinician's communication toolboxes will bring us closer towards a modernized healthcare system.

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Deconstructing and strengthening Canada's health human resource strategy

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Introduction

As the first wave of the 2019 coronavirus (COVID-19) swept across Canada, our initial planning response was centred around immediate issues such as Personal Protective Equipment (PPE) and Emergency Room (ER) or Intensive Care Unit (ICU) capacity.[1] With early interventions, including physical distancing and broad lockdowns, provinces could flatten the curve or at the very least limit a surge of cases that would overwhelm our health system.[2] However, our experience with the first wave of COVID-19 has unearthed a longer-term health systems issue that deserves immediate action: that of inadequate Healthcare Human Resource (HHR) planning and utilization. Specifically, we have identified the following key gaps in Canada's HHR strategy:

1. Canada lacks robust, needs-based national HHR data collection and forecasting

An inadequate supply of healthcare workers (HCWs) affects the ability to fight the pandemic. As frontline HCWs are at an increased risk of contracting COVID-19, regions may see drastic reductions in their front-line workforce.[3] This problem is worsened by inherent shortages in HCWs. This was borne out overseas in New York and parts of Italy.[4,5] Even in Canada, staffing shortages in long-term care resulted in the federal government exhausting almost its entire armed forces to bolster medical capacity in just two provinces.[6] Plans and structures, therefore must be in place to recruit and redeploy HCWs in acute and non-acute settings to respond to pandemics.

2. Current accountability and reporting structures between the federal government and provinces/territories are not clear, transparent, or visible to the public

Currently, the Federal, Provincial, and Territorial Public Health Response Plan for Biological Events (FPT-PHRPBE) bridges the gap between federal and provincial/territorial responses, but it is unclear if its reporting structure is truly operationalized.[7] It is difficult to identify which federal, provincial, and territorial bodies are accountable for each aspect of HHR planning, and this lack of transparency is detrimental to our ability to strengthen our HHR workforce.

3. There is a clear lack of robust planning for HHR needs in community care settings

Canada's initial COVID-19 planning focused on predicting and preparing for surge capacity in acute care settings, and efforts were largely targeted at bolstering physical resources (e.g. PPE, ventilators, overflow hospital spaces) and acute care human resources (e.g. physicians, nurses, respiratory therapists).[1] Although these efforts were necessary, it became apparent that the bulk of COVID-19's impact was occurring outside of acute care institutions. Of all Canadian COVID-19 deaths, 85% occurred in long-term care institutions (LTCs), representing some of the highest international mortality proportions in long-term care settings.[8] While many hospitals did not see the increase in patient volumes they had planned for, community settings such as LTCs, shelters, and prisons are understaffed and most at risk.[9] Canada's most vulnerable, stigmatized and marginalized citizens are at risk for being disproportionally affected by COVID-19.[10]

We therefore propose 3 key areas of action to strengthen Canada's HHR planning moving forward.

Area of action 1: invest in needs-based data collection

To inform pandemic planning and decision making, governments require data on current HHR, community needs, and projections of spread. Unfortunately, this data collection is regionally and professionally isolated. Outside of the military, the government would be challenged to identify what resources are needed or available.

Canada needs a national health workforce planning agency to fill this gap, as is done in other countries with more successful COVID-19 responses.[11] This agency could engage in the collection of provincial data regarding the current healthcare workforce, develop needs-based forecasts for health resource planning, and develop plans, models, and procedures for pandemic redeployment. Besides immediate pandemic response, such an agency would increase our ability to harness national data and research for overall health systems strengthening for generations to come. Lack of foresight and planning in this department may lead to severe shortages in the healthcare workforce that can overwhelm the healthcare system. This was made clear in Italy, where a lack of HCWs, PPE, and overloaded health system resulted in an exponential growth in cases and high mortality rates up to 8-12%.[12]

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Area of action 2: develop a federal accountability plan for HHR oversight

As mentioned, the FPT-PHRPBE is a complex and difficult-to-find governance structure that is responsible for HHR oversight in Canada.[13] Although there is an organizational chart outlined on their document, it is unclear what is under provincial/territorial jurisdiction and what is under federal jurisdiction. This plan is also difficult to understand and locate, and inaccessible to various levels of government and the public alike.

Canada must follow the lead of countries like New Zealand that have robust accountability structures for HHR oversight.[11] One way to operationalize this is to have an accessible and up-to-date centralized COVID-19 response website that states the roles of each jurisdiction and relevant body in a format understood by the public. Making lines of accountability clear to the public from the federal government downwards signals to Canadians that we are aware of our jurisdictional responsibilities and are unified across our provincial and territorial borders. Lack of federal accountability and leadership in the United States led to the country being overwhelmed with cases despite its strong healthcare capacity. The United States comprises 5% of the world population but constitutes over 25% of the world's COVID-19 cases.[14,15]

Area of action 3: understand our care needs in the community and strengthen our community workforce

To avoid repeating such calamitous outcomes in LTCs, prisons, shelters, and other community settings, it is imperative that provinces identify essential personnel (i.e. outside of direct medical staff) across the entire spectrum of community care. For example, New Zealand's robust pandemic plan articulates the impact of a surge on phone triage personnel, public health educators, community pharmacists, doctors, nurses, funeral home workers, and coroners. In Ontario, the Minister of Health has pushed for contingency plans, including recruiting a back-up pool of workers with transferable skills (e.g. food service preparation) to fill in gaps in the LTC workforce. We must learn from these jurisdictional solutions and provide robust national guidance on how to operationalize these contingency plans.

To this effect, we propose a new Federal Health Transfer to provinces that supports the collection of data regarding personnel needs in community care settings during non-pandemic times, the projection of expected surge needs of this workforce and the projections additional resources, such as living accommodations, transportation, and hazard pay that may be needed to support this workforce. A Community Care HHR Working Group should be established at the national level with provincial/territorial representation to provide guidance to provinces/territories on how to collect the above data, how to make surge projections, and how to allocate funds across the community care sector. By setting this guidance nationally, we can ensure equitable and accessible deployment of surge resources across provinces/territories in the event of a second COVID-19 wave or future pandemic.

Implementation challenges

While we believe these solutions would be beneficial to Canada's pandemic response, there are several implementation challenges. First, lack of cooperation with all provinces/territories may cause insufficient compliance and adoption of recommended solutions. For instance, the Government of Quebec, "considers Health Human Resources planning to be its exclusive responsibility".[16] Such individualistic and fractured responses can be avoided by ensuring appropriate representation from provinces and territories. This will also provide flexibility in adoption of our solutions, so each province and territory can tailor it to best fit their unique needs and challenges. Second, because federal and provincial funding is limited, our recommendations will require managing and redirecting funds. This is further complicated by short-lived windows of opportunity in public policy implementation.[17] The COVID-19 pandemic has highlighted faults in our healthcare system and provides a minute window of opportunity for implementing innovative health system changes. We recommend the government take decisive action. If the window of opportunity is exceeded, the public will lose interest in pandemic planning and it will no longer be a priority. We may find ourselves no more prepared during the next global outbreak.

Conclusion

Canada's response to the COVID-19 pandemic has exposed limitations in our HHR planning. First, to address the lack of needs-based national HHR data collection and forecasting, we must implement a national health workforce planning agency. This agency would be responsible for data collection, both within and outside of a pandemic, in order to ensure we have robust longitudinal data collection systems in place across the nation. Second, we must develop a federal accountability plan for HHR oversight clear to both those responsible and the public. Finally, we must acknowledge that any robust HHR plan must also anticipate the needs of community organizations to be successful. By addressing these 3 current gaps, we can ensure that Canada's healthcare system is strong and ready to face future pandemic events.

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COVID-19: a psychological nightmare

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Abstract

The COVID-19 pandemic has dramatically influenced our lifestyles and sleep habits, compromising our ability to effectively process and regulate emotions. We explore a neurobiological perspective to illustrate that dreams and nightmares during the pandemic may be indicative of an increased emotional load in our waking lives. We also propose that the combined impact of daily stressors and poor sleep behaviours brought on by the COVID-19 pandemic may lead to detrimental psychological health outcomes. These negative effects are ultimately perpetuated through a vicious cycle, necessitating the development of appropriate and timely interventions. We suggest that dreams and nightmares can showcase the role COVID-19 as a chronic population stressor. As this pandemic ensues, researchers should not overlook the importance of dreams and how sleeping habits are linked to waking emotional states.

As COVID-19 emerged as a global crisis, reports of wild and vivid dreams increased during the pandemic, prompting research into the content, frequency, and tone of these dreams.[1-3] Vivid and bizarre dreams can be described as dreams that contain powerful imagery. Nightmares are a subcategory of vivid dreams, characterized by both vivid imagery and heightened negative affective tones.[4] In the wake of the pandemic, higher levels of distress and the presence of vivid dreams are evident in recent literature.[5,6] The reports on dreams and nightmares during the COVID-19 pandemic illustrate a link between dreams, life events, and psychological distress.

Research emerging during the pandemic has only begun to explore the negative consequences of the COVID-19 crisis on sleep and emotional distress. While COVID-19 has a more direct impact on certain individuals, like medical workers and inpatients, a shift in sleep patterns appears widespread even in the general population.[7] Self-reports of sleep habits from Italy during lockdown demonstrate a change in sleep patterns among university students and working professionals. Bedtimes and wake up times have been delayed significantly with exacerbated effects on university students.[8,9] Changes in sleep habits consequently reduce quality of sleep, which may increase susceptibility to emotional distress.[9,10]

In this article, we explore the combined impact of life stressors and altered sleep behaviours during COVID-19 on the long-term psychological well-being of the general population. We propose that pandemic-related changes in stress and sleep compromise the brain's ability to regulate emotions, which may have further consequences on psychological health. We discuss how the underlying functional connectivity of emotion-related brain areas are altered in the face of stress, and thus also propose the unique role of dreams as an early indicator of emotion dysregulation.

Previous research has uncovered a significant link between our waking life stressors and dreams. It appears that the experiences and stimuli we encounter every day in the real world influence the kinds of dreams we have and how frequently we have them. Indeed, research has highlighted that traumatic experiences, such as natural disasters, vehicle accidents, and violent attacks, heavily influence dream content.[11,12] One example comes from a study conducted on the 1989 San Francisco earthquake. Following the catastrophe, the incidence of nightmares in individuals living in San Francisco was doubled compared to individuals living in Arizona who were at a greater distance from the earthquake.[12] These results highlight a link between life events, dream content, and nightmare frequency, and are suggestive of a pattern that may be similarly seen during the pandemic.[2]

Neuroscience research can explain why individuals experience more nightmares during times of stress. Dreams serve an important purpose — they help us process our emotions.[10] Research has shown that our emotion centres in the brain, including the amygdala, ventromedial prefrontal cortex, and hippocampus, are activated during sleep.[10,13] As we sleep, the amygdala and hippocampus work in tandem to revisit and store memories from our waking lives.[14] During sleep, when the brain replays memories, the functional connectivity between the amygdala and hippocampus is downregulated. As a result, the activity of the amygdala, normally activated by stressful events, is also downregulated thereby allowing the emotional tones to be dissociated from the memory. This allows the amygdala to be less reactive when we face similar stressors in the future.[14] Stripping the emotional context of memories is the brain's method of regulating our emotions.[13]

In addition to downregulated activation between the hippocampus and the amygdala during sleep, the functional connectivity of the amygdala and the ventromedial prefrontal cortex increases after sleep. This helps us regulate our emotional and behavioural responses to a stressor.[13,14] In particular, the ventromedial

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prefrontal cortex is involved in the evaluation of whether events are threatening and require attention. It also allows us to appraise situations in our waking lives in adaptive ways, which is why our response to stressors may be less reactive when facing them a second time.[14] These neurobiological processes during sleep are the brain's mechanisms for managing stress.

However, during COVID-19, individuals are experiencing inadequate or disrupted sleep.[7–9] Sleep deprivation interferes with the neurobiological processes of sleep, making individuals increasingly sensitive to environmental stressors and altering the ways in which they understand, express, and modify their emotional responses.[15] Thus, the cumulative effects of suboptimal sleep and elevated stress likely underlie the rise in negative emotionality observed during the COVID-19 pandemic.[5,10] Specifically, recent reports show that anxiety, stress, and depression have increased in the general population as a result of the spread of COVID-19.[8,16] While these negative emotions can often lead to more cautionary avoidance behaviours in the short-term, such as staying at home to avoid contracting COVID-19, they can be maladaptive in the long-term as lack of sleep compromises emotional processing.[17,18]

Given the uncertainty of how lifestyles could change in response to the spread of the virus, the stress imposed by COVID-19 is unpredictable and persistent. The elevated levels of distress currently experienced by the general population may last months longer than the stressor itself, potentially characterizing COVID-19 as a chronic stressor. Since chronic stress and sleep disruptions are associated with mental health, we may see a continued rise in psychological illness within the general population with considerable public health implications—a possible secondary impact of the pandemic.[19,20]

While current research has already highlighted the immediate psychological impacts of COVID-19, we have yet to discover the full extent of the secondary, long-term impacts of the pandemic as a chronic stressor on different populations. For example, one study showed that women were twice as likely to experience depression under chronic stress compared to men.[21] Other studies have shown that individuals with pre-existing health conditions may experience exacerbated psychological effects under chronic stress.[22] Certain personality traits such as high emotional reactivity and sensitivity to sensory processes and environmental stimuli may contribute to the nightmare susceptibility.23 These studies underscore the importance of not only investigating the long-term effects of COVID-19-related chronic stress, but also identifying groups that are especially vulnerable to its negative psychological outcomes.

Evidently, the reciprocal relationship between heightened emotional distress and sleep disruptions is a vicious cycle that may result in poor long-term psychological outcomes.[13,14] The pandemic has undoubtedly caused greater levels of stress. To process the flood of emotions in our waking lives, the brain requires the regulatory role of sleep. With disrupted sleep, the brain is less effective at carrying out emotion regulation processes. This can lead to further emotional distress and interfere with our ability to handle stressful situations in our waking lives. Without intervention, the cycle repeats and may increase the likelihood of negative long-term outcomes on our psychological well-being.

In summary, we have outlined the importance of vivid dreams and nightmares in signaling an increased emotional load in our waking lives. Yet, the increase in vivid dreams is just the tip of the iceberg. The persistence of such dreams and nightmares showcases the role of COVID-19 as a chronic population stressor. As this pandemic continues, researchers should leverage the unique opportunity of the pandemic to further explore and understand how our dreams and sleeping habits are tied to waking emotional states. In doing so, we may better position ourselves to understand the long-term impacts of COVID-19 on the mental health of the general public.

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Canada's infant mortality: a developing world within its borders

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Abstract

The infant mortality rate is the number of child deaths under 1 year of age/1000 live births. It is a central indicator of both health system effectiveness and socioeconomic conditions. However, Canada's infant mortality rate is unacceptably high for its level of healthcare and socioeconomic development. Canadians living in income-deprived areas and those experiencing health inequities have higher infant mortality rates than those in other areas. We introduce feasible healthcare practitioner activities that will promote improved social environments for children and contribute to bridging gaps in infant mortality.

Introduction

The health of Canadian children is rooted in profound social and economic inequities. Among these imbalances are poverty, inadequate housing, food insecurity, racism and the Indigenous peoples' history of persecution by colonial policies and practices.[1]

The purpose of our commentary is to provide an introductory framework of Canada's infant mortality. We include feasible activities for healthcare practitioners (HCP) that will foster and promote improved social environments for all children in Canada.

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Infant Mortality Rate

The infant mortality rate (IMR) is the number of child deaths under 1 year of age/1000 live births.[1] In the first month of life, infant deaths (neonatal mortality) in Canada are mainly due to prematurity, congenital malformations, infection, and birth complications.[1] Premature births are most common and increasing due to rising maternal age and multiple births from assisted reproductive technology. Later infant deaths after 1 month of life result from sudden infant death syndrome and infection, including diarrhea and pneumonia.[1] In developing countries, prominent causes of infant death are malaria, measles and malnutrition.[2]

Socioeconomic influences are a major contributor to infant death. Factors may include exposure to household smoke, low maternal education, inadequate housing, lack of access to healthcare, food insecurity, poverty, and unemployment.[1] Importantly, public health measures, such as sanitation, access to clean water, and immunization, promote infant survival.[3]

The IMR is a central indicator of local health system effectiveness and socioeconomic conditions.[4] It is also an important measure of advancement toward the United Nations Sustainable Development Goals of peace and prosperity for all people.[5]

Canada Ranks Low Amongst Peer Countries

Canada boasts a publicly funded universal healthcare system. However, its 2019 IMR of 4.4 infant deaths per 1000 live births is high for the country's level of socioeconomic development.[3] Most peer Organization for Economic Co-operation and Development (OECD) countries have surpassed Canada and achieved better rates. For example, Japan's IMR which was 31 in 1960 is now 1.7 – half the Canadian rate. Other countries, such as Finland (3.3), Sweden (2.4), and Italy (2.7), have lower IMR. Among 17 fellow OECD countries, Canada ranked 5th in 1960 and today has the

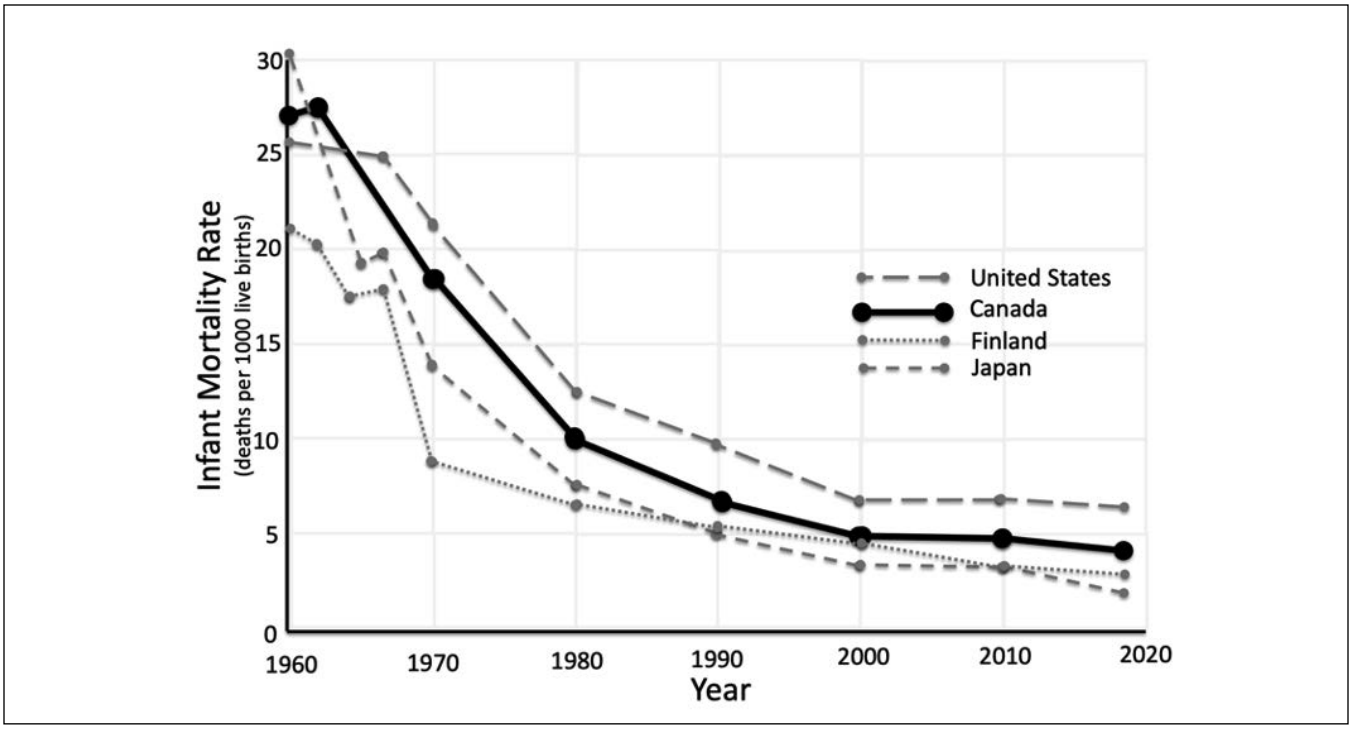

Figure 1. Trends in infant mortality rate, 1960–2019. Note: Graph for Canada and selected Organization for Economic Co-operation and Development Countries. Infant mortality rates 2019: US (5.8), Canada (4.4), Finland (3.3), Japan (1.7). Data for most countries are based on a minimum threshold of 22 weeks of gestation period (or 500 grams birthweight) to remove the impact of different registration practices of extremely premature babies across countries. Adapted from OECD Health Statistics 2019.[6]

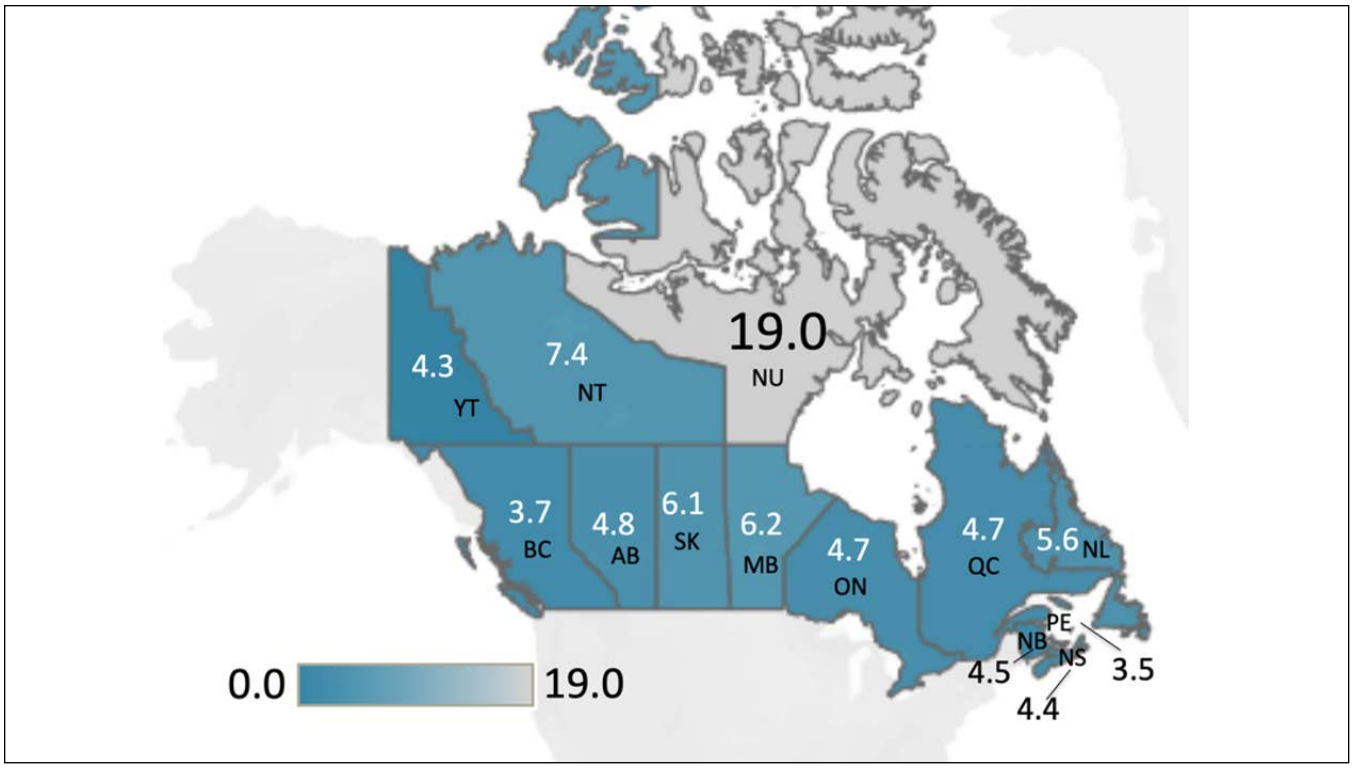

Figure 2. Infant mortality rate by province and territory (5-year average, 2011-16). Note: NU, Nunavut. NT, Northwest Territories. YT, Yukon. BC, British Columbia. AB, Alberta. SK, Saskatchewan. MB, Manitoba. ON, Ontario. QC, Quebec. NB, New Brunswick. NS, Nova Scotia. PE, Prince Edward Island. NL, Newfoundland and Labrador. Adapted from Statistics Canada.[15]

second highest IMR. Only the United States (US) (5.8) continues to perform worse than Canada (Figure 1).[3]

Capturing data has been challenging with variations in countries' registering practices for preterm infants. Canada and the US register a high proportion of babies weighing less than 500 g with low odds of survival and higher infant mortality.[6] There are also greater numbers of infants born early due to use of new medical technologies in high-risk deliveries. Furthermore, new fertility programs have resulted in increased multiple births and premature babies at higher risk of infant death. Although researchers caution interpretation, IMR is the single most comprehensive indicator of health in a society and long-established measure of child and family well-being.[3,7]

Canada's Within-Country Pattern is Striking

Canada's infant mortality is not equally distributed among its provinces and territories (Figure 2). Compared to peer OECD countries with IMRs below 4, only British Columbia and Prince Edward Island rank on par. Four provinces (New Brunswick, Nova Scotia, Ontario, Quebec) and Yukon are below the Canadian average. By contrast, four provinces (Alberta, Newfoundland and Labrador, Manitoba, Saskatchewan) and two territories (North West Territories [NWT], Nunavut) are above the Canadian average.

The IMR of NWT and Nunavut are outliers (2.0 and 5.1 times higher than the national average, respectively).[3] The leading causes of infant death in these territories are sudden infant death syndrome, respiratory infection, and prematurity. Maternal smoking, overcrowding and teenage pregnancies, which are prominent among Indigenous communities, are major contributing factors.6 Genetic factors may also play a role.[8]

Canadians living in the most income-deprived areas with more poverty, unemployment, low education, food insecurity and poor housing, have higher IMRs (1.6 times) than those in the least deprived areas.[1] The Public Health Agency of Canada reported that health inequities are disproportionately experienced by Indigenous peoples and result in higher IMR. This is seen when comparing Inuit (3.9 times), First Nations (2.3 times) and Métis (1.9 times) populations to the overall Canadian rate.[1,7] Therefore, awareness that Canada's IMR is unequally distributed and strongly associated with socioeconomic status can promote upstream policies and programs to address social inequities.[1]

Healthcare Setting Activities

Clinical and complementary activities of HCP can impact infant mortality by integrating social dimensions into the delivery of healthcare.[9] Activities that may contribute to bridging the gap towards healthy equity include:

1. *Adjustment* in clinical activities to reduce social inequities. Examples include breastfeeding practice support, safe sleep education, newborn screening, immunization, and parental counselling to reduce unintentional injuries.
2. *Assistance* to reduce social risk by connecting parents to social care resources. Referrals may include preconception and prenatal care, education on maternal vitamin supplementation, counselling for women who drink alcohol during pregnancy, and smoking cessation programs.[10]
3. *Alignment* by healthcare systems to understand, organize and deploy social care assets. These include improving tracking and census of infant deaths, standardizing birth registration, research to understand variations in IMR among vulnerable populations, and implementation of low technology ideas.[11] Japan's Mother-Child Handbook and Finland's "baby box" (a collection of high-quality baby essentials given to new mothers) are good examples.[12,13]
4. *Advocacy* to promote policies of social equality in education, family income and material wealth that influence maternal and infant health, such as advocating for a basic income guarantee and subsidized day care.[3]

Finally, HCPs need to collaborate with partners to transform systems, practices and policies that address social and health inequities experienced by vulnerable populations, including those who live in income-deprived areas and Indigenous peoples.

Conclusion

The Infant Mortality Rate is a sentinel indicator of child health and societal well-being. Compared to peer countries, Canada's IMR is unacceptably high in the presence of universal healthcare and an advanced level of socioeconomic development. These challenges are rooted in the social and health disparities of vulnerable populations. The activities of HCPs must aspire to "ensure with the maximum extent possible the survival and development of the child."[14]

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What drives resistance to Public Health measures in Canada's COVID-19 pandemic? An online survey of Canadians' knowledge, attitudes, and practices

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Abstract

Background: The ongoing COVID-19 pandemic has spread across 188 countries and claimed over 300,000 lives so far. Despite strong public health messaging and strict community restrictions in Canada, misconceptions and high-risk behaviours such as mass public gatherings have contributed to its spread across the country. Local data on the knowledge, attitudes, and practices from high-case areas could inform public health messaging during the current unprecedented pandemic.

Study Objective: To collate and describe the knowledge, attitudes, and practices of highly affected Canadian communities related to the COVID-19 pandemic and to evaluate factors associated with risky behaviours in order to inform public health policies and communication.

Methods and Study Design: Information on COVID-19 knowledge, attitudes, and practices was collected via online convenience sampling from 1,593 Canadians between 6 to 26 April, 2020. The high outbreak provinces of Alberta and Ontario were targeted.

Findings: While knowledge of COVID-19 transmission and prevention was high (mean knowledge score of 10.5/12 (88%)), a significant minority of respondents (32%) expressed at least one attitude resistant to public messaging that could hamper containment efforts: visiting crowded places other than grocery stores or pharmacies, close encounters with non-household members, and intention not to isolate if having mild flu symptoms, or known COVID-19 exposure. Factors associated with these risky behaviours included low COVID-19 knowledge (OR 1.2 (95% CI 1.1-1.3), p=0.0057), feeling not worried (OR 2.9 (95% CI 2.2-3.9), p<0.001), and feeling uninformed about the pandemic (OR 1.6 (95% CI 1.1-2.3), p=0.030). Respondents reported high acceptance of a potential vaccine (93%) and endorsed a wide-spread vaccination strategy (81%).

Interpretation: Low levels of knowledge and worry regarding COVID-19 may be key contributors to resistance against public health messaging. A potential vaccine, if made available to the general public, would likely be widely accepted.

Introduction

Background

The first case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), was documented in December, 2019, in Wuhan, China.[1] Being highly infectious, the virus has spread rapidly across the world and consequently has spurred a pandemic as declared by the World Health Organization on March 11, 2020. In Canada, COVID-19 was first documented in January, 2020 and now has spread to all provinces, bringing the country to a total of 327,313 cases and 10,187 deaths, as of this writing.[2,3] Throughout Canada's response to the pandemic, public health officials have regularly implored citizens to practice physical distancing, which refers to keeping a physical distance of at least two meters apart.[4] Many other intensive control strategies have taken place across the country as well, including the closure of public spaces and non-essential services, community containment, timely case detection, thorough contact tracing and management, isolation for infected and suspected cases, and mandatory masks in enclosed public spaces.[5,6] In response to lower caseloads, public health authorities have relaxed certain measures such as opening up many public spaces, restaurants, bars, and gyms, and consequently, case load numbers have risen steadily since.[7,8]

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Despite strong health messaging efforts throughout the pandemic, there have been many reports of people not adhering to their province's public measures, which furthers the risk of disease spread in communities.[9,10] To better understand this resistance to messaging, data on community-wide knowledge, attitudes, and practices (KAP) pertaining to COVID-19 could prove insightful.[11-13] For example, during the 2003 SARS outbreak, surveys found that people were more likely to take extra protective measures against infection if they had a higher perceived risk of infection.[14] Additionally, a KAP study focusing on China during the initial COVID outbreak demonstrated that higher levels of knowledge were associated with both greater protective practices and optimism.[11] As of now, there is no effective treatment or vaccine against COVID-19, which highlights the extreme importance of public awareness and compliance to infection control strategies. This may be even more important in the low-resource regions of Canada that may lack the capacity and essential healthcare resources necessary for an efficient and effective response to the pandemic.[15]

Study Objective

The rapid spread of COVID-19 demonstrates the need for swift assessment of the Canadian public's KAP pertaining to the disease. Our objective was to describe the KAP of Canadian communities highly affected by the COVID-19 pandemic and to evaluate factors associated with risky behaviours. This was accomplished via an online survey questionnaire targeting Alberta and Ontario, two of Canada's most affected provinces, between April 6 and 26, 2020.[7] Findings from this study will be able to inform health communication efforts and streamline Canada's pandemic response.

Methods

Study Design

A cross-sectional survey was designed for the study and adhered to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement. Due to the rapid spread of the disease and public health measures put in place during the pandemic, it was not possible to conduct a community-based national sampling survey. We therefore used rapid open online surveys with convenience sampling to reach across large geographic areas with no face-to-face interaction. The survey adhered to the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) checklist (Appendix A).[16] The study was approved by the Health Research Ethics Board of the University of Alberta.

Participants

To recruit respondents, we relied on the authors' networks to distribute the survey using a one-page poster that was posted and shared on various social media platforms including Facebook, Twitter, and Instagram. The survey was also featured on the websites and Twitter pages of local news media companies. As such, the response rate is unknown. A total of 1593 individuals (1118 female) responded and completed the survey between April 6 and 26, 2020. The survey was purposively targeted to residents of Alberta (n=997) and Ontario (n=434), the most affected English-speaking provinces, via the aforementioned distribution networks. However, residents from other provinces and territories were also eligible to respond (n=161). Respondents were required to speak English and be above the age 16 to participate.

Survey Questionnaire

A 43 item questionnaire was developed based on a COVID-19 KAP questionnaire used in China and an Ebola KAP study in the Democratic Republic of the Congo.[11,17] Respondents were required to provide informed consent via a click box prior to beginning the voluntary survey. In addition to participant demographics, questions focused on several key constructs relevant to public messaging with respect to COVID-19:

1. *Knowledge*. To assess knowledge of COVID-19, participants were asked 12 questions pertaining to the presentation, transmission, and treatment of COVID-19 adapted from a previous KAP survey.11 A cumulative knowledge score was computed by assigning one point for each answer in agreement with current scientific knowledge, and no point assigned for an incorrect answer or for answer "I don't know".

2. *Attitudes*. The overall perception of COVID-19 risk was assessed by the question "are you worried about COVID-19?"[17] Two questions assessed optimism regarding the control of the COVID-19 pandemic globally, and within Canada.[11]

3. *Practices*. Seven items were included that related to precautionary practices adopted since the onset of the pandemic and intentions for if one were to get ill or be exposed to an infected individual.[11,17] Four of these items identified risky behaviours and participants were determined to be "resistant" to public health messaging by identifying with any of the four behaviours: visiting crowded places, close encounters with non-household members, and intention to not isolate if having mild flu symptoms or if had known exposure to COVID-19.

4. *Interest and attitude toward potential COVID-19 vaccine.* We included two items adapted from a previous survey.[17] Vaccine acceptance was operationally defined as an affirmative response to "A vaccine against COVID-19 is needed in Canada".

Statistical Analysis

GraphPad Prism version 6 (GraphPad Software Inc., La Jolla, CA, USA, 2012), and R (version 3.6.3, R core team, 2020) were used for data analyses. We examined associations between dichotomous variables using the two-tailed Pearson Chi-Square or Fisher's exact test, as appropriate. Associations between knowledge and demographics were evaluated with one-way analysis of variance (ANOVA) and multivariable linear analysis, while binary logistic regression analysis was used to examine associations with attitudes and practices.

Results

A total of 1593 participants were surveyed in Canada between 6 and 26 April, 2020. The participants' demographics and associated mean knowledge scores are shown in Table 1. Participants' KAP pertaining to COVID-19 are shown in Table 2.

The mean COVID-19-related knowledge score was 10.5/12 (88%) with a standard deviation of 1.1. Knowledge scores significantly differed across sex ($p=0.0017$), marital status ($p<0.001$), and number of co-habitants living in a residence ($p=0.0039$) (Table

1). In particular, of all the demographics evaluated, multiple linear regression analysis demonstrated lower levels of knowledge scores in males (versus females, β: -0.212 (95% CI -0.089 - -0.335), p<0.001), those who are single (versus married or common law, β: -0.257 (95% CI -0.112 - -0.402), p<0.001), as well as an ordinal relationship of decreasing mean knowledge scores (10.52, 10.52, 10.49, 10.43, 10.35, and 10.13) with an increasing amount of co-habitants in the residence ranging from none, one, two, three, four, and five or more co-habitants in the residence, respectively (β: -0.065 (95% CI -0.021 - -0.110), p=0.0039). Additionally, COVID-19 knowledge was positively associated with the affective response of "worried" (β: 0.188 (95% CI 0.039 - 0.336), p=0.013), and negatively associated with the response "I don't know" (β: -0.320 (95% CI -0.037 - -0.603), p=0.027), in relation to the question asking if worried about the COVID-19 pandemic.

Regarding preventive practices implemented since the COVID-19 outbreak, participants with higher knowledge scores were more likely to report avoiding crowded places (β: 0.290 (95% CI 0.097 - 0.482), p=0.0032), not meeting up with non-household members within 1 meter (β: 0.178 (95% CI 0.049 - 0.307), p=0.0071), avoiding physical contact with others (β: 0.524 (95% CI 0.190 - 0.857), p=0.0021), and washing hands more frequently (β: 0.266 (95% CI 0.023 - 0.509), p=0.032). Additionally, participants with higher knowledge scores were less likely to wear a mask (β: -0.125 (95% CI -0.001 - -0.248), p=0.048) or gloves (β: -0.157 (95% CI -0.043 - -0.271), p=0.0069) as a protective measure. COVID-19 knowledge scores were also positively associated with feeling informed about the pandemic (β: 0.597 (95% CI 0.401 - 0.794), p<0.001). A majority of participants felt informed (80%)

Table 1. Demographics of cohort and associated knowledge scores pertaining to COVID-19

	n (%)	Knowledge score (mean +/- standard deviation)	p-value
Sex			0.002
Male	455 (29)	10.3 ± 1.2	
Female	1118 (70)	10.5 ± 1.1	
Other	13 (1)	10.1 ± 2.1	
Age group (years)			0.38
16 - 29	825 (52)	10.4 ± 1.0	
30 - 49	424 (27)	10.5 ± 1.1	
50+	341 (21)	10.5 ± 1.2	
Marital Status			0.001
Married or common law	689 (44)	10.6 ± 1.1	
Single	828 (52)	10.4 ± 1.1	
Other	65 (4)	10.3 ± 1.3	
Education			0.18
High School and below	208 (13)	10.4 ± 1.1	
Bachelor's degree (in process of or completed)	882 (56)	10.4 ± 1.1	
Post-graduate degree (in process of or completed)	489 (31)	10.5 ± 1.2	
Occupation			0.17
Student	568 (38)	10.4 ± 1.1	
Total Non-Student	942 (62)	10.5 ± 1.1	
Province			0.30
Alberta	997 (63)	10.5 ± 1.1	
Ontario	434 (27)	10.5 ± 1.1	
Other	161 (10)	10.3 ± 1.2	
Place of residence			0.43
Urban	1340 (85)	10.5 ± 1.1	
Rural	243 (15)	10.4 ± 1.2	
# of co-habitants			0.004
Alone	197 (12)	10.5 ± 1.1	
1 co-habitant	571 (36)	10.5 ± 1.1	
2 co-habitants	288 (18)	10.5 ± 1.1	
3 co-habitants	341 (21)	10.4 ± 1.1	
4 co-habitants	122 (8)	10.4 ± 1.1	
5+ co-habitants	71 (4)	10.1 ± 1.3	

Table 2. Knowledge, attitudes, and practices related to COVID-19 transmission, prevention, and treatment

	Response n (%):		
	Yes	**Don't know**	**No**
Knowledge about COVID-19 prevention and treatment			
Main clinical symptoms are fever, fatigue, dry cough, and muscle aches	1492 (94)	17 (1)	83 (5)
Unlike the common cold, stuffy nose, runny nose, and sneezing are less common	1193 (75)	200 (13)	197 (12)
Currently there is no effective cure, but early supportive treatment can help most patients recover	1449 (91)	81 (5)	69 (4)
People who are elderly or have chronic illnesses are more likely to have severe cases	1578 (99)	6 (0)	9 (1)
Those fully recovered from COVID-19 infection are still infectious and can transmit the virus to others	269 (17)	591 (37)	732 (46)
Animals, such as pets and livestock, can transmit COVID-19 to people	316 (20)	428 (27)	847 (53)
People without symptoms can still transmit COVID-19 to others	1564 (98)	11 (1)	14 (1)
The virus spreads most commonly via respiratory droplets of infected individuals	1556 (98)	12 (1)	23 (1)
It is not necessary for children and young adults to take measures to prevent infection of COVID-19	43 (3)	7 (0)	1540 (97)
To prevent infection, individuals should avoid going to crowded places and taking public transportation	1574 (99)	3 (0)	11 (1)
Isolation and treatment of people who are infected with COVID-19 are effective ways to reduce spread	1569 (99)	10 (1)	12 (1)
People should be immediately isolated after having contact with someone infected with COVID-19. In general, the observation period is 14 days.	1576 (99)	6 (0)	9 (1)
People can wear general medical masks to prevent the infection of COVID-19*	736 (46)	183 (12)	668 (42)
Attitudes toward COVID-19			
Worried about COVID-19	1257 (79)	75 (5)	252 (16)
Agreement COVID-19 will eventually be controlled	1228 (77)	293 (18)	65 (4)
Confidence Canada will eradicate COVID-19	849 (54)	417 (26)	318 (20)
Protective practices (since the onset of the pandemic, frequency of participants who…)			
Wear a mask when leaving home	421 (27)	5 (0)	1151 (73)
Wear gloves as protection when leaving home	557 (35)	8 (1)	1012 (64)
Avoid physical contact with other people	1525 (97)	10 (1)	43 (3)
Wash their hands more often	1487 (94)	6 (0)	83 (5)
Visit crowded places other than grocery store, pharmacy, or gas station	138 (9)	0 (0)	1441 (77)
Meet up with non-household friends/family within 1 meter distance	364 (23)	4 (0)	1210 (77)
Intentions of participant…	**Self-isolate for 14 days**	**Don't know**	**Go about activities as normal**
If had mild symptoms of flu, would…	1399 (89)	103 (7)	75 (5)
If had known exposure to someone infected with COVID-19, would…	1505 (95)	48 (3)	26 (2)

*This question was not included in the knowledge score as there was conflicting information on the protective efficacy of wearing a mask during the survey period

Table 3. Factors associated with resistance versus compliance, based on grouping four putative indices of resistance to COVID-19 public messaging

	Response, n (%)[1]:			
	Resistant[2] (n=502)	Compliant (n=1088)	OR (95% CI)[3]	p-value
Male vs female sex	166 (33)	282 (26)	1.4 (1.1-1.7)	0.0071
16 - 29 years old vs 30+ years old	286 (57)	530 (49)	1.4 (1.1-1.7)	0.0066
Single vs Married/common law	283 (56)	536 (49)	1.4 (1.1-1.7)	0.0046
High School and below vs some university & above	62 (12)	146 (13)	0.9 (0.66-1.2)	0.58
Student vs Non-student	197 (39)	366 (34)	1.3 (1.0-1.6)	0.046
Alberta vs Ontario	349 (70)	640 (59)	1.5 (1.2-2.0)	<0.001
Urban vs Rural	426 (85)	902 (83)	1.0 (0.78-1.4)	0.82
Alone vs 1+ co-habitant	76 (15)	121 (11)	1.4 (1.0-1.9)	0.029
Not worried about COVID-19 vs worried	133 (26)	118 (11)	2.9 (2.2-3.8)	<0.001
Feel not informed about COVID-19 vs informed	54 (11)	74 (7)	1.7 (1.1-2.4)	0.01
COVID-19 knowledge score (mean ± standard deviation)	10.3 ± 1.2	10.5 ± 1.1	..	<0.001

[1]All response values are in reference to the bolded demographic or characteristic only, including the percentage of total responses which is indicated in brackets. The non-bolded demographic or characteristic is shown only to indicate the comparison cohort used to calculate p-values

[2]Respondents were classified as "resistant" if they answered "yes" to visiting crowded places other than grocery stores, pharmacies, or gas stations, or to meeting up with non-household family and friends within one meter. Respondents were also classified as "resistant" if they responded "go about activities as normal" in response to intentions if respondent had mild symptoms of cold or flu, or if respondent were exposed to someone known to be infected with COVID-19.

[3]The Odds Ratio is comparing the bolded demographic or characteristic with the corresponding non-bolded demographic or characteristic

and reported public health authorities (1218/1593, 85%), media (1218/1593, 76%), and family and friends (443/1593, 28%) as main sources of public health information during the pandemic.

A considerable minority of participants (32%) engaged in or supported at least one behaviour that was considered to be "resistant" to public health messaging: visiting crowded places, close encounters with non-household members, and intention to not isolate if having mild flu symptoms or if known exposure to COVID-19 (Table 3). Key demographics and attitudes associated with these risky behaviours are shown in Table 3.

Table 4 shows the factors that are associated with each risky behaviour. Most notably, participants "not worried" about COVID-19 was associated with all four risky behaviours (p<0.001).

A binary logistic regression analysis of significant factors associated with behaviours resistant to public messaging is shown in Table 5.

Our survey was primarily targeted at residents of Alberta and Ontario (Table 2), two of the three most affected provinces in Canada. Ontarians were more likely to report a perceived personal risk of being infected with COVID-19 if at work or school (OR 1.3 (95% CI 1.0-1.7), p=0.038) or when using public transit (OR 1.5 (95% CI 1.1-2.0), p=0.012), while also more likely to wear masks in public (OR 2.1 (95% CI 1.7-2.7), p<0.001). Interestingly, Albertans were significantly more likely to endorse meeting up with non-household member (OR 2.0 (95% CI 1.5-2.7), p<0.001). Our survey

Table 4. Factors associated with the four putative indices of resistance to COVID-19 public messaging

	Response n (%)[1]:			
	Visit crowded places		Meet with non-household within 1 m	
	Yes (n=138)[2]	No (n=1441)	Yes (n=364)	No (n=1210)
Male vs female sex	49 (36)	400 (28)	121 (33)*	327 (27)
16 - 29 years old vs 30+ years old	83 (60)	734 (51)	210 (58)*	604 (50)
Single vs Married/common law	81 (59)	740 (51)	202 (55)*	615 (51)
Student vs Non-student	59 (43)	504 (35)	140 (38)	421 (35)
Alberta vs Ontario	92 (67)	899 (62)	270 (74)***	718 (59)
Alone vs 1+ co-habitant	25 (18)*	171 (12)	59 (16)*	136 (11)
Not worried about COVID-19 vs worried	44 (32)***	207 (14)	99 (27)***	152 (13)
Feel not informed about COVID-19 vs informed	13 (9)	115 (8)	34 (9)	94 (8)
Lower COVID-19 knowledge score (mean ± standard deviation)	10.2 ± 1.2**	10.5 ± 1.1	10.3 ± 1.2**	10.5 ± 1.1
	If had mild symptoms of flu, would…		If had known exposure to COVID-19, would…	
	Go about activities as normal (n=75)	Self-Isolate for 14 days (n=1339)	Go about activities as normal (n=26)	Self-Isolate for 14 days (n=1505)
Male vs female sex	34 (45)***	380 (28)	13 (50)*	419 (28)
16 - 29 years old vs 30+ years old	32 (43)	729 (54)	9 (35)	781 (52)
Single vs Married/common law	37 (49)	727 (54)	12 (46)	779 (52)
Student vs Non-student	24 (32)	503 (38)	6 (23)	541 (36)
Alberta vs Ontario	41 (55)	891 (67)	14 (54)	949 (63)
Alone vs 1+ co-habitant	9 (12)	172 (13)	5 (19)	181 (12)
Not worried about COVID-19 vs worried	30 (40)***	204(15)	15 (58)***	223 (15)
Feel not informed about COVID-19 vs informed	11 (15)	108 (8)	2 (8)	119 (8)
Lower COVID-19 knowledge score (mean ± standard deviation)	10.2 ± 1.4	10.5 ± 1.1	9.7 ± 1.6***	10.5 ± 1.1

[1]All response values are in reference to the bolded demographic or characteristic only, including the percentage of total responses indicated in brackets. The non-bolded demographic or characteristic is shown only to indicate the comparison cohort used to calculate p-values

[2]P-values were obtained for each comparison of the bolded demographic or characteristic with the corresponding non-bolded demographic or characteristic

*p<0.05, **p<0.01, ***p<0.001

Table 5. Binary logistic regression analysis of significant factors associated with behaviours resistant to public messaging

	OR (95% CI)[1]	p-value
16 - 29 years old vs 30+ years old	1.3 (1.0-1.9)	0.046
Alberta vs Ontario	1.6 (1.3-2.1)	<0.001
Alberta vs other provinces	1.7 (1.1-2.5)	0.010
Not worried about COVID-19 vs worried	2.9 (2.2-3.9)	<0.001
Not worried about COVID-19 vs unsure if worried	3.4 (1.9-6.2)	<0.001
Feel not informed about COVID-19 vs informed	1.6 (1.1-2.3)	0.030
Lower COVID-19 knowledge score	1.2 (1.1-1.3)	0.0057

[1]The Odds Ratio is comparing the bolded demographic or characteristic with the corresponding non-bolded demographic or character

also included 1340 (85%) urban participants and 243 (15%) rural participants but found no significant differences between their attitudes or practices (p>0.05 for all comparisons).

Vaccine acceptance was universally high (93%) and did no differ significantly by sex, age, marital status, education, occupation, or location (p>0.05 for all comparisons). Alternatively, vaccine acceptance was significantly associated with higher knowledge scores (p<0.001), being worried about COVID-19 (OR 20.4 (95% CI 8.4-49.5), p<0.001), optimism in controlling the pandemic (OR 8.1 (95% CI 3.4-19.7), p<0.001), and feeling informed regarding COVID-19 (OR 3.9 (95% CI 1.7-9.3), p=0.0049). Participants supported a wide-base vaccination strategy (81%).

Discussion

Contemporaneously with the unfolding COVID-19 pandemic in Canada, we collected data on community KAP related to COVID-19 to improve public health messaging and response. To the best of our knowledge, this is the first study evaluating the KAP of Canadians regarding COVID-19, as well as the most extensive KAP study examining potential determinants of risky practices that could further exacerbate infection spread. Our survey results indicated that a substantial minority of participants (32%) endorsed one of four behaviours reflecting "resistance" to public health measures: visiting crowded places, close encounters with non-household members, and intention not to isolate if having mild flu symptoms, or known exposure to COVID-19. Factors associated with resistance included male sex, 16-29 years old age group, a single relationship status, the occupation of "student", residing in Alberta, living alone, being "not worried" about COVID-19, feeling uninformed on the pandemic, and having a low level of knowledge about COVID-19.

In agreement with findings from China, being male, being a student, and having a low level of knowledge about COVID-19 were the factors that were significantly associated with risky behaviour.[11] These results may be explained by previous studies which documented increased risky behaviour in males and with younger age.[18,19] Therefore, special attention towards improving COVID-19 education in these targeted populations may be beneficial in preventing outbreaks. This may be especially important for post-secondary institutions that return from online classes to in-person studies. Studies from the 2002-2004 SARS outbreak demonstrated that a higher perceived risk of infection was associated with an increase in preventative infection measures.[14] This is consistent with our findings that the participants who were "worried" about COVID-19 were significantly more likely to wear masks and gloves in public, avoid physical contact, and increase their frequency of hand washing. Additionally, this group was significantly less likely to endorse risky behaviours in all four survey questions evaluating social resistance. While 79% of respondents were "worried" about COVID-19, a Liberian Ebola study suggests that the public's level of worry will decrease in step with the number of regional cases.[20] This phenomenon may have explained the spike in Canadians ignoring mandated public health measures, including the outright protesting of such measures, as regional infection rates declined.[9,10,21] Prompt and effective reporting of outbreaks may encourage community members to maintain compliance with public health measures.

Our survey found a high knowledge level regarding COVID-19 in our respondent group, as indicated by a mean knowledge score of 10.5/12 (88%), which is similar to findings in China (90%)[11] but higher than a comparable USA KAP study (80%).[13] Our data suggest that female sex, being married or being in a common law relationship, and living with less co-habitants are factors that are associated with higher levels of knowledge pertaining to COVID-19. As females were overrepresented in our sample (70%), this may overestimate our COVID-19 knowledge findings. Interestingly, unlike other studies, we found that a higher education level was not associated with greater mean knowledge scores.[11-13] Knowledge of avoiding crowded places and proper isolation protocol after exposure to COVID-19 were both >97% in our group and in China.[11] Despite this, 9% of our respondents (versus 3.6% in China) had recently visited crowded places other than grocery stores and pharmacies, suggesting that a substantial minority of Canadians might endorse this risky behaviour.[11] This finding may further the understanding of why community transmission in Canada has been primarily driven by event-specific outbreaks with large gatherings.[22]

As KAP studies can be powerful informants for outbreak response teams, further evaluation is needed in Canada with a random nationally representative sample. The COVID-19 pandemic, and in turn the public health response, is ever evolving necessitating periodic assessment of the population's KAP to maximize public health measure adherence. Special attention should also be paid to low socioeconomic populations as they have been identified as a risky demographic in several international studies.[11-13] As was done in China, further subgroup analysis within identified risk-seeking demographics, such as males and those who are single, may be beneficial.[23] Finally, the utility of KAP data would be maximized by assessing the preferred means of communication for specific demographics.

The findings in this study are subject to several limitations. While we adapted survey questionnaire items from previous studies, the instrument has not been extensively validated in different contexts.[11,17] Knowledge regarding COVID-19 transmission and prevention is a moving target and may change as the pandemic proceeds. Due to time constraints and the need to conduct the survey as the pandemic evolves, the comprehension of survey questions in French or other languages was not evaluated. The survey was not a random nationally representative sample, but rather an online sample that intentionally targeted high frequency outbreak provinces. As with much of online sampling, self-selection bias may have leant preference to high-knowledge individuals, disadvantaging individuals in remote communities and those without access to the internet.

Despite these limitations, the findings from this report suggest that residents with low levels of knowledge and worry regarding COVID-19 are more likely to resist public health messaging. Given the high infection rate of the current pandemic, the resistance of a minority of the population, as demonstrated by engagement in risky behaviours, could result in a significant spike in cases. This spike could be especially devastating in communities that have low healthcare resources. Health education initiatives targeting demographics associated with low knowledge, such as males and those who are single, could therefore facilitate adherence to public health measures.

Author's Contributions

JGU conceived and designed the study, conducted the data collection, wrote and critically reviewed the manuscript. PB conducted the data collection, wrote and critically reviewed the manuscript. DR performed the data analysis and critically reviewed the manuscript. TH supervised the study, wrote and critically reviewed the manuscript.

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Trends in pharmacotherapy for anxiety and depression during COVID-19: a North York area pilot study

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Abstract

Introduction: During the COVID-19 pandemic, with the implementation of social distancing regulations, there is increased concern around the mental health of the general population, including depression and anxiety. Mental health prescribing trends in Canada during COVID-19, at the time of writing, have not been investigated.

Methods: This pilot study collected refill information of 365 patients from an independent community pharmacy in North York, Ontario to compare (1) initiation, (2) dose change, (3) dispensing frequency, and (4) defined daily dose of first-line antidepressants as defined by the Canadian Network for Mood and Anxiety Treatments and other select medications, including Z-drugs and benzodiazepines. Data from January 1 to May 31, 2019 were compared with data from January 1 to May 31, 2020.

Results: The number of newly initiated antidepressant and antianxiety medications during the COVID-19 pandemic was not significantly affected compared to the same months in the prior year (Z=-1.149, p=0.251). Upon investigation of logistic regression, age was significantly correlated to antidepressant initiation in the year prior (p=0.038) whereas it was not during COVID-19, which may represent an increase in antidepressants in the younger population. There was a significant difference in the number of dose changes, which occurred between the two years, showing significantly more increases and switches of therapy (p=0.008) during COVID-19. There was significantly more frequent dispensing of benzodiazepine tablets (Z=2.402, p=0.016) in the first five months of 2020 compared to those of 2019. There were no statistically significant changes in the number of defined daily doses.

Discussion: There are shifting trends in mental health prescribing. This result is concerning during a time when accessing appropriate mental health care is significantly impacted. This study emphasizes the need for benzodiazepine deprescribing due to the increase in benzodiazepines dispensed and the risk of misuse, tolerance, and dependence with long-term benzodiazepines.

Introduction

In late 2019, multiple COVID-19 disease (Sars-CoV-2) outbreaks were being reported in Wuhan, China. Months later, in early 2020, the World Health Organization declared the COVID-19 virus outbreak a pandemic.

In order to slow the onslaught of individuals infected with the virus, many countries implemented lockdowns and the closure of public spaces, local stores, and recreational parks, as well as mandated social distancing regulations. Some of the key features of self-management of depression including exercise, yoga, acupuncture, and adequate sleep are likely to have faced massive disruption due to these changes.[1] Other aspects of mental wellbeing which are likely to have been impacted include social interactions, in-person psychotherapy appointments, and all-time high unemployment rates.[2] Since social distancing has been mandated, Canadians have reported a worsening of their mental health and many have reported feeling anxious or "on-edge".[3]

The medications included in this study were the first-line treatment options from the 2016 Canadian Network for Mood and Anxiety Treatments (CANMAT).[1] Two of the classes were selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). SSRIs and SNRIs, the most commonly prescribed antidepressant medications, are typically taken daily and increase the neurotransmitter serotonin in the brain to improve or stabilize mood. Another included class were benzodiazepines (BDZs), which may be taken daily, but are more often taken "as needed". BDZs exert their anxiolytic effect through the GABA receptor. Non-Benzodiazepine Benzodiazepine Receptor Agonists (BZRAs) or "Z-drugs" were also included, which are used for sedation in anxiety or insomnia.

It has been established in the literature that non-clinical factors play a role in antidepressant and antianxiety medication use: social isolation, unemployment, and loneliness are associated with higher use of anxiolytics and antidepressants.[4,5] Those who live alone have higher antidepressant use rates than those living with someone.[6] In the elderly, social disconnectedness increases perceived social isolation and in turn, increases depression and anxiety symptoms.[7]

These studies have shown consistent results in their establishment of a pronounced effect on General Anxiety Disorder-7 score, Symptom Check List-90 index score and Zung Self-Rating

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Depression Scores during COVID-19.[8,9] Higher prevalence of generalized anxiety symptoms, depressive symptoms, and sleep quality disturbances have been demonstrated to disproportionately affect the younger populations during this time.8 The majority of the studies published used online questionnaires and survey data to establish mental health trends. It is not clear from these studies whether the changes were resulting in more diagnoses and prescribing or whether it was simply a phenomenon observed through self-reporting.

One of the few publications which investigated the effects on prescribing is a trend report by Express Scripts published in April 2020. This report showed an increase in claims of antidepressant, anxiolytic, and hypnotic/sedative medications by 18.6%, 34.1%, and 14.8%, respectively, from January 2020 to the week that COVID-19 was declared a pandemic.[10] This report did not disclose any data after March 15, 2020. This report also did not compare the 2020 trends to any baseline trend.

What the body of literature cannot tell us at this point is any Canadian trends in the prescribing and dispensing of mental health medications. It also cannot tell us what trends occurred in medication dispensing in the months following the initial pandemic announcement. "Trends" specifically referred to the (1) initiation, (2) dose or therapeutic change, (3) dispensing frequency, and (4) defined daily dose (DDD) of selected mental health medications. To come to this assessment, OVID and SCOPUS were used as search engines. Keywords used with the corresponding search methods can be found in the supplementary appendix. Relevant studies were selected based on author discretion.

Methods

Research ethics approval was obtained in June 2020 from the University of Toronto Faculty of Pharmacy Undergraduate Research Ethics Committee. This pilot study was conducted using data collected from the pharmacy software system at a community pharmacy located in North York, Ontario. All data from the pharmacy software system on fill rates of one or more of the selected medications at this community pharmacy between January 1, 2019 to May 31, 2020 were included.

The collected data were used to investigate the pharmaceutical trends of select antidepressant, anxiolytic, and hypnotic/sedative medications dispensed during that timeframe. The list of selected medications consisted of SSRIs and SNRIs, as they are the preferred initial therapy for treatment of anxiety and depression, and all first-line treatment options from the 2016 CANMAT that are available in Canada.1 BDZs and Z-drugs were also included, as both these classes of medications are commonly used to treat acute anxiety or sleep disorders. The full list of medications investigated are presented in Appendix 1. The study population consisted of patients who filled one or more of the listed medications presented in Appendix 1 between January 1, 2019 and May 31, 2020, with no exclusions. These included both "regular users", defined as those who filled all their prescriptions at this pharmacy, and "occasional users", defined as those who filled only some of their prescriptions at this pharmacy.

In accordance with Division (1) clause 2.C of the Personal Information Protection and Electronic Documents Act (PIPEDA), informed consent was not required as all information collected was de-identified and used solely for the purpose of this study.

Data Collection

Data on (1) initiation, (2) dose or therapeutic change, (3) dispensing frequency, and (4) DDD of select medications were collected, and data from January 1 to May 31, 2019 were compared to data from January 1 to May 31, 2020. The age and gender of patients who filled one or more of the selected medications were collected for analysis of trends as well. In this study, gender referred to that which was listed in the pharmacy operating system, which was either indicated on the individual's Ontario Health Card or self-identified by the individual.

Initiation of Selected Medications

Initiation of a medication was defined as the patient's first fill of the medication at the pharmacy since October 2018. Data were collected from as far back as October, such that three-month supply data extending to January 2019 could be captured to assess for dose changes. Only changes made beginning January 1, 2019 were taken into account for the analysis. The number of initiations was measured monthly across the first five months of this year and the previous year to observe any trends which may be consistent with the initiation of antidepressants during the implementation of social distancing measures.

Changes of Selected Medications (dose and drug)

Dosage change of a medication referred to the increase or decrease in strength of the medication and/or a change in the therapy. It was calculated as the number of dose and/or therapeutic changes per month.

Dispensing Frequency of BDZs

Fill frequency was measured as the quantity of pills of BDZs dispensed monthly. This was chosen as an independent measure from DDD for the BDZ medications due to the commonly prescribed "as needed" nature of this class.

DDD

The DDD of five classes of mood and antianxiety medications were measured. Medications were grouped as SSRIs, SNRIs, BDZs, Z-drugs, and others in order to determine their consumption.[11]

Confounding Variables

Changes in prescribing patterns

Prescribing patterns by clinicians in the area can influence pharmaceutical trends observed in the community pharmacy. Principal investigators reviewed specialties and recent moves into and out of the area that could potentially affect prescribing patterns (i.e. new mental health clinics opened up within a 10 km radius of the pharmacy). No significant changes to practice in the area were found.

Table 1. Sociodemographic variables of sample population

Variable	n (%) or mean (SD)
Gender, n (%)	
Female	223 (61)
Male	142 (39)
Age, mean (SD), years	46.78 (18.24)

Sociodemographic Variables

In the Bayview Village neighbourhood where this community pharmacy is located, there was an average household size of 2.22 persons, and a population density of 4,195 per square km.[12] In terms of cohabitation and loneliness considerations, 50.2% of individuals over 15 years of age were married in this neighbourhood and 22.2% of individuals were seniors living alone.[12] With respect to other social factors, 59.7% were immigrants, with 64% having a mother tongue which was not English.[12] The median family income in this neighbourhood was $67,355, with 24.5% living in poverty.[12] Such demographics can be considered by those hoping to extrapolate these pilot data to other populations.

Analysis

Outcome variables were presented as mean ± SD of 2019 and 2020. IBM SPSS software was used to analyze trends of data collected. Comparison of the following outcomes, (1) number of new prescriptions per month received at the pharmacy, (2) number of dose changes (increase and decrease) and drug changes per month, (3) total number of pills of BDZs per month, and (4) DDD of SSRI, SNRI, BDZs, Z-drugs, and others per month for each month from January to May of 2019 and 2020, was conducted.

Results

Investigators extracted medication fill history between June 25 to 28, 2020 from community pharmacy software. Data were collected from October 2018 to May 2020, inclusive. Data from this entire period were collected due to a software hindrance, which did not allow for the collection of two independent periods of 5 months. However, only two periods of five months (January 1 to May 31, 2019 and January 1 to May 31, 2020) were used for analysis. A total of 365 prescription fill results were collected. These were de-identified by assigning participant numbers and entered into IBM SPSS software for analysis.

Outcomes

Sociodemographic variables of patients

Data were collected from patients with a mean age of 46.78 ± 18.24 years, with 61% of patients identified as female (Table 1).

Initiation

The monthly number of initiations from the first five months of this year were not statistically significantly different from the number of initiations during the first five months of the previous year (17.0 ± 14.92, 25.8 ± 17.54, respectively, Z=-1.149, p=0.251) (Figure 1). There was no more than one initiation per unique patient per year.

Table 2. Mean ± SD and Mann-Whitney (z-score and p-value) of defined daily dose of medications dispensed from January to May of 2019 and of 2020

Medication category	Jan to May 2019 (mean ± SD)	Jan to May 2020 (mean ± SD)	Z (p)
SSRIs	2353.10 ± 251.56	2044.30 ± 586.76	-0.940 (0.347)
SNRIs	577.61 ± 149.35	744.34 ± 258.00	-0.946 (0.344)
Benzodiazepines	247.29 ± 109.62	351.20 ± 57.68	-1.567 (0.117)
Z-drugs	498.53 ± 164.95	523.40 ± 184.78	-0.104 (0.917)
Others	518.70 ± 228.21	466.10 ± 217.87	-0.731 (0.465)

The logistic regression model of 2019 showed that age was significantly correlated to the likelihood of antidepressant initiation (p=0.038), with increasing age being associated with an increased likelihood of initiating an antidepressant. The logistic regression model of 2020 showed that age was not correlated (p=0.624) (Table 3).

In 2019 and 2020, gender was not significantly correlated to the likelihood of antidepressant initiation (p=0.082, p=0.699, respectively) (Table 3).

Changes to Selected Medications (dose and drug)

The number of monthly dose changes during the COVID-19 pandemic was statistically significantly different compared to the number of dose changes from the previous year (3.2 ± 0.837, 0.80 ± 0.837, respectively, z=-2.546, p=0.008). There were significantly more increases and switches of therapies per month during the COVID-19 pandemic compared to the same months in the previous year (2.8 ± 0.2, 0.6 ± 0.244, respectively, z=-2.739, p=0.008). The maximum observed number of dose changes or drug switches per patient per year was 2.

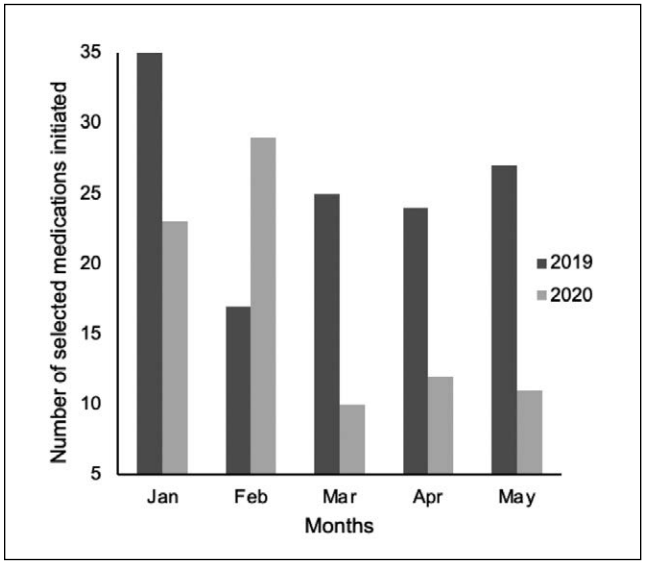

Figure 1. Number of antidepressants initiated per month in 2019 (dark grey) and 2020 (light grey).

Table 3. Binomial logistic regression of the initiation of antidepressants in 2019 and 2020

2019	β	SE	p
Age[a]	0.013	0.006	0.038*
Gender	0.434	0.249	0.082
2020	**β**	**SE**	**p**
Age[a]	-0.004	0.007	0.634
Gender	-0.105	0.272	0.699

[a]Average age of patients who filled an antidepressant in 2019 and 2020 was 49.96 ± 1.83 years and 45.78 ± 2.31 years, respectively.

* $p < 0.05$

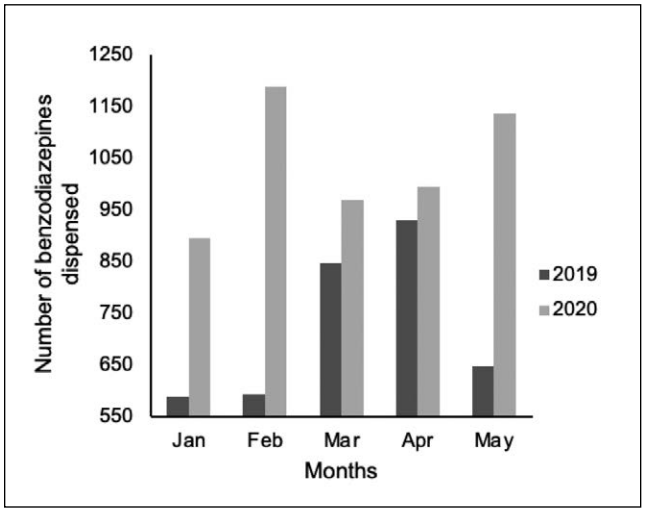

Figure 2. Dispensing frequency of benzodiazepines per month from January to May 2019 (dark grey) and 2020 (light grey).

Table 4. Binomial logistic regression of the volume of benzodiazepine tablets dispensed in 2019 and 2020

2019	β	SE	p
Age	0.39	0.015	0.010*
Gender	1.669	0.538	0.002*
2020	**β**	**SE**	**p**
Age	0.029	0.012	0.018*
Gender	-0.785	0.457	0.086

* $p < 0.05$

Table 5. Defined daily dose of selective serotonin reuptake inhibitor (SSRI), serotonin and norepinephrine reuptake inhibitor (SNRI), benzodiazepine (BDZ), Z-drugs, and others calculated from January to May in both 2019 and 2020

Months	SSRI	SNRI	BDZ	Z-drugs	Others
Jan-19	2055.5	777.15	230.4667	449.333	863.5
Feb-19	2203.5	411.9	174.375	242	312
Mar-19	2503.5	559.8	154.3125	645.333	607
Apr-19	2634	673.275	431.1875	634.667	324
May-19	2279	465.9	246.125	521.333	487
Jan-20	2763	996	305.8375	474.333	418.5
Feb-20	2516.5	1032.5	428.4875	833	574.5
Mar-20	1552	559.8	283.2125	350.333	787
Apr-20	1420	673.275	370.9875	432	271.5
May-20	1970	460.125	367.45	527.333	279

Dispensing Frequency

There was a 43.7% increase in BDZ dispensing in the first five months of this year compared to the year prior. The number of BDZ tablets dispensed monthly during the COVID-19 pandemic was statistically significantly higher compared to the previous year (1037.4 ± 122.24, 721.6 ± 156.87, respectively, z=-2.402, p=0.016) (Figure 2).

The logistic regression model showed that age was significantly correlated to the quantity of BDZs dispensed in 2019 and in 2020 (p=0.010, p=0.018, respectively), with increasing age being associated with an increased likelihood of dispensing a BDZ (Table 4). The average age of patients who dispensed a BDZ in 2019 and 2020 was 52.37 ± 2.11 years and 52.8± 2.37 years, respectively.

In 2019, gender correlation was statistically significant (p=0.002). However, during COVID-19, gender was not significantly correlated (p=0.086) with BDZ dispensing. In 2019 and 2020, females received 69.23% and 53.84%, respectively, of all dispensed BDZs.

DDD

The DDD of SSRIs, SNRIs, BDZs, Z-drugs, and others in 2019 and 2020 were calculated (Table 2) and a Mann-Whitney test was conducted (Table 5). The test did not show a statistically significant change in DDDs dispensed for any of the medication classes.

Confounding Variables

Changes in Prescribing Patterns

Within a 10 km radius, there were five doctor's offices, two hospitals, and three medical clinics. Based on a review of specialty services and practice updates online, there were no practice changes between January 2019 and May 2020 in the area that were considered to have a significant impact on the prescribing patterns of mental health medications.

Discussion

The observed increase in dose changes, specifically significantly more increases and switches of therapy and anxiolytic dispensing during COVID-19, is in agreement with the previously reported literature on mental health trends and reinforces the concerns researchers and health care providers have raised during this pandemic.[3,8,9]

There was an age correlation of initiating pharmacotherapy in 2019, but lack of age correlation during COVID-19. This lack of correlation during COVID-19 likely reflects an increase in initiations in the younger population. This is consistent with a previous study, which established that mental health was disproportionately impacting the younger population.8 Half of the world's students are affected by the closure of educational institutions, and recent graduates are affected by the significant rates of unemployment and economic disruption.[2,13] This finding is important when considering where public health resources should be allocated and how the mental health of the younger population can be supported.

There was no significant increase in overall antidepressant initiations, which was inconsistent with trends reported by Express Scripts in the beginning of 2020, where they saw an increase in antidepressant medications.[3] This may be explained by the closure of clinics and decreased number of in-person doctor's appointments, limiting access, which particularly may impact the elderly.[14] Technological barriers can also prevent access to telemedicine and virtual appointments.[14]

There was a significant increase in BDZ dispensing and a significant increase in antidepressant dose or drug change. This is consistent with Canadians self-reporting more anxiety and worsening mental health and with the trend report by Express

Scripts, which observed an increase in claims for anxiolytics during the first three months of 2020.[3,10]

There was a lack of significant increase in BDZ initiation, and an increase in BDZs dispensed. This may represent a worsening in the mental health of patients who were previously diagnosed with and treated for depression and/or generalized anxiety disorder during the pandemic. In the available studies, the pandemic has been shown to possibly play a role in the relapse of anxiety symptoms.[15]

The increase in BDZ dispensing during the pandemic reinforces the rising concern health care providers and researchers have expressed about the mental health crisis in elderly individuals during COVID-19.[15,16] In addition, age was positively correlated with BDZ dispensing during this time and in the year prior. There is also concern regarding the risk of adverse effects associated with BDZ use and its appropriateness in this age group. BDZs are commonly reported to increase the risk of falls and fractures in the elderly, and thereby increase morbidity and mortality.[17,18] BDZs are indicated for short-term treatment of anxiety, but are often misused. The long-term use of BDZs is associated with harm and can increase the risk of dependence and substance abuse.[19,20]

Health care professionals' awareness of these shifting trends will be important moving forward. First, appropriate follow-up on this medication therapy is critical for its safety. This includes monitoring for adverse reactions following prescribed dose increases and therapy changes as well as increased consumption of "as needed" medications. Deprescribing will also be an important tool moving forward. Physicians and pharmacists must pay attention to the ongoing appropriateness of pharmacotherapy.

The awareness of these trends is also critical for the consideration of how these trends will affect future mental health phenomena. This study hopes to emphasize the importance of deprescribing BDZs in the near future, as the pandemic evolves. Evidence-based guidelines for deprescribing BDZs have been established. Discussion of the manifestation of anxiety, how a dependence on BDZs will be avoided, and nonpharmacologic strategies to cope with these episodes will benefit patient care.

Limitations

Data were collected from one community pharmacy in North York, Ontario. Results are representative of the socioeconomic, ethnic, age, and cultural factors of the patients of this pharmacy, but may not be representative of the population at large. Results may disproportionately represent prescribing practices of the doctors who are located closer to the pharmacy. Results may disproportionately represent dispensing practice and clinical services of an independently owned pharmacy. Limitations of DDD are that it is not always reflective of standard doses in clinical practice, and specialized populations, such as adolescent and pediatric populations, do not receive "standard" doses. Limitations exist as to the "baseline" year established as 2019. Further data from previous years would help to reinforce a baseline of psychiatric medication prescriptions dispensed.

Future directions

Our pilot study informs areas where larger population research should be conducted. This includes prescribing patterns of BDZs and age association in a larger population during COVID-19, as the situation evolves.

Pharmacotherapy trends are one manifestation of the decline in mental health control. Research is warranted to investigate the shifting control of other manifestations, including eating disorders, substance abuse, and self-harm.

It is generally recommended that longer-acting BDZs be prescribed as rescue treatments in anxiety disorders rather than shorter-acting agents, as there is a decreased comparative likelihood of developing a dependence. Future research should seek to understand which BDZs are being prescribed at the highest rates during COVID-19 to determine whether inappropriate short-acting therapy trends must be addressed.

Further, it is recommended by the Canadian Agency for Drugs and Technologies in Health (CADTH) that BDZs be used as a short-term treatment for generalized anxiety disorder.[19,20] Future studies and guidelines must ensure that either deprescribing or adequate follow-up is in place.

Appendix 1

List of Medications our Study Looked at [ATC in brackets]

SSRI

- Citalopram [N06AB04]
- Escitalopram [N06AB10]
- Fluoxetine [N06AB03]
- Fluvoxamine [N06AB08]
- Paroxetine [N06AB05]
- Sertraline [N06AB06]

SNRI

- Desvenlafaxine [N06AX23]
- Duloxetine [N06AX21]
- Milnacipran [N06AX17]
- Venlafaxine [N06AX16]

Benzodiazepine

- Alprazolam [N05BA12]
- Bromazepam [N05BA08]
- Chlordiazepoxide [N05BA02]
- Clobazam [N05BA09]
- Clonazepam [N03AE01]
- Clorazepate [N05BA05]
- Diazepam [N05BA01]
- Flurazepam [[N05BA01]
- Lorazepam [N05BA06]
- Midazolam [N05CD08]
- Nitrazepam [N05CD02]
- Oxazepam [N05BA04]
- Temazepam [N05CD07]
- Triazolam [N05CD05]

Z-drugs

- Zolpidem [N05CF02]
- Zopiclone [N05CF01]

Other

- Bupropion [N06AX12]
- Mirtazapine [N06AX11]
- Vortioxetine [N06AX26]

Supplementary Appendix

Literature Search Strategy

Keywords

1. SSRI OR selective serotonin reuptake inhibitor OR benzo* OR antidepressant
2. COVID OR COVID19 OR COVID-19 OR Sars-CoV-2 OR coronavirus OR pandemic OR quarantine OR social distanc* OR isolation
3. initiat* OR precrib* OR take OR taking OR consum* OR trend
4. Dose adj3 increase OR Dose adj3 change OR Dose adj3 escalat* Dose adj3 adjust*
5. Medication refill* OR prescription refill* OR medication fill* OR fill* behaviour OR refill behaviour OR as adj1 needed OR prn OR rescue
6. Depression OR anxiety

Search Strategy (MEDLINE Database)

- 1 and 2 and 3
- 1 and 2 and 4
- 1 and 2 and 5
- 2 and 6

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Incidence, associated risk factors and cumulative risk scores: a retrospective chart review of a single center's experience with bone cement implantation syndrome in a low and middle income country, South Africa

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Abstract

Background: Cemented arthroplasty is appropriate management for displaced neck of femur fractures. However, it is associated with Bone Cement Implantation Syndrome (BCIS), characterized by a drop in systemic blood pressure, hypoxia, unexpected loss of consciousness, and cardiovascular collapse. This study aimed to quantify the incidence of BCIS in a low and middle income country (LMIC), to compare whether similar risk factors exist as compared to high income countries. It also aimed to assess whether cumulative risk factors were associated with severe grades of BCIS.

Methods: A retrospective chart review analyzed consecutive adult patients undergoing cemented arthroplasty between January 2016 and July 2017 at Addington Hospital, KwaZulu-Natal, South Africa. The lowest blood pressure and oxygen saturation at defined points were compared to baseline readings, and patients were graded as grade 1, 2 or 3 BCIS. Records were analyzed for the presence of risk factors, of which 16 were identified and compared to the occurrence of BCIS. Factors deemed statistically significant were combined and a cumulative risk score was compared to the grades of BCIS.

Results: The total incidence of BCIS was 45.79%. The incidence of BCIS grade 1, 2 and 3 were 34.58%, 5.61%, and 5.61% respectively. Independent significant factors included ASA ≥3, hypertension, previous cerebral ischaemia, previous myocardial ischaemia, and renal failure. A statistically significant difference existed between various grades of BCIS and cumulative risk scores for each grade. The mean risk score for no BCIS, grade 1, 2 and 3 BCIS were 0.77 ± 0.75, 1.81 ± 1.15, 3.0 ± 0.63, and 3.5 ± 1.05 respectively.

Conclusions: This study reported the incidence of BCIS, risk factors associated with BCIS, and that cumulative risk factors increased the grade of BCIS. Grade 1 and grade 3 BCIS occurred more commonly in our institution than in the reported literature.

Background

Hemiarthroplasty and total hip arthroplasty are common and appropriate management strategies for displaced neck of femur fractures.[1] While the best method for implanted prosthesis fixation remains controversial, cement fixation of the femoral stem prosthesis with polymethyl methacrylate (PMMA) has been deemed superior, and cement use is therefore justified, in that it offers better long term viability, reduction in post-operative pain, and improved post-operative mobility, with quicker return to baseline function.[2-6]

Bone cement implantation syndrome (BCIS) is a well described complication of cemented arthroplasty.[9] It is associated with a series of characteristic clinical features, including a drop in systolic blood pressure >20 % from baseline, moderate hypoxia with oxygen saturation <94%, unexpected loss of consciousness, cardiovascular collapse requiring cardiopulmonary resuscitation, and, in some cases, death.[3,10] These can occur at the time of cement and prosthesis insertion, joint manipulation, or deflation of limb tourniquet, if used.[7]

The seminal classification of BCIS by Donaldson et al. grades the syndrome according to severity, as follows:[3]

- Grade 1: Moderate hypoxia (SpO_2 <94%) or a decrease in systolic arterial pressure >20%
- Grade 2: Severe hypoxia (SpO_2 <88%) or a decrease in systolic arterial pressure >40% or unexpected loss of consciousness
- Grade 3: Cardiovascular collapse requiring cardiopulmonary resuscitation.[3]

Severe grade BCIS would constitute grade 2 or 3.[11]

Olsen et al. reported the total incidence of BCIS, irrespective of grade, to be 28%, with incidences of grade 1, grade 2, and grade 3 to be 21%, 5.1% and 1.7% respectively.[11] A recent single centre study reported a day-of-surgery mortality rate to be 0.67%.12 In a large study, Pripp et al. demonstrated that 58% (95% CI 28% – 76%) of perioperative mortalities in the surgical

management of hip fractures were associated with cement use.[13] A retrospective review by Hossain et al. concluded that the 48 hour perioperative mortality following cemented hemiarthroplasty is around 1% (p<0.001), with an increased risk of perioperative death in cemented implant insertion, as compared to uncemented implant insertion.4 A further comparative between cemented and uncemented patients undergoing hemiarthroplasty by Olsen et al. showed that 28% of patients had symptoms of hypotension and hypoxia in the cemented group, versus 17% in the uncemented group (p=0.003). Furthermore, 7% of patients in the cemented group developed severe symptoms versus zero patients in the uncemented group(p=0.003).14 BCIS has been reported in as many as 74% (95% CI, 69.5% – 78.6%) of cancer patients following cemented arthroplasty, with occurrence of grade 1, 2, and 3 being 62.5%, 11%, and 0.5% respectively.[15]

Independent pre-operative risk factors for the development of BCIS, studied in high income countries, are reported to be increased age, American Society of Anaesthesia (ASA) scores of ≥3, chronic obstructive pulmonary disease or other pre-existing lung disease, medication with diuretics and warfarin, osteoporosis, pre-existing pulmonary hypertension, significant cardiac disease, and cancer, specifically pulmonary metastasis.[7,11,15] Surgical risk factors implicated include the use of long stem femoral prosthesis, having generated higher intermedullary pressures, pathological fractures, and intertrochanteric fractures.[7]

The etiology and pathophysiology of BCIS are not fully understood. Proposed theories exist for the mechanism of the syndrome. The embolic theory, which is most commonly accepted, suggests that during cementation, intramedullary contents such as bone fragments, fat, and fragments of PMMA, under pressures greater than 300mmHg as cement expands in the canal, are potentially forced into the systemic circulation, causing embolization of debris into the pulmonary vasculature.[7,16] The resultant mechanical damage to the vascular endothelium triggers vasoconstriction and inflammatory mediator release, as well as immune mediator release.[3] The ventilation/perfusion mismatch that ensues causes hypoxia, and the raised pulmonary vascular resistance leads to right ventricular dysfunction and circulatory collapse.[3] A case report of a patient undergoing cemented hemiarthroplasty, demonstrated, via transoesophageal echo, the presence of embolic mass from the main pulmonary artery to the inferior vena cava during circulatory collapse and cardiac arrest.[17] Emboli with significant pulmonary shunting have been demonstrated in 93% of patients with cement use.[18] However, not all patients develop clinically significant symptoms, which supports the theory that baseline characteristics may play a role in the ability of a patient to tolerate the embolic load produced during cementation. Post mortem findings have been able to demonstrate the presence of bone marrow elements in pulmonary vasculature, as well as adherent to endocardium, hepatic, and renal vasculature.[19] A less favoured theory suggests a type 1 hypersensitivity reaction to PMMA.[3] Higher concentrations of plasma histamine have been reported in patients with PMMA use.[20] However, due to similar clinical features, differentiation between the two theories is difficult in practice.

Anaesthetic strategies to prevent BCIS start with identification of the at risk patient, via a careful pre-operative assessment.[21] Risk factors which have been deemed to be significant should raise a red flag, triggering a high index of suspicion for the development of BCIS.

Intravascular optimization, via goal-directed therapy, has been shown to reduce perioperative mortality and shorten hospital stay.[22,23] However, it has little bearing on the grade of BCIS that ensues.[24]

Surgical strategies to prevent BCIS include intramedullary lavage, drying of the femoral canal, and ensuring adequate hemostasis prior to cementing.[3,7,25] Techniques such as cement gun use, and drilling of a distal venting hole results in a more even distribution of pressure and release of excessive pressure, reducing potential for embolization.[8,11]

Scope

While the incidence of the different grades of BCIS ranges significantly in the literature, to our knowledge, a study has not been performed to determine the incidence of the syndrome, as classified by Donaldson et al., in a South African setting.[3] Exploring the incidence in an LMIC, as well as comparing whether similar or different risk factors exist in LMIC populations as compared to HIC populations, will allow for refinement of peri-operative risk stratification and ultimately prevention of morbidity and mortality. This study therefore aimed to answer the following:

- What is the overall incidence and incidence of each grade of BCIS in a LMIC country and is this comparable to HIC?
- What independent pre-operative factors exist that may lead to the development of any grade of the syndrome in a LMIC population, and are these similar to those identified in HIC?
- Is the cumulative presence of factors deemed independently significant associated with an increased likelihood of severe grade BCIS?

Ethics approval

The study was approved by the University of KwaZulu-Natal Bioethics Research Ethics Committee. (Ref No. BE451/17)

Methods

Data Collection

A retrospective chart review was conducted. The review analyzed all consecutive adult patients undergoing cemented arthroplasty between January 2016 and July 2017 at Addington Hospital, KwaZulu-Natal, South Africa. Inclusion criteria was any patient undergoing cemented arthroplasty. Patients undergoing uncemented procedures, and those with incomplete medical and anaesthetic records were excluded.

Demographic information (age, gender), date of presentation, date of surgery, medical history and date of discharge were collated. Anaesthesia charts were reviewed for type of anaesthesia and ASA rating.

Blood pressure and oxygen saturation recordings were noted at three points: [1] prior to delivery of anaesthesia (baseline), [2] the lowest reading following cement implantation, and [3] the lowest reading post completion of surgery. Points [2] and [3] were then compared to point [1], and a percentage decrease from baseline readings was calculated. Documentation of circulatory collapse, resuscitative efforts, and outcomes were captured. This allowed for a classification of BCIS, as per the criteria outlined by Donaldson

et al., as well as a calculation of overall incidence and incidence of each individual grade of BCIS.

Factors identified in the patient records included age >65, ASA grade, gender, HIV status, hypertension, diabetes, cardiovascular disease, previous cerebral ischaemia, previous myocardial ischaemia, cardiac failure, pre-existing lung disease, renal failure (defined as a creatinine >150mmol/L or documented renal failure), impaired liver function tests, history of previous cancer, cerebellar disease, and thyroid disease. Once identified, these were compared to the occurrence of BCIS. Furthermore, those deemed independently significant were collated and assessed for a relationship between the cumulative risk score and the grades of BCIS.

Records of patients who died during the perioperative period were analyzed for identified risk factors, grade of BCIS, first warning sign following cementation, resuscitative efforts, outcomes, and post-mortem findings.

Statistical Analysis

Descriptive statistics were used to summarize demographic and clinical characteristics of the patients. Incidences were calculated as a percentage of total study population, and means were reported using two standard deviations.

Logistic regression reporting odds ratios (Chi-squared test) was performed with BCIS as the primary outcome to compare the presence of individual baseline characteristics and potential risk factors.This was done to determine whether an independent relationship existed between the various factors and the development of BCIS. A p value of ≤0.05 was considered statistically significant. Factors deemed significant on a univariate level were then combined to form a risk score. A Kruskal-Wallis-H test was conducted to determine if the cumulative risk score was different in the four grades of BCIS. Each grade of BCIS was then assessed for mean number of risk factors. Stata version 15 was used to analyze the data.

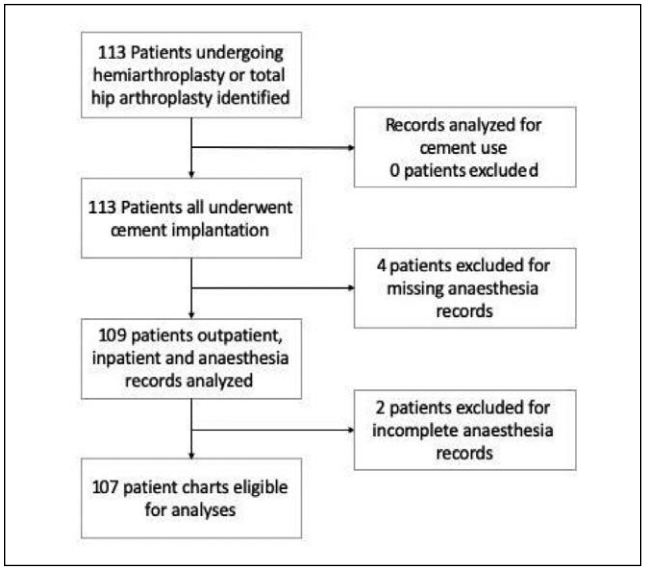

Figure 1. CONSORT diagram showing recruitment of patients.

Results

The medical records of 113 patients were reviewed. 107 patients were included, as per the consort diagram. (Figure 1)

The total incidence of BCIS of all grades was 45.79% (49/107). The incidence of BCIS grade 1, 2, and 3 were 34.58%, 5.61% and 5.61% respectively. A total of 5/107 (4.67%) were on-table deaths.

The baseline characteristics of patients presenting for cemented arthroplasty are presented in Table 1. The mean age of patients presenting for cemented arthroplasty was 72.98 years (±11.29), and 87 (81.30%) patients were 65 years or older. With regard to sex, 65 patients were female (60.75%) and 42 were male (39.25%).

Table 1. Baseline characteristics and Logistic regression reporting odds ratios, with BCIS as primary outcome.

Baseline	n (%)	No BCIS	BCIS	Odds Ratio, 95% CI	p-value
Gender					
Male	42 (39.25%)	23	19	0.96 (0.44 – 2.10)	0.93
Female	65 (60.75%)	35	30	1.03 (0.48 – 2.26)	0.93
Age					
≥65	87 (81.31%)	45	42	1.73 (0.63 – 4.76)	0.27
<65	20 (18.69%)	13	7		
ASA					
≥3	28 (26.17%)	7	21	5.46 (2.06 – 14.43)	0.0003
1-2	79 (73.83%)	51	28		
Hypertension					
Yes	72 (67.29%)	33	39	2.45 (1.24 – 7.03)	0.012
No	35 (32.71%)	25	10		
Cardiovascular Disease	5 (4.67%)	1	12	8.48 (2.30 – 48.20)	0.0001
Yes	102 (95.33%)	57	37		
No					
Previous Myocardial Ischaemia					
Yes	19 (17.76%)	1	18	33.09 (14.21 – 59.89)	0.001
No	88 (82.24%)	57	31		
Cardiac Failure					
Yes	5 (4.67%)	1	4	5.06 (0.54 – 46.92)	0.11
No	102 (95.33%)	45	57		
Diabetes					
Yes	37 (34.60%)	16	21	1.96 (0.88 – 4.41)	0.98
No	70 (65.42%)	42	28		
Pre-existing lung disease					
Yes	9 (8.41%)	3	6	2.56 (0.80 – 10.8)	0.19
No	98 (91.59%)	55	43		
Renal Impairment					
Yes	19 (17.76%)	3	16	8.89 (2.40 – 32.8)	0.001
No	88 (82.24%)	55	33		
Liver impairment					
Yes	5 (4.67%)	2	3	1.82 (0.29 – 11.40)	0.51
No	102 (95.33%)	56	46		
Cancer history					
Yes	3 (2.80%)	1	2	2.42 (0.21 – 27.59)	0.46
No	104 (97.20%)	57	47		
Cerebellar disease					
Yes	1 (0.09%)	0	1	1 (omitted)	-
No	106 (99.01%)	58	48		
Thyroid Disease					
Yes	2 (1.87%)	1	1	1.18 (0.07 – 1.90)	0.90
No	105 (98.130	57	48		
HIV positive					
Yes	4 (3.74%)	3	1	0.38 (0.10 – 4.97)	0.39
No	103 (96.26%)	55	48		

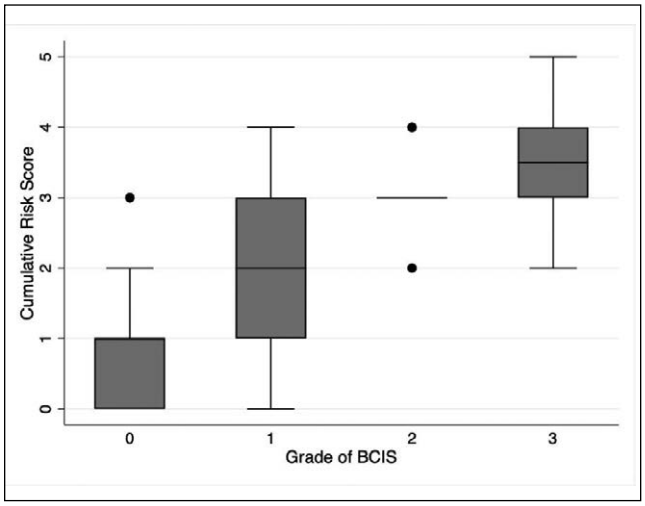

Figure 2. Box plot showing cumulative risk scores for grades of BCIS.

A total of 29 patients (27.10%) had an ASA classification ≥3. A total of 13 baseline medical factors along with age ≥65, gender and ASA classification ≥3 were accepted for analyses. The mean delay to surgery was 5.21 (±2.95) days, and the mean post-surgical days in hospital was 4.20 (±3.30) days. A total of 4 patients underwent general anaesthesia and the remaining underwent regional anaesthesia, with the mean intrathecal dose of 0.5% bupivacaine being 2.31 mL (±0.33 mL).

The results of the logistic regression reporting odds ratios with BCIS of any grade as the primary outcome are displayed in Table 1. Of the 16 analyzed characteristics, a total of 5 factors have been shown to be statistically significant for the development of BCIS. These are ASA ≥3 (OR 5.46, 95% CI 2.06 – 14.43, p = 0.0003), hypertension (OR 2.45, 95%CI 1.24 – 7.03, p 0.012, previous cerebral ischaemia (OR 8.48 95%CI 2.3- - 48.20, p = 0.0001), previous myocardial ischaemia (OR 33.09 95%CI 14.21 – 49.98, p = 0.001), and renal impairment (OR 8.89 95% CI 2.40 – 32.8, p = 0.001).

The 5 identified independent risk factors were further analyzed for their cumulative relationship with the various grades of BCIS. A Kruskal-Wallis-H test showed that there was a statistically significant difference in the cumulative risk scores between the 4 groups, $\chi 2$ (2) = 39.13, p = 0.0001. The mean cumulative risk scores for no BCIS, grade 1, 2, and 3 were 0.77 ± 0.75, 1.81 ± 1.15, 3.0 ± 0.63, and 3.5 ± 1.05 respectively. The minimum, median, and maximum risk scores for each grade of BCIS are represented in Figure 2.

A total of 8 peri-operative deaths occurred. The all cause peri-operative mortality was therefore 8.41%, with 6 (5.6%) deaths being related to grade 3 BCIS. There were 5 on-table deaths, 1 death on day 2 post-surgery in ICU, and 2 deaths on day 1 post-surgery in the ward. A summary of their peri-operative course is displayed in Table 2. Of the 5 on-table deaths, 4 were over the age of 65, and 4 displayed significant pre-operative comorbidities, including hypertension, previous myocardial ischaemia, previous cerebral ischaemia, and renal impairment. All 5 patients were classified as ASA ≥3. There were 5 patients who developed circulatory collapse at the time of cement and femoral stem insertion and 1 at the time of wound closure. First warning signs included a drop in oxygen saturation, confusion, and a decrease in blood pressure. While all patients received appropriate resuscitative efforts, only 1 patient was successfully resuscitated and admitted to ICU. However, she died on day 2. A post-mortem performed on two of the patients reported multiorgan failure as a cause of death. The other patients did not receive post-mortems.

Discussion

To our knowledge, a study investigating the incidence of BCIS, and grading according to Donaldson et al. had not yet been done in a South African setting.[3] The results indicate that grade 1 BCIS is common, with grade 2 and grade 3 occurring less commonly.

The incidence of BCIS varies greatly across the literature. A similar study conducted by Olsen et al. reported the total incidence of BCIS, irrespective of grade to be 28%, with incidences of grade 1, grade 2, and grade 3 to be 21%, 5.1%, and 1.7% respectively.[11] This study showed the total incidence of BCIS to be 45.79%, with grade 1 and grade 3 BCIS occurring in 34.58% and 5.60% of the study population, respectively. These are significantly higher than the incidence reported by Olsen et al. This study reported a similar incidence of grade 2 BCIS of 5.60%. The mortality rate following the development of grade 3 BCIS was 5.60% and is significantly higher than the on-table mortality rate of 0.26% reported by Tan et al.[12] The possible reasons for a higher incidence in this study are three-fold: firstly, Olsen et al.'s study population was ten-fold higher than this study population. Secondly, all arthroplasty performed by the institution in this study utilized cement. In other institutions, consideration to offer patients non-cemented arthroplasty would have resulted in patients at risk of BCIS being selected out of the study population, therefore reducing the incidence of all grades of BCIS, particularly, the incidence of the higher grades of BCIS. This can be further substantiated in more recent work by Olsen et al., which demonstrated that 28% of patients undergoing cemented arthroplasty developed symptoms of hypotension and hypoxia, versus 17 % in the uncemented group, with 7% of patients developing severe symptoms, compared to 0% in the uncemented group.[14] Finally, the hospital in this study is a regional hospital in a LMIC, which would cater for patients with significant risk factors, and a proportion of low risk patients may have been managed at the district hospital level.

Independent pre-operative factors that have been shown to increase the incidence of BCIS in this study include ASA score ≥3, hypertension, previous cerebral ischaemia, previous myocardial ischaemia, and renal impairment. Similarly Olsen et al. have reported ASA score of 3 or 4 as an independent risk factor for high grade BCIS.[11] This demonstrates that similar risk factors exist for the development of BCIS in HIC and LMIC population groups.

Cardiac disease has been reported as a risk factor by Olsen et al., and substantiates the association of hypertension and previous myocardial ischaemia found in this study.[14] Two known mechanisms for peri-operative myocardial infarction are acute coronary syndrome and imbalanced supply-demand relationships in patients with long-standing coronary artery disease.[26] Patients with hypertensive disease or previous myocardial ischaemia would be intolerant of sudden changes in hemodynamics. Qi et al. demonstrated significant changes in haemodynamics during cementation, with decreases in systolic blood pressure

Table 2. Baseline characteristics and Logistic regression reporting odds ratios, with BCIS as primary outcome

Patient	Age/ Sex	On table death	Delay to surgery	Risk score	Significant co-morbid illness	Anaesthesia	Preceding event	First warning sign	Resuscitation	BCIS Grade	Post-mortem
1	63 Male	yes	5 days	4	HTN, CVI, CF, COPD, renal/liver impairment, cerebellar disease	Spinal1.8ml 0.5% bupivacaine + 10mcg fentanyl	Cement and Femoral stem insertion	Decrease in SpO_2, confusion	IV fluids, Intubation, CPR, vasopressor inotropes	3	Multi-organ failure
2	71 Female	yes	9 days	3	HTN, previous MI, DM	CSE: 1ml spinal 0.5% bupivacaine + 9ml epidural 0.5% bupivacaine	Cement and Femoral stem insertion	Decrease in SpO_2	IV fluids, intubation, CPR vasopressor inotropes	3	Not done
3	77 Female	yes	5 days	2	HTN	Spinal: 2.6ml 0.5% bupivacaine	Cement and Femoral stem insertion	Decrease in SpO_2, decreased LOC	IV fluids, vasopressor	3	Not done
4	90 Female	yes	8 days	4	HTN, previous MI, DM, COPD, RF	Spinal: 2.5ml 0.5% bupivacaine	Wound closure	Decreased blood pressure	IV fluids, vasopressor	3	Not done
5	91 Female	no	1 day	1	Nil	Spinal: 2ml 0.5% bupivacaine	n/a	n/a	found unresponsive in ward day 1 post op	0	Not done
6	80 Female	no	2 days	2	HTN, previous CVA	Spinal: 1.8ml 0.5% bupivacaine + 2.5mcg sufentanil	n/a	n/a	No: found unresponsive in ward day 1 post op	2	Not done
7	84 Male	no	1 day	3	HTN, CVS disease, DM, RF	Spinal: 2.2ml 0.5% bupivacaine	n/a	Increasing inotrope requirements	Yes: IV fluids, inotropes Demised day 2 ICU	3	Multi-organ failure
8	78 Female	yes	3 days	3	HTN, CVS disease, previous MI, CF	Spinal: 2.2mls 0.5% bupivacaine	Cement and femoral stem insertion	Decrease in SpO_2 and LOC	IV fluids, inotropes	3	Done – report lost

Hypertension (HTN), Cerebrovascular Ischaemia (CVI), Cardiac failure (CF), Chronic obstructive pulmonary disease (COPD), Myocardial Ischaemia (MI), Diabetes Mellitus (DM), Renal Failure (RF), Combined Spinal Epidural (CSE), Loss of consciousness (LOC), Intravenous (IV), Cardiopulmonary resuscitation (CPR)

of 10-20mmHg and Clark et al. demonstrated a 33% transient reduction in cardiac output during cementation.[9,10] It is therefore understandable why hypertensive disease and previous myocardial ischaemia may increase the risk for BCIS. Previous cerebral ischaemia, identified as a significant factor in this study, has not been analyzed in similar research. Since hypertension is a known risk factor for the development of cerebral ischemia, the apparent link to the development of BCIS may be due to the underlying hypertensive vascular disease.[27] Renal impairment, identified as an independent risk factor in this study, was also identified as an independent risk factor in a more recent study by Olsen et al.[14]

Despite the large burden of disease that HIV disease places on LMIC populations, no significant higher risk for the development of BCIS was identified in the HIV positive patients, as compared to the HIV negative patients.

To our knowledge, no other study exists investigating the relationship between cumulative risk factors and grade of BCIS. We report a statistically significant difference between the cumulative number of independent risk factors and the grade of BCIS, with a significantly greater mean number of risk factors being present for the more severe grades of BCIS, that being 3 and 3.5 for grades 2 and 3 respectively. The Association of Anaesthetists of Great Britain and Ireland recommend a three-stage process to reduce the incidence of morbidity and mortality associated with BCIS. Their process aims to identify patients that are at high risk for cardiorespiratory compromise.[21] Our findings suggest that patients with a risk score ≥ 3 would significantly increase the risk for the development of grade 2 and 3 BCIS. This finding supports the safety guidelines outlined by Griffiths et al., allowing for appropriate identification of patients at risk for the development of grade 2 and 3 BCIS, assessment of the appropriateness and necessity for cement use, as well as preparation for the prevention and management of the syndrome, should it occur. It aids in appropriate planning for post-operative placement and monitoring of these patients, by pre-operatively securing high dependency facilities.

Limitations

The study was conducted in a district hospital, in a low to middle income country, South Africa. This therefore limits the generalizability of the results. Due to the retrospective study design, data collection was limited to existing data in medical records. Absent data regarding surgical techniques could therefore not be considered. Moreover, anaesthesia provider- and surgeon-related factors such as case volume or experience were not taken into account. Post-mortems are not consistently performed. This study has been limited by its small scale and cohort of patients. Finally, by virtue of the hospital being regional in nature, expected well patients may have been managed at district level, and their outcomes therefore not included in the study.

Recommendations

It is recommended that larger multicentre studies be done in LMIC populations to validate the findings presented. Despite the limitations of this study, it is recommended that the risk score as described be used as a starting point for awareness of patients at risk of developing BCIS, such that they can be appropriately risk stratified.

Conclusion

This study reported the incidence of the various grades of BCIS, and the risk factors associated with the development of BCIS in patients undergoing cemented arthroplasty at a single centre in KwaZulu-Natal, South Africa. This study also reported that cumulative risk factors increase the grade of BCIS that occurs. Grade 1 and grade 3 BCIS occurred more commonly in our institution than in the reported literature. Significant pre-operative factors for the development of BCIS are hypertension, previous myocardial or cerebral ischaemia, renal impairment, and ASA score ≥3. These are noted to be consistent with findings in high income countries.

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Tuberculosis and COVID-19: an overview of two health emergencies

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Abstract

Currently, a battle against the clock has been unleashed to deal with SARS-CoV-2, which to date has caused approximately nine hundred thousand deaths. Science has made significant efforts to characterize the COVID-19 virus and understand it from its origin to its transmission. Goals of the scientific community include controlling the propagation of the disease by developing hundreds of diagnostic tools and the future generation of a vaccine for this recent infection. Its counterpart, the *Mycobacterium tuberculosis* bacillus, causes more than 1.5 million deaths a year despite being an ancient disease. Its diagnostic methods are debatable due to the scarcity of effective options. Consequently, tuberculosis has spread mainly in developing countries that are not currently able to mitigate the infection. This paper compares two infectious diseases through a global narrative review and comprehensively describes what is known to date about two global health emergencies: tuberculosis and COVID-19.

Introduction

Infectious diseases are caused by pathogens, including bacteria, viruses, parasites and fungi.[1] These microorganisms have been responsible for provoking a great health threat worldwide with greater repercussions since the 20th century due to the resurgence of tuberculosis (TB), the increase in patients with acquired immunodeficiency syndrome (AIDS), severe acute respiratory syndrome (SARS) as well as influenza, and finally, the pandemic caused by coronavirus disease 2019 (COVID-19).

In 2018, TB caused 1.5 million deaths, and 10 million people became ill. It is estimated that a quarter of the world population has latent TB, wherein they carry the bacillus but do not transmit it or experience the disease.[2] Two years later, COVID-19 appeared, which within seven months of onset, has caused more than 19.7 million confirmed cases and approximately 730 000 deaths.[3]

COVID-19, the acronym for "coronavirus disease 2019", is a disease generated by the SARS-CoV-2 virus, which emerged in December 2019. This disease caused a clinical picture of high fever and respiratory distress in patients from Wuhan, Hubei Province, China.[4] The disease spread in such a way that on January 31, 2020, the World Health Organization (WHO) confirmed it to be a "Public Health Emergency of International Concern."[5] Nations worldwide have struggled with the large number of positive cases of COVID-19 that are reported daily, while improving access to rapid diagnostic tests, researching medical treatments that reduce mortality, and conducting a search for an effective vaccine.

Given the limited number of studies linking both illnesses, this report supports the literature with a narrative review comparing two infectious diseases considered by the WHO as global health emergencies: TB and COVID-19. In this way, it covers issues such as transmission, pathogenicity, diagnostic tools, clinical manifestations and treatment for SARS-CoV-2 and *Mycobacterium tuberculosis* (MTB), as well as current topics of discussion such as the role of the BCG vaccine on the pandemic. The purpose of the document is to discern particularities between both microorganisms so that the treatment and diagnosis of TB is not neglected during the pandemic, or in turn, special attention is given to patients who carry a co-infection with COVID-19. Furthermore, the article encourages authorities and governments to protect society from curable and preventable diseases such as TB by strengthening health systems and managing them responsibly.

We considered relevant articles published since 2000 in these databases: PubMed, Google Scholar, ScienceDirect, ClinicalTrials.gov, along with the WHO guidelines. Original research, book chapters, cohort studies, and reviews written in English and Spanish were searched using the keywords: COVID-19, tuberculosis, epidemiology, pathogenicity, transmission, and co-infection. This was done without location restriction. Non-indexed information and any studies based on SARS, MERS and *Mycobacterium tuberculosis* complex (MTBC) were excluded.

Etiology

SARS-CoV-2 belongs to the betaCoV category of the Coronaviridae family.[6] It is a single-stranded positive-sense RNA virus (ssRNA+) enveloped with glycoproteins as a crown, and has a 30-kb genome (Figure 1). The translation of two-thirds of the genome produces two polyproteins (pp1a and pp1b), which after proteolytic processing, give rise to 16 nonstructural proteins (nsp) that participate in the synthesis of negative chain RNA, the

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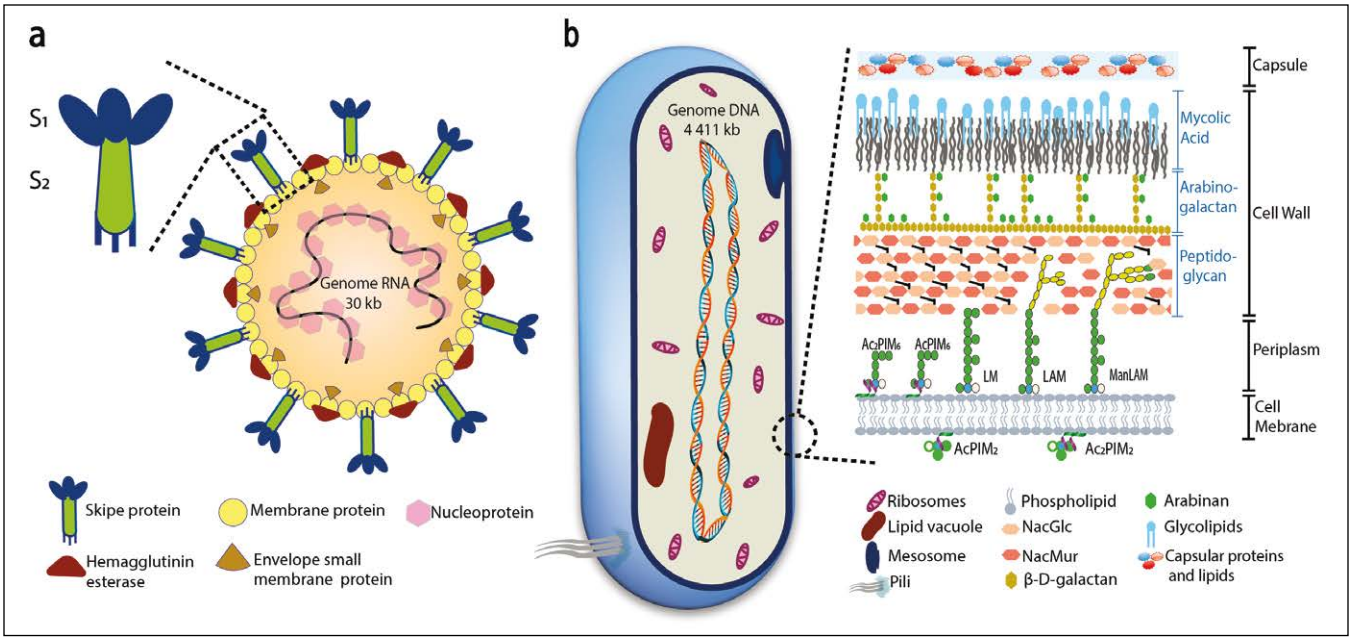

Figure. 1 Structure of SARS-CoV-2 and MTB[9,10]. a) Structure of SARS-CoV-2. The viral particle contains structural proteins, including the nucleocapsid (N), membrane (M), envelope (E), and spike (S) proteins, and has two subunits: the S1 receptor binding subunit and the S2 membrane fusion subunit. b) MTB structure. In the cell wall facing the cytoplasm, the plasma membrane incorporates lipids of four phosphates: monoacyl phosphatidylinositol dimannosides ($AcPIM_2$) and diacyl phosphatidylinositol dimannosides (Ac_2PIM_2); facing the capsule, the plasma membrane incorporates the following lipids: monoacyl phosphatidylinositol hexamannosides ($AcPIM_6$) and diacyl phosphatidylinositol hexamannosides (Ac_2PIM_6). The lipoglycans of the periplasm are lipomannan (LM), lipoarabinomannan (LAM) and LAM with mannose (ManLAM). The peptidoglycan network consists of N-acetyl-glucosamine (GlcNAc) and N-acetyl-muramic acid (MurNAc). The cell wall is characterized by a dense layer of mycolic acids and glycolipids reinforced by the bacterial capsule.

replication of the genome, and the production of subgenomic RNA.[7] One-third of the missing genome encodes the four structural proteins of the virus: the spike (S), membrane (M), envelope (E) and nucleocapsid (N) proteins.[8]

SARS-CoV-2 is phylogenetically related to RaTG13-CoV, SARS-CoV and pangolin-CoV viruses since they share a homology of 96.2%, 79.5% and 91.02%, respectively. This could indicate that it is a zoonotic infection.[11]

Unlike COVID-19, TB does not have a zoonotic origin. In fact, MTB is presumed to have appeared before the Neolithic demographic transition.[12] TB is caused by MTBC that includes several species of Mycobacteria such as *M. tuberculosis*, *M. africanum*, *M. canetti*, *M. bovis*, *M. microti*, *M. pinnipedi*, *M. caprae* and *M. bovis*.[13]

MTB, the etiological agent of TB, belongs to the family Mycobacteriaceae and is characterized by being an acid-alcohol-resistant, Gram-positive, nonmobile and non-spore-forming bacteria. These bacteria are rod shaped and measure 0.2 to 0.6 mm wide and 1 to 10 mm long.[14] The cell wall has a complex structure made up of proteins and lipids on the outside with an internal compartment of peptidoglycan, arabinogalactan, and mycolic acid, which form a thick layer known as the AG-PG-MA complex (Figure 1).[15] MTB is an obligate aerobic pathogen that has a genome of 4 411 529 bp and encodes 4 000 genes, of which 601 are essential.[16]

MTB and SARS-CoV-2 Replication

COVID-19 infection is initiated by interaction of the viral particle with specific proteins on the cell surface. In fact, receptor binding and membrane fusion are critical steps in the S protein and hemagglutinin esterase-mediated infection cycle. Protein S has a hectomer that contains two subunits: S1, which generates a conformational movement to expose its binding domain to the N-terminal receptor peptidase of ACE2 (angiotensin-converting enzyme 2) of the host cell, and S2, which fuses the viral RNA with cell membranes.[17] After receptor binding, the viral envelope and the cell membrane admit the entry of the virus by endocytosis and release SARS-CoV-2.

Using cellular ribosomes, the genetic material of the virus is translated into pp1a/b and into structural proteins. After a process of proteolysis allows them to fragment into small mRNAs that contain nsp1-nsp16 together with S, M, E, and N proteins, replication can begin. The envelope glycoproteins are located in the lumen of the endoplasmic reticulum or the Golgi apparatus to form the nucleocapsid, and enable the formation of viral particles so that they are transported through vesicles and leave the cell by exocytosis.[18]

On the other hand, MTB encodes the secretion complex ESX-1 to generate the lysis of the macrophage cell wall and promote cytosolic translocation.[19] These bacilli have a short generation time of 24 hours. To initiate replication, MTB duplicates its genetic material and its biomass. The two copies of DNA are segregated into nucleoids that are located at the poles of the cell. During this event, the maturation of the FtsZ ring directs the division of the pathogen. The daughter cells invaginate into an envelope layer and are sealed, the autolysin hydrolases digest the excess peptidoglycan between the septa, and the daughter cells are released. Modifications of this process have been contemplated where an asymmetric cell division is generated, especially in drug-resistant MTB.[20]

To avoid pathogen multiplication, macrophages respond by

producing reactive species of oxygen and nitric oxide. MTB detects this oxygen-deficient environment with reduced nutrients and enters a latent state in which it stops multiplying and activates anaerobic metabolism. Bacteria persist in this state in different tissues for a long time, and mycobacteria produce specific proteins that act as reanimation promoting factors capable of resuscitating latent bacilli.[21]

Both microorganisms use the immune system to their advantage. Mycobacteria contain large numbers of cellular receptors which mediate intercellular adhesion and phagocytosis. MTB eludes its degradation by appropriating host proteins such as coronin-1 that prevent phagosome-lysosome fusion. It is hypothesized that mycobacteria could be labeled with antibodies against ubiquitination.[22] Contrastingly, the SARS-CoV-2 virus developed an immuno-evasion mechanism through the formation of double vesicles to prevent recognition of the dsRNA. Moreover, nsp1 degrades cellular RNA to prevent innate immune response while nsp14 and 16 form a cap to evade pattern recognition receptors. The nps3 protein encodes the papain-like protease (PLpro), which cleaves viral polyproteins and antagonizes the IFN response.[23]

Transmission

COVID-19 is an infection that can be contracted by direct contact with the causative agent, and can diffuse among humans through community spread. Transmission arises when an infected person exposes respiratory droplets (5 to 10 μm in diameter) through expectoration or sneezing that enter the nose or mouth of nearby individuals.[24] Since the ACE2 cell receptor is expressed in the intestines, kidneys and heart, in addition to being expressed in the esophagus and lungs, there is a fecal-oral transmission of SARS-CoV-2.[25]

Similar to the virus, TB is transmitted by pathogenic bacilli through the expectoration or sneezing of a sick individual. However, unlike COVID-19, TB can spread through the air by droplet nuclei (1 to 5 μm in diameter) containing 1 to 3 bacterial cells, which is a sufficient amount to invade macrophages present in the pulmonary alveoli, and cause infection when a healthy person inhales them.[26]

SARS-CoV-2 can remain viable for 3 to 72 hours on materials such as plastic and stainless steel, which is a shorter period of time than the half-life of MTB.[27] The survival of tubercle bacilli can vary. The drug-sensitive strains survive from approximately 1 to 7 days, while TB-MDR strains survive on surfaces for up to 21 days.[28] Transmission of MTB in a confined environment is more likely than it is outdoors because droplet cores are kept less diluted; this exposes the family and the environment of the patient to a highly contagious ambience. Therefore, shelters, prisons and hospitals are potentially at risk.

Pathogenicity

The lungs are the preferred site for the establishment of SARS-CoV-2 and MTB. To initiate the infection, SARS-CoV-2 crosses the nasal and laryngeal membranes to reach the lungs. After massive replication, the virus is released into the peripheral blood and causes viremia, where it binds to the ACE2 receptor present in spermatogonial, leydig, sertoli, gastric, duodenal and rectal cells. In this way, a variety of organs are involved during the disease.[29,30] COVID-19 is aggravated by the release of pro-inflammatory and immuno-activating cytokines, and creates a self-sustaining inflammatory process that triggers catastrophic respiratory failure.[31]

In primary TB, the bacilli enter the body through the pulmonary alveoli where they are assimilated by macrophages. The bacilli that survive digestion of phagolysosome generate a stage of symbiosis and replicate in macrophages while circulating in the lymph.[32] The pathogen generates lysis of macrophages due to its intense proliferation, and infects new cells in organs that may be of preference, such as the lungs, lymph nodes, bones, kidneys, and larynx. This process causes inflammation of the pleural surfaces in the patient. After 2 to 8 weeks, with the desire to contain the infection, the body responds with a delayed hypersensitivity reaction, and forms a pulmonary granuloma containing infected macrophages, foam cells and epithelioid macrophages in its nucleus surrounded by lymphocytes, T cells, CD4, CD8, B cells, and NK cells.[33] This formation allows the destruction of the pathogen-carrying macrophages and creates caseous necrosis, establishing a hostile environment for bacteria that will persist as latent TB.[32]

In postprimary TB, the patient may experience exogenous reinfection, or latent bacilli may be reactivated in the manner of endogenous reinfection. In the latter case, a process of liquefaction of the caseous centre allows the multiplication of the bacillus and generates great amounts of toxic antigens in the tissue. The walls of the bronchi become necrotic and form cavities, the liquefied material flows into the airways, and can infect other sections of the lungs, ultimately causing extrapulmonary TB.[34,35]

Diagnostic Tools

Coronavirus has different ways to be detected, and the gold standard is reverse transcriptase polymerase chain reaction (RT-PCR), which involves extracting RNA from the virus, synthesizing cDNA, and amplifying its genetic information. This trial has a sensitivity between 66% and 80%, depending on the viral load of the patient.[36] At the same time, the identification of specific genes has been applied using RT–qPCR or by reverse transcription loop-mediated isothermal amplification (RT-LAMP), which has a detection probability of 95%.[37,38] The highest rates of positivity are manifested using samples of bronchoalveolar lavage fluid, sputum, and nasal swabs.[39] Currently, it is preferred to use saliva and nasal swabs, which have sensitivities of 91% and 98%, respectively.[40] In the future, it is planned to use CRISPR Cas 13 as a promising protocol because it recognizes 10 to 100 copies per μL of sample, and can be read in only 1 hour.[41]

Another tool of choice is computed tomography, which is a fast, accurate and effective technique that allows identification of ground-glass opacity and lung anomalies typical of COVID-19. Before manifesting clinical symptoms, the lung shows signs of disease, so the sensitivity of this technique is 97%.

We currently have serological tests that evaluate the patient's response to the virus.[42] When symptomatology for COVID-19 exists, blood, plasma or serum samples are tested using a qualitative assay to identify the antibodies that the host develops from contact with the pathogen. These tests have a sensitivity of 57-69% for IgM and 81-86% for IgG, and are fast as well as inexpensive.[43]

In the case of TB, molecular assays are performed using sputum, urine, or tissue that are placed in a disposable cartridge from the GeneXpert equipment for DNA amplification. This

method detects MTB and its position against rifampicin. Though this technique has a sensitivity of 98.6%, it is expensive, and due to the economic limitations that nations most affected by TB go through, it is difficult to acquire.[44]

Despite the fact that MTB can lodge in any organ, the thorax is more frequently affected, and imaging plays a fundamental role in its diagnosis. Radiography may display cavities, consolidations and centrilobular nodules, and this method has shown a sensitivity of 78% if interpreted by trained personnel.[45]

The Interferon-Gamma Release Assay (IGRA) measures the amount of INF-γ produced by T cells after being stimulated by MTB antigens in the blood. Its sensitivity is 93%.[46,47]

Microbiological methods for diagnosing MTB include Ziehl-Neelsen staining, an accessible technique for developing countries, but with a sensitivity of 55%. Variations in the method have been postulated with the application of auramine-based fluorescence microscopy (LED-FM) to increase its sensitivity by approximately 10%; however, this requires extra equipment for its application.[48] Additionally, the microscopic observation drug susceptibility technique (MODS) allows for the detection of the bacillus and its sensitivity to rifampicin and isoniazid through sputum. It has a sensitivity of 91.3% to 98%, but the disadvantage lies in the operator exposure.[49] The gold standard method to determine the presence of TB is bacteriological culture, generally used on Lowenstein-Jensen solid medium. This assay has the capacity to detect 1×10^2 bacilli per mL, and yields a sensitivity of 93%. The timely diagnosis of diseases is essential for treatment. Unlike COVID-19, the main drawback of bacterial culture for TB is that it can take between 4 to 12 weeks.[50]

The Mantoux intradermal reaction or tuberculin test consists of evaluating the hypersensitivity that an individual produces to a purified protein derivative (PPD) of MTB. Its disadvantage is the generation of a cross-reaction with the tuberculosis vaccine derived from Bacille Calmette Guérin (BCG) or with nontuberculous bacteria. The test is evaluated 72 hours after its application and has a sensitivity of 94%.[47,51]

Clinical Manifestations

There are risk factors for both infections, including hypertension, lung diseases, diabetes, cardiovascular conditions and obesity. In patients suffering from SARS-CoV-2, their symptoms are aggravated by producing an acute respiratory distress syndrome that can culminate in death.[52] This situation is similar to TB, wherein vulnerable communities suffering from conditions such as HIV/AIDS, diabetes, kidney disease, organ transplants and cancer have weakened immune systems.[35]

A very pronounced difference between COVID-19 and TB is the onset of the disease. The entry of SARS-CoV-2 and its replication from the beginning of the infection occurs between 4.1 to 7 days; however, cases have been reported in which this period has become 12.7 days. On the other hand, MTB is a silent pathogen that can remain latent throughout the life of the host or may even generate gradual symptomatology that has the potential to manifest itself in several weeks or months.[53]

The most common symptoms in patients with COVID-19 are fever, cough, myalgia and dyspnea; less common symptoms include the production of sputum, headache and hemoptysis, as well as gastrointestinal conditions such as vomiting and diarrhea.[4,54,29] These symptoms are similar to those manifested by TB. The main sign is prolonged cough accompanied by sputum that may or may not be bloody with fever, hemoptysis, dyspnea, weight loss, night sweats, and lack of appetite.[55]

COVID-19 strongly impacts the lung, causing pneumonia affecting 3.3 lobes on average. It causes abnormal findings such as alveolar edema and growing ground-glass opacities that, in the worst case, can lead to "white lung."[56,57] A similar image occurs in TB, in which an initial lesion generates pleural effusion, lung cavities, hilar or mediastinal lymphadenopathy, calcified tuberculomas and emphysema due to affected nodes that obstruct the bronchi.[35] In both conditions, there is an asymptomatic population; however, in those with symptoms of advanced TB, it has been shown that they are capable of emanating 1.5 to 4 billion bacilli every day.[53]

Treatment

To date, though there is no specific treatment to combat COVID-19, a method to reduce its effects and help patients overcome the disease has been sought. Supportive therapy is recommended using oxygen 10 L/min and 30 L/min for severe and critical patients, respectively.[58] To neutralize the action of SARS-CoV-2, remdesivir has been used. This antiviral reduces viral load in animal models and appears to decrease recovery time and induce clinical improvement in COVID-19 patients. Improved effects have been observed in combination with lopinavir and ritonavir.[59–61] The antimalarial drug, chloroquine, blocks viral infection in vitro similar to the effect generated by favipiravir tested in humans.[62]

Convalescent plasma therapy has also shown effective results against COVID-19. Patients receive neutralizing antibodies that stimulate the immune battle and decrease the viral titer.[63] Furthermore, intravenous transplantation of mesenchymal stem cells, which secrete anti-inflammatory factors that regulate the immune response and prevent the cytokine storm have been used. [64]

To date, there is no vaccine available for SARS-CoV-2. However, there are 156 candidate vaccines for preclinical evaluation and 42 under clinical evaluation. In this last group, ten vaccines are in phase III and are based on the inactivation of the virus, viral vectors, protein subunit or RNA.[65]

In contrast to COVID-19, TB has a vaccine that has been applied in newborns, but it has a variable effectiveness in adolescents and adults.[66] In the case of developing latent TB, the WHO advises administering isoniazid or its combination with rifapentine.[67] In drug-sensitive tuberculosis, treatment adds rifampin, pyrazinamide, and ethambutol. In cases of drug resistance, the patient's treatment includes drugs such as levofloxacin, moxifloxacin, bedaquiline, clofazimine and cycloserine or terizidone.[68] The effectiveness of the treatment is variable due to the abandonment of therapy, the incorrect and irregular use of medicines, and even the low permeability of the MTB cell wall towards drugs.[69] It has been reported that approximately 60% and 40% of patients with multidrug-resistant (MDR-TB) and extensively drug-resistant (XDR-TB), respectively, are treated successfully.[70] Despite the fact that these drugs are new, resistance to them has already been reported. Such is the case for bedaquiline, which causes side effects such as nausea, hemoptysis, arthralgia and even unilateral deafness, which overwhelm patients and lead them to abandon treatment.[71]

During TB therapy, the WHO advises performing a monthly culture, but most countries opt for microscopic smear to control tuberculosis. Similar to COVID-19, the treatment of TB emphasizes

modifying the immune response through the use of host-directed therapies. This consists of administering small molecules with or without drugs to act by modulating the functions of the host cell. In this way, they counteract reactive oxygen species, cytokine production, autophagy induction, and peptide synthesis. This therapy is promising because it avoids contact with MTB and therefore the generation of resistance.[72,73]

Epidemiology

The reproductive number provides a direct estimate of transmission by showing the infections that may exist after a primary case. SARS-CoV-2 has a basic reproduction rate (R0) of 2.28, meaning that each person carrying the virus transmits the infection to approximately 2 individuals.[74] For TB, the R0 value varies by nation. In developed countries, effective reproduction rates of 0.24 and 0.59 have been reported for the Netherlands and the United States, respectively.[75] For developing nations, an R0 of 3.55 has been calculated in India, a value similar to that found in China (a neighboring country to Southeast Asia that had 44% of new TB cases in 2018), whose effective reproductive number corresponds to 4.3.[76] These data presume that economic and social conditions have an impact on equity in health. Due to airborne transmission of MTB, it has been estimated that in a confined, unventilated site, the effective reproduction rate is 14.22 to 44.13.[77]

The reproductive number is influenced by the genetic variability of the pathogen. SARS-CoV-2 has evolved in different ways according to its nsp. The L form is the main, most frequent and aggressive state that derives from the S form, a secondary type that has been present to a lesser extent during the pandemic.[78] In contrast, it has been reported that MTBC contains 7 lineages associated with different geographical regions. Lineages 1 and 3 are limited to East Africa and Asia. Lineage 2, also known as the East Asian lineage, which includes the Beijing strain family, is distributed in Asia, Russia and South Africa. Lineage 4 or the Euro-American lineage, is typical of Asia, Europe, Africa and America. Lineages 5, 6 and 7 are distributed throughout the Gulf of Guinea, West Africa and Ethiopia.[79] The seven phylogenetically distinct lineages can determine the clinical outcome of pulmonary and extrapulmonary TB.[80] As lineages 2, 3, and 4 are known as modern for their genetic changes and are strongly associated with drug resistance (MDR-TB or XDR-TB) and outbreaks of disease in younger patients, they have significant potential to expand.[81] Further, the migration of patients has caused several of the lineages to leave their geographical region of origin. Such is the case with the Beijing lineage, which is known for its high virulence and is associated with drug resistance. It has been found in South America and Europe.[82,83]

The Infectious Disease Vulnerability Index, RAND, is based on the political, economic, public health, demographic, developmental, and environmental factors to rank nations according to their susceptibility to infectious diseases.[84] The ranking indicates that the so-called "infectious diseases hot spot belt" is led by 5 countries in the African continent; this is consistent with the figures of TB, as 2.5 million people in Africa fell ill in 2016.[85] Nonetheless, the RAND ranking does not explain the transmission of COVID-19 given that until 10 August 2020, the entire African continent had only registered around 895,696 positive cases of COVID-19 and 16,713 deaths. This is a reduced number compared to United States – a country that is not vulnerable to infectious diseases – which, as of the same date, had 4.9 million cases with 160,989 deaths.[3] These data confirm that developed countries have had the resources to overcome outbreaks of infectious diseases such as TB; however, developing countries see the greatest impact. In the case of COVID-19, this event has not been observed due to the lack of available treatments and the speed of infection initiation.

The End of TB program has been in force since 2016 and seeks to diagnose and treat infectious cases until the incidence is reduced by 90%.[86] Unfortunately, it is stated that the goal of eliminating TB by 2035 is unlikely to be met, as progress is still very slight.[87] The WHO suspects that the number of TB deaths has increased because of the pandemic. This entity assumes that a 50% reduction in global detection during 3 months of confinement could increase the number of deaths by 26%.[88]

In the nations most affected by TB, it has been found that the cases focus on vulnerable groups, which include low-income and low-education families, people deprived of liberty, those with poor living conditions, people with pre-existing diseases, malnutrition, or HIV, indigenous communities, populations in border crossings, those who are migrating, and those who have limited medical access.[89] In the case of COVID-19, the vulnerable sectors have not yet been clearly established. Several studies argue that low educational level, being a man, not married, coming from a low to middle income country, and socioeconomic deprivation associate a higher risk of death due to SARS-CoV-2.[90–92] It is expected that in the future COVID-19, as well as TB, will end up being associated with people with limited resources.[91,93]

BCG Vaccine and Its Relationship to COVID-19

BCG is the only vaccine developed to fight TB. It has been used for almost 100 years since Albert Calmette and Camille Guérin attenuated the strain from *M. bovis*.[94] In the current pandemic, a link between BCG vaccination and morbidity and mortality of COVID-19 has been discussed. It is conjectured that countries without a BCG vaccination program show a higher number of people affected by SARS-CoV-2. This is presumed to be the case in Europe where the nations most affected by the pandemic have abandoned the application of BCG for decades.[95]

BCG vaccination reduces infant mortality from infections other than TB due to a potential heterologous effect.[96] It has been determined that the population previously immunized responds more effectively against nonmycobacterial diseases, such as influenza A, as it produces a high antibody response.[97] The beneficial effect of BCG vaccination on different diseases can be explained by the intervention of the vaccine on the patient's immunity. Its application stimulates gene promoter regions to participate directly in the remodeling of signal transduction molecules and in the inflammatory response based on the production of proinflammatory cytokines such as TNF-α and IL-6. High IL-1β levels showed a protective effect in viral infections.[98,99] This causes the host to reprogram monocyte epigenetics and respond to a stimulus with trained immunity or innate immune memory.[100] Certain literature states that vaccination has a protective effect in the course of the SARS-CoV-2 pandemic; in countries that use BCG vaccination, the mortality is 5.8 times lower than that in those regions that have suspended its application.[101] Additionally, it has been exposed that SARS-CoV-2 has caused a case fatality rate of 5.2% and 0.6% for countries that have abandoned vaccination

and for those that still administer it, respectively.[102] These values are subject to variation due to circumstances, including the start of the pandemic, migration, demography, and health systems among others.[103] At the moment, there is no clear evidence of a relationship between the two factors. To clarify this, several trials are in the process of evaluating the performance of the BCG vaccine in medical personnel exposed to the virus. Such is the case of a study developed in Medellín-Colombia, a nation with compulsory vaccination, and wherein the incidence of COVID-19 will be measured after the application of the vaccine and a placebo.[104] Other trials have assessed the capacity of the centennial vaccine in countries with optional vaccination, such as the Netherlands, seeking to minimize absenteeism in medical personnel by applying the BCG vaccine.[105]

Conclusions

Both infectious diseases, TB and COVID-19, are etiologically different, but they selectively attack the lungs, and several symptoms are analogous. For these reasons, they generate a similar clinical picture. Although TB can be treated with a range of drugs, every day their effectiveness is counteracted by their improper use and evolution of the bacillus. In contrast, COVID-19 does not have a defined therapy, but fortunately there are cases of recovery. Airborne transmission of TB is a critical factor for its progression, and people with this condition are at high risk of acquiring a simultaneous infection with COVID-19.

Currently COVID-19 has hit the world due to its transmission capacity and the lack of optimal treatment; however, TB is a curable and preventable disease that, despite having been declared by the WHO as a world emergency in 1993, continues to claim victims and has not been controlled. It is necessary to strengthen the health system to encourage prevention and proper treatment of TB, especially in developing countries, which at present have the largest number of cases.

Due to the continuously developing information about SARS-CoV-2, the data are not currently definitive. Nevertheless, the need for knowledge has generated the union of the scientific community in order to safeguard health. It is essential to provide resources for health and research that allow us to intervene quickly in the face of new diseases such as COVID-19 and to combat older ones such as TB.

The narrative and global scope of this review misses the geographically nuanced factors that affect pathogenicity, treatment, diagnostic tools, and other aspects of both tuberculosis and COVID-19. This article denotes the most valuable aspects of both microorganisms through an exhaustive analysis of the most recent literature. Given that TB is a worrisome social disease, in the future it is expected to have safer drugs without side effects, faster, more sensitive diagnostic methods and global access.

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Early trial results of SARS-CoV-2 vaccines: a review

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Abstract

Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) initially emerged in Wuhan, China in December 2019. The virus causes the disease that is termed COVID-19 and has led to a global pandemic. As of October 16, 2020, it has led to more than 39 million cases worldwide and has killed more than 1 million people. Since the posting of the SARS-CoV-2 genome, vaccine development has begun around the world, with Canada placing orders for millions of vaccine doses through advanced purchasing agreements (APA) with major developers. As of July 2020, early human clinical trial results of three vaccine candidates, namely ChAdOx1, Ad5-nCoV, and mRNA-1273, have been published, two of which are included in Canada's APAs.

Objective: The aim of this review is to examine and summarize early clinical trial results of the three aforementioned COVID-19 vaccine candidates as of July 20th, 2020. The primary focus of this review will be the methods, procedures, results, and discussions of each published study.

Methods: All vaccine candidates undergoing human trials were searched and identified using PubMed through a combination of search terms. Only the most recent human trial report published in peer-reviewed journals between May 15th and July 20th, 2020, was selected for each vaccine candidate.

Results and Conclusion: The review concludes that all three vaccine candidates have demonstrated a strong safety profile, as well as a robust immune response in the participants of their respective trials. All three vaccine candidates have shown strong immunogenicity, in terms of receptor-binding domain-specific antibody response and neutralizing antibody response. No serious adverse effects were observed in the three trials and all local or systemic reactions were self-limiting. Both ChAdOx1 and Ad5-nCoV will be moving on to phase 3 clinical trials, with mRNA-1273 moving on to phase 2 trials, before the end of 2020.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a coronavirus that belongs to the β-coronavirus cluster and emerged initially in Wuhan, China in December 2019.[1] The virus causes the disease that is termed COVID-19, which is the third known zoonotic coronavirus disease, with the two previous disease types being severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS).[2] The virus was found to be a positive-sense single-stranded ribonucleic acid (RNA) virus, with 88-89% similarity to two SARS-like coronaviruses derived from bats, namely bat-SL-CoVZC45 and bat-SL-CoVZXC21.[1] It also shares a 79% similarity to the SARS virus and 50% similarity to the MERS virus.1 A study by Li et al. analyzed the first 425 confirmed cases in Wuhan, and found evidence of human to human transmission, as well as estimating that the virus has a R0 value of 2.2.[3] The World Health Organization (WHO) declared the COVID-19 outbreak to be a global pandemic on March 11, 2020.[4] As of October 16, 2020, it has spread to almost every country in the world, leading to more than 39 million cases and over 1,000,000 deaths worldwide.[5]

Antibodies are proteins produced by the immune system in response to foreign microbes or cancer cells.[6] They attach to these foreign substances in order for the immune system to sense and eliminate them.[6] The main five types of antibodies include: IgA, IgG, IgM, IgD, and IgE.[6] However, only a small subset of antibodies that bind a virus are neutralizing antibodies.[7] Neutralizing antibodies bind to a virus in a way that inhibits infection.[7] This can be achieved through blocking virus interaction with the receptor of the target cell or through binding a viral capsid to inhibit the uncoating of the genome.[7] A titre is a laboratory measurement that determines the amount or concentration of antibodies, in the blood.[8] In clinical evaluation of vaccines, geometric mean titre (GMT) is typically the standard to determine the average antibody response in a group of subjects.[9] Another measure of antibody response is seroconversion, which is the period during which antibodies become detectable in the blood.[10] Individuals who have detectable antibodies are seropositive, and those who have do not are seronegative. T cells,

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in addition to antibodies, are part of the adaptive immune system and are crucial to the immune response against viral infections.[11] T cells are produced in the bone marrow and develop their own T cell receptors that are specific to one type of antigen.[11] The antigen marks a virus-infected cell and prompts the T cell to eliminate that target.[11] Due to their importance in fighting viral infections, antibody and T cell responses make them important measures in vaccine development.

As a response to the COVID-19 pandemic caused by this novel coronavirus, Canada has announced purchasing agreements (APA) with several vaccine developers (shown in Table 1).[12–18]

The objective of this review was to examine and summarize the most recent published clinical trial results COVID-19 vaccines as of July 20th, 2020. The summary will focus primarily on the methods and procedures, results, and discussions of each published study.

Methods

A list of all COVID-19 vaccine candidates currently in development was obtained through the Government of Canada website.19All vaccine candidates undergoing human trials were searched and identified using PubMed to obtain any published data from their studies. Additional vaccine candidates were identified in PubMed through combinations of search terms "SARS-CoV-2", "COVID-19", "vaccine", "trial", and "safety". The time range for the search was set between May 15th and July 20th, 2020, and only the most recent human trial report was selected for each vaccine candidate. Only peer-reviewed published literature was included. Their respective methods and results were subsequently reviewed and summarized. The aspects of methods reviewed included vaccination schedule and adverse event report. The aspects of results reviewed included reports of adverse effects and immunogenicity of the vaccine candidates, with all numeric results included in this review having a p-value < 0.05, if significant.

Results

The search resulted in the finding of published clinical trial data for three vaccine candidates: ChAdOx1, Ad5-nCov, and mRNA-1273. Only two of these vaccine candidates, namely ChAdOx1 and mRNA-1273, have an APA with the Canadian government.[12]

ChAdOx1

ChAdOx1 nCoV-19 is a vaccine candidate developed by the University of Oxford and pharmaceutical company AstraZeneca. They published their first human trial results on July 20th, 2020. The vaccine candidate consists of the chimpanzee adenovirus vector, ChAdOx1, without the ability to replicate while containing the full-length structural surface glycoprotein (spike protein) of SARS-CoV-2.[20] In a previous study using rhesus macaques, the vaccine candidate was able to protect the lungs from damage and produce a robust immune response when the rhesus macaques were exposed to high doses of SARS-CoV-2.[21] The vaccine candidate was administered through an intramuscular injection to the deltoid muscle, at a dose of 5×10^{10} viral particles.[10,20]

The study published was a phase 1 and 2 single-blinded randomized controlled trial, performed at five different testing centres in the United Kingdom. Participants were between the ages of 18 and 55 and underwent a screening visit, where a full medical history and examination was completed, along with blood and urine tests. Exclusion criteria included: individuals with a history of confirmed SARS-CoV-2 infection, front-line health workers and other individuals who are at higher risk for SARS-CoV-2 exposure pre-enrolment, and those who had a new onset of COVID-like symptoms since Feb 1, 2020.[20] Participants were randomly assigned to receive either the ChAdOx1 nCoV-19 vaccine or the MenACWY vaccine. MenACWY was utilized as a comparator placebo vaccine, as opposed to saline, in an effort to blind the participants. Since viral vector vaccinations are known to elicit local or systemic reactions, a lack of reactions from saline would unblind the participants who had notable reactions, thus MenACWY was chosen as placebo.[20] MenACWY vaccine is routinely given to teenagers in the United Kingdom to prevent meningococcal disease, and would typically produce mild reactions such as redness at injection site, nausea, fatigue, headache, and fever.[22] Thus, the presence of these reactions would sufficiently blind the participants.

Table 1. Summary of the Canadian advanced purchasing agreement of COVID-19 vaccines as of September 25, 2020[12–18]

Developer	Astra-Zeneca/ Oxford	Janssen Pharma Co.	Moderna	Novavax	Pfizer/ BioNTech	Sanofi/ GSK
Type	Non-replicating viral vector	Non-replicating viral vector	mRNA	Protein subunit	mRNA	Protein subunit
Dose requirements	2 doses	1/2 doses	2 doses	2 doses	2 doses	1/2 doses
Dose reserved	~ 20 million	Max 38 million	Min 20 million	~ 76 million	Min 20 million	Max 72 million
Storage temperature	2-8 °C	2-8 °C	-24 °C	2-8 °C	-70 °C	2-8 °C

Participants were recruited in 4 separate groups. Group 1 (the phase 1 component of the study) consisted of intensive early follow-up visits at days 3, 7, 14, 28, and 56 after vaccination to ensure safety and immunogenicity. Group 2 consisted of participants who had higher blood volumes drawn for humoral and cellular immunogenicity assessment than group 4. Group 4 consisted of participants who only had a serum sample drawn for humoral immunology assessments. Group 3 consisted of a non-randomized group ($n = 10$) that received a booster shot 28 days after the first dose. Group 3 participants were not blinded and had the same extensive follow-up as group 1 following each dose. All participants across the groups had blood samples taken, along with clinical assessments, at days 0 and 28 and will also be followed up at days 184 and 364. After vaccination, all participants underwent a 30-60 min observation period in the clinic and were asked to record any adverse events using electronic diaries during the 28-day follow-up period. Adverse events were graded as mild, moderate, severe, and potentially life-threatening.[20]

Cellular responses were assessed using an ex-vivo interferon-γ enzyme-linked immunospot (ELISpot) assay, as a way to enumerate antigen-specific T cells. Humoral responses were assessed using a standardized total IgG enzyme-linked immunosorbent assay (ELISA) against trimeric SARS CoV-2 spike protein, a multiplexed immunoassay (MIA), three live SARS-CoV-2 neutralization assays (PHE, MNA and Marburg), and a pseudo-virus neutralization assay (PseudoNA). Convalescent plasma samples from adults with positive SARS-CoV-2 infections were obtained from symptomatic

patients admitted to hospital or healthcare workers who did not have symptomatic infections. These samples were tested using the aforementioned assays as well.[20]

Prophylactic paracetamol was given to 56 participants in the ChAdOx1 nCoV-19 group and 57 in the MenACWY group, and was found to reduce the incidence of adverse events. Common adverse events in both groups included pain, tenderness, fatigue, headache, fever, muscle ache, malaise, chills, and feeling feverish. The prevalence of these events among these groups are displayed in Table 1.[20]

In dose groups 1, 2, and 4, where no subsequent booster shot was given, as well as the ChAdOx1 nCoV-19 group where only one dose was administered, antibodies targeting SARS-CoV-2 spike protein peaked by day 28 (median ELISA units [EU] = 156) and remained elevated until day 56 (EU = 119). Among the 10 participants in group 3 who received a booster shot, the median antibody concentration on day 56 was increased to 639 EU. By day 28, similar increases in serum antibody levels to both the spike protein and the receptor-binding domain (RBD) were observed, regardless of booster shot. Paracetamol use did not appear to affect immunogenicity. On day 28, the PHE assay determined that 100% (35/35) of participants achieved neutralizing titres. The MNA assay also found that titres inducing 80% virus neutralization was achieved in 91% (32/35) participants after one dose, and in 100% (9/9) of participants following the booster dose. In the Marburg assay, it was found that just one dose of the vaccine candidate resulted in 62% (23/37) of participants having neutralizing antibodies that completely inhibited the cytopathic effect of SARS-CoV-2 by day 56. The same occurred in 100% (10/10) of participants after a booster dose.[20]

The preliminary findings show that the vaccine candidate ChAdOx1 nCoV-19, given as a single dose, was safe and tolerated, despite the fact that it has a higher reactogenicity profile than the control vaccine, MenACWY. No serious adverse reactions to the vaccine candidate occurred, with the majority of adverse events reported being mild or moderate in severity, and self-limiting. The use of prophylactic paracetamol also appeared to increase tolerability among the participants, while reducing potential confusion between short-lived vaccine-related symptoms and actual COVID-19 symptoms.20 Additionally, the use of prophylactic paracetamol did not impact immunogenicity.[20]

In previous clinical studies exploring DNA vaccines on rhesus macaques, neutralizing antibodies targeting the different epitopes of the spike glycoprotein were associated with protection from COVID-19.[23] In addition, there is increasing evidence to suggest that T cell responses play an important role in COVID-19 mitigation, as robust T cell immunity was found in individuals who were asymptomatic or had mild COVID-19 symptoms.[24] Older individuals also remain disproportionately affected by the more severe and fatal cases of COVID-19,[25] so it is important that any vaccines developed are safe and tolerable for older age groups.

The limitations of this study include: a short follow-up, small sample size in the prime-boost group, and the single-blinded design. However, staff undertaking clinical evaluation and laboratory staff were blinded. The findings are also not easily generalizable. While the methods of the study did not specify ethnicities and age distribution among the trial groups, the discussion of the study does state that the sample is composed of relatively young and healthy, mostly Caucasian participants. Future studies should assess the vaccine in other population groups including the elderly, those with comorbidities, and in ethnically diverse populations. The participants in this study will be followed for at least one year in order to further report on the safety, tolerability, immunogenicity, and efficacy of the vaccine candidate. The preliminary results of this study support future phase 2 and 3 trials. Phase 3 trials have begun in Brazil, South Africa, and the UK. These trials will evaluate vaccine efficacy in diverse populations such as children, healthcare workers, and older age groups.

Ad5-nCov-2

This phase 2 study, published on July 20, 2020, was a randomized, double-blinded, placebo-controlled trial of the Ad5-nCoV (Ad5) vaccine candidate.[26] This vaccine candidate is an adenovirus vector vaccine developed by CanSino Biologics Inc., and its phase 1 trial data was published on May 22, 2020.[27] The phase 1 study of this candidate was the first published human trial report of any SARS-CoV-2 vaccines.[27] It was a recombinant adenovirus type-5 vectored vaccine candidate that expresses the spike glycoprotein of the SARS-CoV-2 virus strain; however, it did not have replicating abilities.[27] The aim of the phase 2 study was to determine an appropriate dose for a phase 3 efficacy study.[26]

This study was randomized, double-blind, and placebo controlled. It was conducted at a single testing centre in Wuhan, China, involving healthy adult participants with no upper age limit. Exclusion criteria included: HIV positivity, previous SARS-CoV-2 infections, and the presence of mental disease, history of allergies, or serious cardiovascular disease. The placebo shot contained no viral particles but shared identical packaging as the vaccine candidate. Three treatment groups (1×10^{11} viral particles/mL [medium],[27] 5×10^{10} viral particles/mL [low],[27] and placebo) were randomized using software at a 2:1:1 ratio. In total, 603 participants were recruited and screened, with 95 individuals excluded, leaving 508 eligible participants in the trial. Of these, 253 were randomly assigned to the medium dose group, 129 to the low dose group, and 126 to the placebo group. A single injection of the vaccine candidate or placebo was administered intramuscularly in the arms of the participants, and they were monitored for 30 minutes afterwards for immediate adverse reactions. All participants were followed up for any local or systemic adverse reactions within 14 days and adverse events within 28 days after the injection. Participants also self-reported any serious adverse events throughout the study.[26]

Blood samples were collected from participants immediately before vaccination, as well as at days 14 and 28 post-vaccination. The measurement of specific antibody responses against the RBD were done using ELISA kits. The neutralizing antibody responses to live SARS-CoV-2 virus or a pseudo virus, made of a vesicular stomatitis virus pseudo virus system expressing the SARS-CoV-2 spike glycoproteins, were also measured. Additionally, cellular immune responses before and 28 days after the vaccination were also measured. The cellular immune responses of the expression of interferon (IFN) γ, which demonstrates positive T cell responses, were detected by ELISpot assay, and serum neutralization assay was used to assess neutralizing antibody titers. Follow-up appointments were scheduled on days 14 and 28, and 6 months post-vaccination to assess safety and immunogenicity.[26]

Within 14 days post-vaccination, at least one adverse reaction

was reported by 72% (183/253) of the participants in the medium dose group and 74% (96/129) of the participants in the low dose group; this was significantly higher than the adverse reactions reported in the placebo group (37% (46/126)). The most common adverse reactions in the experimental vaccine groups were pain at the injection site, fatigue, fever, and headache. The incidence rate is outlined in Table 2.[26]

Table 2. Prevalence of local or systemic adverse events among the participants receiving the ChAdOx1 nCoV-19 experimental vaccine or the MenACWY control vaccine[20]

	Incidence in the ChAdOx1 nCoV-19 group		Incidence in the MenACWY group	
	Without paracetamol	With paracetamol	Without paracetamol	With paracetamol
Pain	67%	50%	38%	32%
Tenderness	83%	77%	58%	46%
Fatigue	70%	71%	48%	46%
Headache	68%	61%	41%	37%
Fever (min 38°C)	18%	16%	< 1%	0%
Fever (min 39°C)	2%	0%	0%	0%
Muscle ache	60%	48%	Not specified	Not specified
Malaise	61%	48%	Not specified	Not specified
Chills	56%	27%	Not specified	Not specified
Feeling feverish	51%	36%	Not specified	Not specified

Table 3. The prevalence of local or systemic adverse events among the participants receiving 1×10^{11} (medium dose) or 5×10^{10} (low dose) experimental Ad5-nCoV vaccine[26]

	Incidence in the 1×10^{11} viral particles (medium) dose group	Incidence in the 5×10^{10} viral particles (low) dose group
Fatigue	42%	34%
Fever	32%	16%
Headache	29%	28%
Pain at injection site	57%	56%

While most adverse reactions were reported as either mild or moderate, 9% (24/253) of the participants in the medium viral particles group had severe adverse reactions; this was significantly higher than those in the low viral particles or placebo groups. The most common severe adverse reaction was fever, which was reported in 8% (20/253) of the participants in the medium particles dose group and 1% (1/129) of the participants in the low dose group. These reactions were self-limited and were resolved within 72-96 hours without need for medication. Overall, within 28 days of the injection, 77% (196/253) of the participants in the medium dose group, 76% (98/129) of those in the low dose group, and 48% (61/126) of those in the placebo group experienced at least one adverse event.[26]

RBD-specific ELISA antibody responses induced by Ad5 were detected since day 14, with a higher response in the medium dose group. On day 28, these antibodies peaked at 656.5 in the medium dose group and 571.0 in the low viral particles dose group; 244 of the 253 participants in the medium dose group and 125 of the 129 participants in the low dose group showed seroconversion of the aforementioned antibodies on the same day. No antibody increases from baseline occurred in the placebo group. Neutralizing antibody responses to live SARS-CoV-2 was induced by both doses on day 28, with GMTs of 19.5 and 18.3 in medium and low dose groups, respectively. At 28 days post-injection, seroconversion of neutralizing antibody responses also occurred in 148 of the 253 participants receiving the medium dose and in 61 of the 129 participants receiving the low dose. In terms of neutralizing antibody responses to the pseudo-virus, the GMTs were 61.4 in the medium dose group and 55.3 in the low dose group, with seroconversion also occurring in both groups. Older age (>55) was found to have a negative impact on the RBD-specific ELISA antibody and neutralizing antibody responses to both the live virus and pseudo-virus. Nonetheless, antibodies in both groups remained significantly higher on day 28 when compared to the placebo group, despite old age. Significant SARS-CoV-2 spike glycoprotein-specific IFNγ-ELISpot responses were induced in 227 of the 253 participants in the medium dose group and 113 of the 129 participants in the low dose group. Both groups increased by a factor of 10 in this metric when compared to baseline. No such increase was observed in the placebo group. In terms of immune response, no gender differences were observed.[26]

This study is the first randomized, double-blind, placebo-controlled trial for the Ad5-nCoV vaccine candidate. A single injection of the vaccine candidate at 1×10^{11} viral particles (medium) and 5×10^{10} viral particles (low) was able to induce specific immune responses to the SARS-CoV-2 spike glycoprotein on day 28, with no significant differences observed between the two dose groups. The two doses induced seroconversion of neutralizing antibodies in 59% and 47% of participants and seroconversion of binding antibody in 96% and 97% of participants in the medium and low dose groups, respectively. Positive specific T-cell responses were found in 90% and 88% of participants in the medium and low dose groups, respectively.[26] A dose of 1.5×10^{11} was explored in a previous phase 1 study, but it was not selected for further study.[27]

The most common reactions reported in this study were mild or moderate, though the incidence rate of adverse events such as fever, fatigue, and injection site pain were significantly higher in vaccine recipients than those in placebo recipients. These events are generally resolved within 48 hours. All severe reactions reported were in the medium dose group, except for one adverse reaction that occurred in the low dose group. Overall, the results indicate that Ad5-nCoV has demonstrated a good safety profile in healthy adults.[26]

The limitations of this trial include: lack of diversity in participants (all participants were Wuhan residents, which does not represent a global population), the lack of data beyond 28 days post-vaccination, and the lack of live SARS-CoV-2 exposure post-vaccination to assess efficacy. In addition, this trial began after the full data from its phase 1 study was available, so the researchers did not calculate the sample size based on study power in advance, which could lead to a lack of power to show the difference between the dose groups. These limitations emphasize the importance of an international multicentre, randomized, double-blind, placebo-controlled phase 3 efficacy trial. The immunogenicity and the feasibility of additional dose in the older population will be assessed in another phase 2B trial.[26]

mRNA-1273

The first preliminary report on the effectiveness of mRNA-1273, an mRNA vaccine developed by Moderna was published on July 15th, 2020. The mRNA-1273 vaccine candidate encodes the S-2P antigen, consisting of the SARS-CoV-2 spike protein with a transmembrane anchor and an intact S1-S2 cleavage site.[28] The mRNA-1273 vaccine was manufactured as a sterile liquid for intramuscular injection (concentration = 0.5 mg/mL), with normal saline being used to dilute the solution and prepare the doses administered.[28]

Moderna conducted a phase 1 dose-escalation clinical trial that was designed to determine the safety, reactogenicity, and immunogenicity of mRNA-1273.28 The trial consisted of 45 healthy adults between the ages of 18 to 55 years.[28] The participants received two injections of the vaccine candidate 28 days apart, at a dose of 25 μg, 100 μg, or 250 μg across three trial groups (n = 15).28 Follow-up visits were scheduled 7 and 14 days after each vaccination, as well as on days 57, 119, 209, and 394 of the clinical trial.[28] The participants were given memory aids to record local and systemic reactions for seven consecutive days after each vaccination.[28] They were also instructed to avoid routine use of acetaminophen or other analgesics and antipyretics before or after the vaccinations, but were asked to record any new medications taken.[28] Binding antibody responses to the S2P and isolated receptor-binding domains of the vaccine were assessed using ELISA.[28] To compare the immune response experienced by the participants to the individuals who had SARS-CoV-2 induced infections, 41 convalescent serum specimens from SARS-CoV-2 patients were also tested.[28] A pseudo typed lentiviral reporter single-round-of-infection neutralization assay (PsVNA) and a live wild-type SARS-CoV-2 plaque-reduction neutralization testing (PRNT) assay were used to measure vaccine-induced neutralizing activity.[28]

The vaccine candidate was found to produce no serious adverse effects.[28] Systemic adverse effects were reported by 33% (5/15) participants (33%) in the 25μg group, 67% (10/15) in the 100μg group, and 53% (8/15) in the 25 μg group after the first vaccination.28All adverse effects were reported as mild or moderate in severity.28 Such adverse events increased in occurrence after the second vaccination.[28] Adverse events occurred in 54% (7/13) in the 25μg group, and every participant in the 100μg and 250μg groups, with 3 participants reporting one or more severe events.28 No participants reported fever after the first vaccination, while 40% (6/15) in the 100μg group and 57% (8/15) in the 250μg group reported fever after the second vaccination, with one of the fever events in the 250μg group graded as severe (maximum temperature = 39.6°C).[28] Pain at the injection site was common and local adverse events were nearly all mild or moderate when they occured.[28] The most common adverse events across both vaccinations included fatigue, chills, headache, myalgia, and pain at the injection site.[28]

Binding antibody IgG GMTs to S-2P site increased rapidly after the first vaccination and seroconversion occurred in all participants by day 15. It was also evident that the responses to both vaccinations were dose-dependent,28 with the 25, 100, and 250μg dose groups reaching GMTs of 40,227, 109,209, and 213,526, on day 29, respectively.[28] Similar patterns and magnitudes were also observed in RBD-specific antibody responses.[28] For both assays, the median magnitude of antibody responses after the first vaccination in the 100μg and 250μg dose groups were similar to the median magnitude in convalescent serum specimens from SARS-CoV-2 patients.[28] Furthermore, after the second vaccination, the median magnitude across all dose groups were in the upper quartile of values in the convalescent serum specimens.[28]

Prior to vaccination, no participant had detectable PsVNA neutralization responses.[28] After the first vaccination, neutralization responses were detected in less than half of the participants, with responses being dose-dependent.[28] However, after the second vaccination, such responses were detected in serum samples from all participants.[28] The responses by all dose groups after two vaccinations were similar to the levels seen in the upper half of the distribution for convalescent serum specimens, reaching GMTs of 80.7, 231.8, and 270.2, on day 57, from the lowest to highest dose groups, respectively.[28] Moreover, at day 43, wild-type virus-neutralizing activity capable of reducing SARS-CoV-2 infectivity by 80% or more was detected in all participants using PRNT assay, with the average PRNT response being above the convalescent serum specimen tested.[28]

The development of this vaccine candidate began after the SARS-CoV-2 genome was posted on January 10, 2020, and the manufacture and delivery of clinical trial material was completed within 45 days.[28] The first trial participants were vaccinated on March 16, 2020, just 66 days after the genomic sequence of the virus was posted.[28]

The mRNA-1273 vaccine candidate was able to induce a strong immune response in all 45 participants after two doses of the vaccine, with median immune responses similar to the higher end distribution of patients who were infected with SARS-CoV-2.[28] Both immunogenicity and reactogenicity appear to be dose-dependent.[28] Systemic adverse events were all reported to be mild after the first vaccination, with more severe and frequent adverse events occurring after the second vaccination, particularly in the 250μg group.[28]

Seroconversion also occurred rapidly for binding antibodies, as it occurred within 2 weeks of the first vaccination.[28] Serum neutralization also occurred in all participants after the second vaccination. Previous studies have shown that there is a correlation between serum neutralization activity and the protection for other respiratory viruses.[29] This was further supported by the pre-clinical trial of a DNA vaccine against SARS-CoV-2 in rhesus macaques, as they found existence of a correlation between neutralizing antibody titre and protection against the challenge of SARS-CoV-2.[23]

Participants will be followed for one year after the second vaccination with scheduled blood collections to characterize the humoral and cellular immunologic responses.[28] A phase 2 trial of this vaccine candidate (n = 600) evaluating doses of 50μg and 100μg is ongoing, with a large phase 3 efficacy trial expected to begin during the summer of 2020.[28]

Discussion

Overall, all three vaccine candidates explored have demonstrated a strong safety profile, as well as a capability to induce an immune response. The summary of the key safety and immunogenicity metrics of all three vaccine candidates is shown in Table 4.

The methods used in each of the three trials are similar, as they all have varying degrees of blinding, follow-up, assessment of local or systemic reactions, and measurement of immune response

Table 4. A summary of ChAdOx1, Ad5-nCoV-2, and mRNA-1273 COVID-19 vaccine candidates as of July 2020

Vaccine candidate	ChAdOx1 nCoV-19	Ad5-nCoV-2	mRNA-1273
Vaccine type	Non-replicating viral vector	Non-replicating viral vector	mRNA
Published trial phase as of July 20th, 2020	1/2	2	1
Adverse reactions	Pain, tenderness, fatigue, headache, fever; Very few fever incidents above 39°C; Paracetamol reduced incidence	Pain, fatigue, fever, headache; most events mild/moderate and self-limiting; Paracetamol NOT tested	Pain, headache, fatigue; no fevers after first dose, only one severe fever after second dose; Paracetamol NOT tested
Antibody or RBD-specific antibody responses	Median spike protein-specific antibodies: 156 EU (day 28), 119 EU (day 56), 639 EU (day 56 [booster])	Median RBD-specific antibodies (GMT) at the peak: 656.5 (medium dose), 571.0 (low dose)	Median spike protein-specific antibodies on day 29 (GMT): 40,227 (25 μg), 109,209 (100 μg), 213,526 (250 μg)
Neutralizing antibody seroconversion	100% seroconversion (day 28), 91% seroconversion of antibodies capable of 80% virus neutralization (day 28)	58% seroconversion (medium dose, day 28), 47% (low dose, day 28)	< 50% seroconversion (first dose), 100% seroconversion (second dose)

Table 5. A summary of COVID-19 vaccine candidates with published clinical trial reports (preprints excluded) as of October 19th, 2020[16,20,26-28,30-32]

Vaccine candidate	ChAdOx1-nCov-19	Ad5-nCoV-2	mRNA-1273	rAd26 and rAd5	BNT162b1 and BNT162b2	Unnamed Sinopharm Vaccine
Publication date(s)	July 20th, 2020	May 22nd, 2020 (phase 1); July 20th, 2020 (phase 2)	July 14th, 2020 (phase 1); September 29th, 2020 (expanded phase 1)	September 26th, 2020	October 14th, 2020	August 14th, 2020
Published trial phase(s)	Phase 1/2	Phase 1 and phase 2	Phase 1 and expanded phase 1	Phase 1/2	Phase 1	Phase 1
APA status with Canada	Yes	No	Yes	No	Yes	No
DOI	10.1016/S0140-6736(20)31604-4	10.1016/S0140-6736(20)31208-3	10.1056/NEJMoa2022483 (phase 1)	10.1016/S0140-6736(20)31866-3	10.1056/NEJMoa2027906	10.1001/jama.2020.15543
		10.1016/S0140-6736(20)31605-6 (phase 2)	10.1056/NEJMoa2028436 (expanded phase 1)			

via standard laboratory techniques. However, there are a few differences in their results worth looking at. The trial exploring ChAdOx1 explicitly included Paracetamol use as a part of the study, evaluating its impacts on immunogenicity and effects in reducing the adverse reactions.[20] The same was not done in the other two studies, and its inclusion can be considered a strong point in the ChAdOx1 study, as they did find the Paracetamol to be helpful in reducing adverse effects while not impacting immunogenicity.20 Since this was not explicitly done for the other two vaccine candidates, it should not be assumed that they share this quality. In addition, the ChAdOx1 study also opted to measure antibody responses in ELISA units, while the other two studies used GMT, which makes it difficult to compare the antibody responses across the three studies.[28] However, all three studies indicate baseline antibody levels, which enables one to evaluate the effectiveness of the vaccines based on the immune response compared to baseline.[28] Convalescent serum samples from real-life patients infected with SARS-CoV-2 were also used as a comparator in the ChAdOx1 and mRNA-1273 studies, providing another method to judge vaccine effectiveness.[20,27]

The three studies also share similar limitations. All three studies have limitations when it comes to the sample population, either in terms of size or diversity.[28] Both the ChAdOx1 and Ad5-nCoV studies had a sample size that lacked diversity, with the former being mainly Caucasian, and then latter being only Wuhan residents.20,[26] While the study exploring mRNA-1273 did not explicitly mention such issues, it has a sample size smaller than both ChAdOx1 and Ad5-nCoV, due to its nature as a phase 1 trial.[28] However, many of these issues are expected to be resolved to varying degrees as these vaccine candidates enter larger scale clinical trials.

Since the review of the three studies as of July 20th, much has changed in the landscape of COVID-19 vaccine development. Other vaccine candidates have also had published clinical trial reports since then, making the three vaccine candidates reviewed no longer the only ones with clinical trial data. A list of all published COVID-19 vaccine clinical trial reports as of October 19th, 2020 is shown in Table 5.

Another notable development of COVID-19 vaccine development since the publication of the three studies is the pausing of phase 3 clinical trials of ChAdOx1, and another vaccine candidate by Janssen Pharmaceutical Company, named Ad.26.COV2.S.[33,34] In early September 2020, it was reported that AstraZeneca is pausing its ChAdOx1 vaccine phase 3 trials in Britain after the incidence of transverse myelitis, a spinal inflammation disorder, in a female subject.[35] The trials resumed soon after in Britain, while remaining paused in some other countries.[36] This is not the first pause for this vaccine candidate, as there was another incidence of multiple sclerosis during its trial in July, which was later determined to be unrelated to vaccines. Similarly, in October 2020, Janssen Pharmaceutical Company announced that it is halting further dosing in their COVID-19 vaccine trials, due to safety concerns arising from an incidence of unexplained illness.[34] However, the company has announced it is preparing to resume recruitment for its COVID-19 vaccine trials since no evidence of the vaccine causing the illness was found.[34] The incidence of unexplained illnesses and subsequent pauses of these trials highlights the importance of large-scale phase 3 trials in determining the safety of vaccines in the general population.

Conclusion

In summary, all three experimental vaccine candidates reviewed, ChAdOx1 nCoV-19, Ad5-nCoV, and mRNA-1273, have shown strong immunogenicity and safety profile in their respective phase 1 or 2 human clinical trials. All three vaccine candidates are expected to conduct their respective phase 2 or 3 clinical trials as soon as possible, as well as following up with the participants involved in their published trials.

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The history of neuro-oncologic surgery

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Abstract

While the first autopsy description of a brain tumour was published in the early 1600s, the first successful surgical treatment of a brain tumour did not take place until over 200 years later by William Macewen, initiating the era of modern neurosurgery. Several advancements had to take place in the late-modern era before this was possible. With the advent of anesthesia, surgeons were able to undertake more complex procedures, fostering the development of the meticulous surgical techniques that characterize the field today. Soon after, the development of aseptic technique pioneered by Joseph Lister began to combat the problem of infection which stifled surgical progress in the centuries before its introduction. Thanks to aseptic techniques, the mortality rate of surgeries showed good improvement and made it safer for patients to go under the knife. One last requirement for brain tumour surgery in an era without modern-day neuroimaging technology was the development of cerebral localization, which guided surgeons to the location of lesions in the brain and informed them of which regions were crucial for quality of life of the patient, and thus to be avoided. Therefore, with these three key developments, modern neurosurgery was able to gain a foothold with the first meningioma resection by Macewen, followed by several others in the decades to come. Progress in brain tumour surgery hit its stride in this era with Harvey Cushing and his introduction of meticulous surgical practices, his revolutionary insight into the importance of adequate intracranial pressure control, and finally the introduction of hemorrhage control through numerous techniques. Legacies of the work of early neurosurgeons can be seen in the 21st century as many of the concepts and techniques remain today, albeit moulded and refined over time.

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Introduction

As one of the world's arguably oldest "surgical speciality," the roots of neurosurgery stretch deep into history beginning in the Neolithic period where ancient practitioners used trephination, or drilling holes to open the human skull. The purposes of this technique are unclear, though it is speculated that it was performed for medical and mystical reasons. Famed physician and historian William Osler (1849-1919) wrote that it "was done for epilepsy, infantile convulsions, headache, and various cerebral diseases believed to be caused by confined demons to whom the hole gave a ready method of escape".[1] There is little mention of brain tumours in ancient literature, though it is likely that some of these trephinations were done on patients with brain tumours as the indications for trephination have many overlaps with symptoms of brain tumours, including seizures, changes in behaviour, and headaches. The existence of tumours in the brain was probably unknown until the first autopsy description of a brain tumour was published in 1614 by Felix Plater (1536-1614), a Swiss physician.[2] In an autopsy performed on a man who "lost his mind," Plater discovered an apple-sized encapsulated intracranial tumour that was compressing the brain – a likely meningioma.[2,3] Surgical treatment of brain tumours would not take place until over 200 years later in 1879 with the first successful removal of a meningioma in a young woman by William Macewen (1848-1924), launching the era of modern neurosurgery. Brain tumour surgeries continued to expand as surgical knowledge and technique improved with time, but it was not until the time of Harvey Cushing (1869-1939) that great strides in brain tumour surgeries were made. Cushing, who is thought to be the father of brain tumour surgery, is credited with ushering in a new mindset and style in neurosurgery that would radically change the practice for years to come. Examination of the history of brain tumour surgery illuminates key aspects of the development of neurosurgery as a specialty. In this article on the history of neuro-oncologic surgery, I will discuss the obstacles preventing successful brain tumour surgeries and the technologies that allowed early neurosurgeons to circumvent these challenges, effectively paving the way for the development of neurosurgery as we know it today.

Anesthesia

In the 19th century, two important developments propelled the surgical field in general into a new era of advancement: anesthesia and asepsis. Without these two discoveries, the ability to open the skull and remove tumours in an effective manner would not be possible. William Morton's (1819-1868) demonstration of the anesthetic effect of ether vapour in 1846 during a neck tumour surgery at Massachusetts General Hospital (Figure 1) was a seminal event in the history of surgical anesthesia as it showed

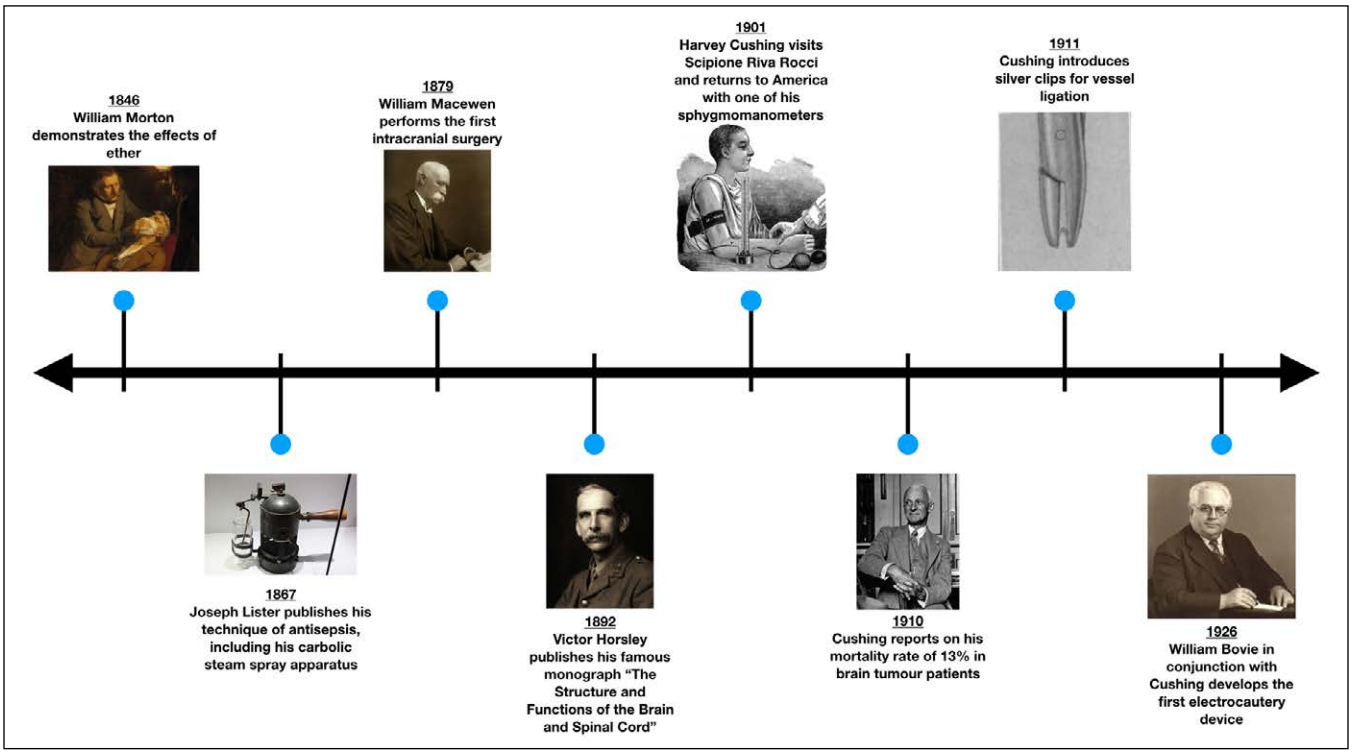

Figure 1. Timeline of seminal events in brain tumour surgery

that anesthesia could be possible and practical.[4] Shortly after, chloroform was introduced by James Simpson (1811-1870) in 1847.[5] Much debate occurred in the neurosurgery sphere in the late 19th century with respect to the merits of ether versus chloroform. Pioneer neurosurgeon Victor Horsley (1857-1916) performed numerous experiments on animals and came to the conclusion that while ether was indeed safer, as it was less toxic to nervous tissue and increased rather than decreased blood pressure, it also caused much "troublesome haemorrhage" and unpleasant post-operative side effects such as headache and vomiting.[6,7] Chloroform, on the other hand, did not aggravate bleeding and had less potent post-operative side effects, but was more dangerous as it affected the respiratory centre in a dose dependent manner. Thus, in light of this, Horsley advocated for using chloroform in carefully regulated doses within precisely tested secure concentrations to avoid respiratory paralysis.[6] However, as evidenced by Harvey Cushing, American surgeons' preferences with regard to anesthetic agents differed from their European counterparts: "In this country [America], where chloroform is doubtless administered less well than ether, the latter is the anaesthetic of choice…"[7] Due to his involvement in an intracranial case using chloroform that tragically turned fatal, Cushing preferred a safer approach and favoured ether over chloroform for this reason, despite being impressed by chloroform's efficacy.[7,8] For Cushing, chloroform should be reserved for multi-staged procedures so as to avoid repeated etherisation and for shorter paediatric cases.[7]

Asepsis

While anesthesia allowed surgeons to operate more deliberately and spared patients great suffering, infection control served as another imposing barrier to neurosurgical progress prior to the 19th century. Elective surgery remained inaccessible since up to 80% of surgeries resulted in hospital gangrene and a mortality rate of nearly 50% for patients undergoing major surgery.[9,10] Louis Pasteur's (1822-1895) work on germ theory in the 1800s deftly overturned the widely-held belief in spontaneous generation and postulated that putrefaction in meat was due to living micro-organisms. Extending off this work, Joseph Lister (1827-1912) used Pasteur's discovery to explain the suppuration of wounds and in 1867 he published his new technique of disinfecting wounds, surgical instruments, and the air surrounding the operating site using a special machine that misted carbolic acid (Figure 1).[11] With this new technique, Lister was able to show in detailed case histories the successful outcomes tied to his new technique; among the few statistics he reports, he demonstrated a drastic reduction of mortality from amputations from 45% to 15%.[12,13] In 1876, Lister toured the United States in order to convince surgeons about surgical antisepsis. In attendance at one conference in Philadelphia was a reputable cranial surgeon, William Keen (1837-1932), who avidly took up Lister's principles and became one of the first surgeons in America to implement them.[14] Improvements on aseptic practices came in the following years with the introduction of heat sterilization of instruments, sterile gowns and caps, surgical masks, and rubber gloves all before the turn of the 20th century. General acceptance and compliance with aseptic principles, on the other hand, would take much longer to permeate the surgical setting.[9]

Cerebral Localization

Though anesthesia and asepsis revolutionized the surgical sphere, there was one missing piece of the puzzle for adequate brain

tumour resection: localization of lesions. By understanding the functions of the various parts of the brain, clinicians were able to determine the site of a lesion based on bedside clinical examination. While it was important to know where in the brain to operate, where not in the brain to operate was arguably just as important since surgery in areas such as those responsible for speech and motor function could have catastrophic consequences for the patient. The concept of cerebral localization allowed surgeons to diagnose patients with improved accuracy and kickstarted the field of neurosurgery.[15] Historians have noted that localization served as an "important epistemic break that signals the rise of modern brain surgery".[16] While it was known that the brain was responsible for perceptive, cognitive, and affective processes since Hippocrates, it was not until the 18th and 19th centuries that specific functions of specific parts of the brain began to be discovered.[17] One of the greatest contributors to the field in the late-modern period was John Hughlings Jackson (1835-1911), who is often called the "Father of Neurology." He was known to be meticulously precise in his clinical observations and histories. Until Hughlings Jackson's discovery, the medulla oblongata was thought to be the source of seizures. However, Hughlings Jackson remarked that patients who suffered blunt head trauma often had hemiplegia on the contralateral face and body. Furthermore, if seizures developed in these patients, they would manifest most often on the hemiplegic side of the body.[18] Hughlings Jackson is also well known for his description of seizure patterns where convulsions would start in one part of the body and travel to the next in a sequential and predictable fashion. For example, convulsions might start from the hand, spread to the arm, and then involve the face. Now dubbed the "Jacksonian march," this observation allowed Hughlings Jackson to hypothesize that the cortex was divided into discrete areas that controlled different parts of the body, and that these cortical areas were contralateral to the body part that they controlled.[19] Epileptic activity would move along the cortex and sequentially involve different areas in accordance to a homunculus. Hughlings Jackson's work would set the groundwork for Gustav Fritsch and Edvard Hitzig who later provided evidence of the existence of a motor cortex in dogs in 1870.[20]

Studies of patients with lesions in various regions of the brain would also provide important hypotheses as to the functions associated to those regions. Pioneering work by scientists such as Paul Broca (1824-1880) and Carl Wernicke (1848-1905) on patients with language defects who later had post-mortem autopsies would give us insight into the structural correlates of language processing in the brain.[21] Some scientists went beyond lesion studies and turned to the laboratory to obtain evidence for cerebral localization. David Ferrier (1943-1928), a respected British neurologist, performed experiments on apes, using electrical stimulation on the primate cortex to produce finely detailed cortical maps.[18] Ferrier's work confirmed many hypotheses set forth by Hughlings Jackson. Horsley also performed ablative experiments on the brain and spinal cord of monkeys and finally published his famous monograph "The Structure and Functions of the Brain and Spinal Cord" in 1892 (Figure 1).[22] All of these works on cerebral localization in the 19th and 20th century would prove immensely useful to neurosurgeons as they navigated through the murky waters of the brain.

Thus, the important information gleaned from work from contributors to the field of cerebral localization, combined with the advent of anesthesia and improvement of infection rates via aseptic techniques pioneered by Lister, gave late-modern neurosurgeons bolstered confidence to perform more complex and daring procedures. In 1881, William Macewen reported in The Lancet of a successful operation for a left-frontal meningioma removal in a 14 year old girl – the first intracranial tumour removal in human history (Figure 1).[23] The girl presented to the Glasgow Royal Infirmary with a firm swelling above the left orbit as well as left-sided headaches and a left pupil that was contracted and unresponsive to light. She soon developed right-sided focal seizures that secondarily generalized and then eventually status epilepticus and clinical deterioration. While he was aided by the hyperostosis of the skull just above the left orbit, Macewen was able to localize the tumour by a number of clinical features: the left fixed pupil, the headaches on the left, and the seizures that commenced on the right side. Macewen used the external deformity as a landmark and was able to enter the skull and remove the tumour from the dura. The girl survived the operation and gradually recovered from post-operative hemiplegia and seizures.[18] The girl was engaged in regular employment and would live for 8 more years before passing away due to Bright's disease.[14] Macewen would go on to perform 21 other neurosurgical cases by 1888 with 18 successful recoveries and only 3 deaths. These promising results were attributed by him to "cerebral localization and good aseptic technique".[14] Macewen's seminal surgery would kickstart the era of modern neurosurgery, and soon following were highly publicized brain tumour surgeries by Alexander Bennett (1848-1901) and Rickman Godlee (1849-1925) in London in 1884 and William Keen in America in 1884.[14,16]

Intracranial Pressure

No discussion about the history of brain tumour surgery is complete without mention of one the pioneers of modern neurosurgery: Harvey Cushing. When Cushing began his career at Johns Hopkins in 1901, the mortality rate for intracranial tumour surgeries was a dismal 19-50%, depending on the location of the tumour, according to Ernst von Bergmann.[24] The cause of increased mortality was due to cerebritis and meningitis secondary to brain fungation from high intracranial pressure (ICP).[25] Most people in the late 19th century had only a vague idea of ICP.[26] Cushing set out to Europe in 1900 to conduct an academic Wanderjahr and ended up working in the laboratory of the physiologist Hugo Kronecker (1839-1914) after being introduced by Theodor Kocher (1841-1917). It was in Bern, Switzerland where he started his groundbreaking work on the physiological effects of increased ICP. By manipulating the ICP of small animals using an intracranial bag of mercury while measuring the blood pressure and pulse, Cushing was able to demonstrate a rise in blood pressure and a decrease in pulse with a rise in ICP. He summarized it as such:

> *"As a result of these experiments a simple and definite law may be established, namely, that an increase of intracranial tension occasions a rise of blood pressure which tends to find a level slightly above that of the pressure exerted against the medulla. It is thus seen that there exists a regulatory mechanism on the part of the vaso-motor centre which, with great accuracy, enables the blood pressure to remain at a point just sufficient to prevent the persistence of an anaemic condition of the bulb, demonstrating that the rise is a conservative act and not one such as is consequent upon a mere reflex sensory irritation."*[27]

Today, the triad of hypertension, bradycardia, and irregular breathing – signs of increased ICP – is named "Cushing's triad" in his honour. When Cushing returned to America from his travels in Europe, he began to put into practice the concepts he discovered through his research. Cushing brought with him a device called the Riva-Rocci apparatus, which was an Italian device for measuring blood pressure, and pushed for the measurement of pulse, respiration, and blood pressure intraoperatively (Figure 1). On his reasoning behind measuring the blood pressure, Cushing stated: "Such a record not only furnishes instructive generical data, but often furnishes a means of properly interpreting the effects, whether beneficial or otherwise, of the various operative steps".[28]

Cushing also applied his principles to the treatment of intracranial tumour patients. Recognizing the need to primarily control the ICP in order to avoid high mortality, Cushing planned his operations in stages. When a patient presented with clinical signs of high ICP, including headache, vomiting, and papilledema, Cushing would first perform a decompressive craniectomy in order to relieve high ICP without even trying to localize the tumour – controlling the ICP was paramount.[26,29] Sometimes he even completed two preliminary decompressions before localizing and removing the tumour in a secondary stage. While Cushing was uncertain if this was the right measure at the time, his persistence and ingenuity paid off. In 1910, Cushing reported on 180 tumour patients that he had operated on and claimed a mortality rate of merely 13%, a vast improvement over the near-50% rate at the beginning of his career (Figure 1).[25,30]

Hemorrhage

Once Cushing had a handle on the problem of ICP, he turned to the next great obstacle in brain tumour surgery: bleeding. Neurosurgery is quite different from other fields of surgery by virtue of the material that neurosurgeons work on. While techniques such as sutures and clamps could be used for hemostasis in general surgery, neural tissue is much too delicate for conventional techniques. Accordingly, neurosurgery had to be done slowly and with scrupulous hemostasis. Cushing, who trained under William Halsted (1852-1922), developed a reputation for being a meticulous surgeon like his mentor. Halsted and Cushing were part of a newer generation of surgeons who turned away from the showy, rapid style of surgery that dominated the surgical sphere in the first half of the 19th century.[31] Cushing employed careful surgical procedures which helped with both infection and blood loss. On the importance of careful hemostasis and slow operating, Cushing wrote:

> "*Neighborhood oozing obscures the clear view essential to the safety of such delicate manipulations as are required for the removal of, let us say, a lateral recess tumor or the trigeminal ganglion; whereas a more general loss of blood with the consequent lowering of arterial tension is a cordial invitation to its near relative shock, favors the onset of respiratory paralysis in cases associated with medullary pressure, makes anaesthesia more dangerous, and lowers resistance to infection through secondary anaemia.*"[32]

Blood loss was a safety issue for multiple reasons, both intraoperatively for the surgeon to operate and for the stability of the patient. As intracranial procedures became more and more complex, they became lengthier and more tedious due in large part to the fact that hemostasis was very time consuming. The risk of hemorrhage, especially with highly vascular tumours, had the potential to delay surgery to a second or even third stage. Cushing developed a number of technical advancements in order to combat this threatening problem. Cushing employed techniques such as using living tissue from the temporal muscle, pieces of formed blood clots, and small pledgets or gauze attached to a black ligature to encourage hemostasis. In 1911, he introduced silver clips consisting of U-shaped pieces of wire that were held in the jaws of clamps and could be directly applied to blood vessels in delicate regions too awkward for ligation (Figure 1).[32] Finally, in one of his greatest contributions to hemostasis, Cushing, in collaboration with William Bovie (1881-1958), introduced the use of electrocautery in neurosurgery (Figure 1).[33] This technique involves passing a high frequency current to cut and coagulate tissue. While initially met with skepticism from surgeons at the time, the technique was efficacious in stopping bleeding and is still used to this day.[34]

Conclusion

The state of brain tumour surgery is often seen as a proxy of the state of neurosurgery as a whole.[35] Throughout the late-modern period, brain tumour surgery and neurosurgery in general underwent significant overhauls in ideas, styles, and technologies and continued to build upon themselves. With the advent of anesthesia, asepsis, and cerebral localization, early neurosurgeons in the late-modern era were able to begin operating in the brain and attempting to remove tumours. Further improvements in ICP control and hemorrhage were introduced by Harvey Cushing in the early 1900s and progress in neurosurgery hit its stride. Neurosurgery as we know it today is celebrated as a triumph of humanity. The latest data on the outcomes of malignant brain tumours shows an average five-year relative survival rate of 35.8% going up to 74.7% in children due in large part to advances in neurosurgery, chemotherapy, and radiation therapy.[36] This advancement would not have been possible without the contributions of the pioneering scientists and neurosurgeons of the late-modern era. While great advancements have been made in neuro-oncology since Macewen's time, much work remains in neurosurgery to improve outcomes for patients with deadly tumours such as glioblastoma and anaplastic astrocytoma.

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Polypharmacy in the age of COVID-19: medication management during a pandemic

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Abstract

Polypharmacy has been implicated in adverse drug events, excessive healthcare spending, and complications in the management of COVID-19. Multimorbid older adults suffer some of the most severe COVID-19 health outcomes and are at the highest risk of polypharmacy. This article aims to highlight the issue of polypharmacy in the context of the current pandemic and suggests several interventions to minimize the disruption of effective care for at-risk populations. Such interventions include coordinating care delivery, changing physician prescribing attitudes, and improving patient health literacy. Polypharmacy is a major contributor to the risk of adverse drug events before, during, and after COVID-19 treatment. Managing polypharmacy is therefore critical to the provision of patient care during the pandemic.

Introduction

In 2016, roughly one-third of elderly Canadians were prescribed five or more different classes of medications.[1] These medications were frequently prescribed in physician offices and hospitals, often to manage the effects of other medication side effects in dangerous prescription cascades.[2] This issue has been widely identified as polypharmacy – defined as the presence of five or more medications daily.[3] Polypharmacy has increased worldwide and has been implicated in adverse drug events (ADEs) contributing to nearly 10% of hospitalizations among the elderly.[4-6] Polypharmacy has also been associated with an increased risk of falls, heart failure, hospitalization, malnutrition, impaired cognition, and, most notably, COVID-19.[6-10]

Polypharmacy is common in older adults, where multimorbidity increases the risk of severe COVID-19 outcomes, including mortality.[3] COVID-19 infections in older adults also present atypically due to several factors including age, comorbidities, and associated polypharmacy.[11] High risk prescribing may also increase risk of infection and adverse events. For example, chronic administration of NSAIDs may be linked to increased expression of ACE2, a potential entry point for SARS-CoV-2 into cells.[12] Prolonged corticosteroids may also increase the risk of viral replication and adverse events.[13] This article argues that coordinating care delivery, changing physician prescribing attitudes, and improving health literacy are useful interventions to minimize the impact of polypharmacy on patients during the COVID-19 pandemic.

Factors contributing to polypharmacy

The causes of polypharmacy can be divided into two categories: patient-related and systems-related. Patient-related factors include attitudes regarding prescribing patterns, as well as knowledge deficits regarding alternative treatment plans and deprescribing options.2,[14,15] Systems-related factors include uncoordinated healthcare delivery and practitioner attitudes.[16-18] For physicians, interventions to mitigate polypharmacy may include: 1) coordinating care delivery through electronic health tools for medication reviews, 2) modifying prescribing attitudes by limiting medications to those recommended by clinical practice guidelines and deprescribing unnecessary medications, and 3) improving patient health literacy.[11,19,20] These interventions can directly improve patient outcomes by safely reducing potentially inappropriate medications (PIMs), which may result in a reduction in all-cause mortality (OR=0.74, 95% CI=0.65-0.84) and falls (OR=0.76, 95% CI=0.62-0.93).[21]

Coordinating care delivery

Uncoordinated care delivery among older patients suffering from multiple chronic diseases contributes to polypharmacy. Coordinated care may be severely lacking for patients bouncing between specialists, hospitals, and family physicians, often resulting in compounding prescriptions.[16] Family physicians have expressed frustrations with extensive medical histories of patients alongside the many changes made during hospital or specialist visits, feeling pressured to continue prescribing according to prior plans made by specialists, and existing guidelines.[14] Since COVID-19 is a multisystem disease largely afflicting older adults with multiple chronic diseases, such patients require personalized comprehensive assessments to optimize medication management.[22] Gaps in care coordination can contribute to polypharmacy during the pandemic and therefore increase the risk of ADEs in this at-risk population.

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While coordinated care delivery has been highlighted as an effective means of managing polypharmacy, it requires a coordinated effort across prescribers, nurses, and pharmacists.[23] One such effort was the 'Care by Design' (CBD) model in a long-term care setting, which showed a decrease in residents with polypharmacy from 86.8% pre-CBD to 79.5% post-CBD (p=0.046).[24] The mean number of medications per resident also decreased from 16.7 (SD 5.6) to 15.5 (SD 6.2) (p=0.037), but not overall use of potentially inappropriate medications (PIMs) (86.2% versus 81.1%, p=0.16).[24] Therefore, coordinating care delivery during the pandemic could provide patients with continued access to medication reviews between providers, thereby reducing the risk of polypharmacy.

Physician prescribing attitudes

Physician prescribing attitudes also contribute to persistent polypharmacy.[25] For example, some physicians may believe that patients expect them to prescribe medications in response to medical complaints and that their patients have no qualms regarding polypharmacy.2,[14] In 2002, almost two-thirds of physician visits ended with a prescription.[26] Rigid adherence to guidelines also leads to an increase in the number of prescriptions for each medical issue, further contributing to polypharmacy.[2,14,17] In some cases, physicians may find it easier to provide prescriptions to frail elderly patients rather than engaging in collaborative decision-making.[17] A recent study found that physicians who ranked the number of medications (p=0.007), risk/benefit information (p=0.017), and the utilization of medication optimization tools (p=0.05) as more important prescribed fewer medications.[27] Less than half of Canadian seniors reported having the potential side effects of medications explained to them by practitioners.[18]

Despite 50% of older Canadians stating they would like to reduce the number of medications they are taking, over 80% would agree to take on more medications if their practitioner deemed it necessary.[28] If, however, physicians sought to deprescribe and simplify medication regimens, they could reduce the risk of medication-related harms during COVID-19 symptom management.[20] A systematic review supports this view, where seven of nine deprescribing studies reported statistically significant reductions in PIMs in the group that sought deprescription.[29] Medication regimens could be simplified by emphasizing patient goals through narrative-based techniques and utilizing shared decision-making models to help patients feel more at ease and willing to disclose information.[26,30-34] The result would ensure that prescriptions match patient goals for care, ultimately reducing the number of PIMs.

Health literacy

The COVID-19 pandemic has highlighted the necessity of health literacy for the effective detection, diagnosis, prevention, and management of communicable diseases.[35,36] This extends to patient knowledge of deprescribing options, identification of potential opportunities for deprescribing, and patient engagement, all contributing to effective approaches to medication management and COVID-19 treatment.[15] Many patients may not know the names of prescribed medications or even their role in treatment, instead only remembering them by colours and dose.[37] Others may believe they have no choice but to continue with medications because stopping them may mean immediate death.[2] Patient knowledge deficits are also influenced by attempts from pharmaceutical companies to encourage patients to seek novel treatments for medicalized issues that may be unnecessary or inappropriate.[2,38] This knowledge deficit increases the risk of PIMs, furthering the risk of ADEs. For example, a recent study found that of over 700 older patients suffering from polypharmacy, only 15% were able to recall indications for each of their medications.[39]

Furthermore, in a questionnaire assessing the impact of consumer-targeted deprescribing initiatives of 352 participants, 78.5% (95% CI 74.2-82.8) had no change or gained trust in choice of medical care, 75.4% (95% CI = 70.7-79.8) appreciated transparency in communication, and 81.9% (95% CI = 77.9-86.0) noted increased trust in their provider.[40] Interestingly, among older patients with lower health literacy, PIMs (OR=1.89, 95% CI=1.15-2.79) and polypharmacy (OR=1.20, 95% CI=1.03-2.15) were more likely.[41] A recent study also found that medication reviews could lead to a mean reduction of 2.36 medicines (SD 1.53) through the deprescribing process, ensuring that currently prescribed medications do not have ADEs and are required for treatment.[42,43] Patient education regarding medication reviews can therefore help simplify medication management during the pandemic, which this paper has already highlighted as beneficial to both patient and practitioner. Encouraging deprescribing education for patients will therefore change patient attitudes towards medication management.[44]

Conclusion

Effective medication management and the importance of deprescribing have been highlighted by the effects of polypharmacy on at-risk patients during the COVID-19 pandemic. If physicians are responsible for starting medications, then it seems reasonable that they manage their rational deprescribing.[45] While long-term changes to address polypharmacy beyond the pandemic will involve engagement with policymakers and drug regulators, clinicians are poised to address the immediate challenges of the situation. This paper has highlighted several possible interventions to reduce potential ADEs in at-risk populations during and after the pandemic. These include coordinating care delivery, modifying physician prescribing attitudes, and improving patient health literacy. Polypharmacy is a major contributor to risks associated with potential ADEs before, during, and after COVID-19 treatment. It is therefore recommended that practitioners consider these issues to ensure effective care during the pandemic.

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The ABCs of COVID-19 in children

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Abstract

Coronavirus Disease 2019 (COVID-19) has become notorious for its transmissibility and virulence among adults and the elderly. However, it is becoming increasingly clear that children are not spared from the grips of this infectious disease. As the six-month anniversary of the pandemic approaches, a notable rise is evident in pediatric COVID-19 cases, particularly severe cases. Yet, coronavirus-related research has been concentrated towards older demographics, the result of which is an insufficient understanding of the disease in children. This makes it more difficult to manage severe pediatric cases in clinical settings. This narrative review presents a summary of COVID-19 literature from a pediatric lens, as it is understood today. It consolidates the range of clinical features observed in child-related cases, evaluates the features unique to pediatric patients and explores the unprecedented spike of multisystem inflammatory conditions coinciding with the pandemic. Regarding the current understanding of COVID-19 in children, three areas requiring further research were identified. First, clinical trials determining the safety and efficacy of remdesivir, and other drug candidates, must be elucidated in pediatric patients. A shift towards larger-scale, multicenter case studies are also needed when examining the poorly understood, child-specific COVID-19 features that have been observed. Further investigation into these features, which include delayed symptoms, prolonged viral presence, and prevalence of asymptomatic cases, may help in achieving a better understanding of the disease pathogenesis in children. Finally, the effectiveness of interventions like aspirin for long-term complications of inflammatory conditions associated with COVID-19, must be established. It is imperative to elucidate the pathogenesis of COVID-19 and gain a better understanding of treatment guidelines for children to manage the mounting rates of infection and cases of increased severity observed in this young demographic.

Introduction

Coronavirus disease 2019 (COVID-19) is a novel respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] Originating from Wuhan, China, this infectious disease swept across the globe in a matter of months and was declared a pandemic by the World Health Organization (WHO) on March 12th, 2020.[2] During the beginning of the pandemic, the largest rates of infection and mortality were seen in the elderly, followed by the adult demographic.[3] These observations stand in contrast to scarce reports of pediatric infection and even fewer instances of child-related mortality.[4,5] With such a large contrast in the way COVID-19 was affecting the young compared to the old, it was initially understood that children were relatively safe from the disease. They appeared to have lower susceptibility to infection and demonstrated resilience against the effects of COVID-19 when infected, since most cases remained mild in severity.[6,7]

Now, almost half a year after the declaration of the pandemic, the understanding of COVID-19 in children is evolving. The pediatric demographic still maintains the lowest rates of infection and mortality.[8] However, child-related cases have been on the rise. A systematic review published in March, estimated that children accounted for 1-5% of diagnosed cases, with the majority of data coming from China.[5] More recent data from July reported that children represented 8.4% of COVID-19 cases in America, increasing 44% from the beginning to the end of the month.[9] Even more concerning is the rise in severe child-related cases. This is reflected by soaring rates of pediatric intensive care unit (ICU) admissions as well as the unprecedented increase in multisystem inflammatory conditions associated with COVID-19.[8,10,11]

However, accompanied by this rise is the current underrepresentation of children in coronavirus research. This is due, in part, to insufficient information gained during the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) outbreaks which occurred in 2002 and 2012 respectively.[12] These coronavirus epidemics saw low numbers of child-related cases, resulting in limited knowledge to help guide pediatric COVID-19 research today.[12] This is further compounded by current research efforts which are focused predominantly on adults and the elderly. While there is a greater need for research targeted towards older demographics in the current climate, it results in gaps of knowledge regarding COVID-19 in children. Given the rise

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in severe child-related cases, it is more important now than ever before to conduct pediatric-focused research. An improved ability to understand and treat the clinical features unique to young COVID-19 patients may help to achieve better clinical outcomes in this demographic.

This article analyzes existing literature to provide an up-to-date account of the ABCs regarding the clinical presentation of COVID-19 from a pediatric perspective so as to elucidate where further research is needed.

Methods

This article is a narrative review. A primary search was conducted on MEDLINE, PubMed, and Google Scholar databases using the following terms: COVID-19 [OR] SARS-CoV-2 [OR] coronavirus [AND] children [OR] pediatric [AND] clinical features [OR] prognosis [OR] Kawasaki disease. Literature was included if it was in English, published before August 17th, 2020 and reported on the clinical features of COVID-19 in children. To increase the comprehensiveness of the review, there were no limitations placed on study methodologies, and preprints were included. A secondary search for grey literature was performed to obtain more timely data and additional information as COVID-19 is a novel disease with limited publications pertaining to children. The same search terms and inclusion criteria were used for the secondary search with the exception of the inclusion date which was extended to August 28th, 2020 to obtain live data from specific databases including clinicaltrials.gov and Virtual Pediatric Systems (myvps.org).

Clinical Features of COVID-19 in Children

Mild - Moderate Clinical Features

Children of all ages, from newborns to adolescents of 17 years can contract COVID-19.[13] The majority of child-related cases, especially during the beginning of the pandemic, have been reported as mild to moderate in severity and mortality is still currently considered rare.[4,14-18] In fact, a pediatric case study completed between January and February observed that over 90% of the 2143 cases involved were asymptomatic, mild, or moderate infections.[7] Most clinical features of viral infection have been observed to last for 1 to 2 weeks and in general, children have presented with symptoms similar to those in adults.[14] This includes the most commonly observed symptoms of fever and cough as well as sore throat, rhinorrhea, sneezing, diarrhea, vomiting, dyspnea on exertion, myalgia and fatigue.[4,14,16,17,19] Children in particular have been observed to present with co-infection frequently. This has been evident through elevated levels of procalcitonin and the detection of influenza A or B, cytomegalovirus, and respiratory syncytial virus.[4,14]

Pediatric cohort studies have also often reported children to present with more upper than lower respiratory tract symptoms.[14] Some studies have even recorded an absence of pulmonary problems and abnormalities on chest x-ray results altogether.[4,16] It is possible that, in children, infection is more likely to be contained in the upper respiratory tract which may explain why viral infection presents mildly in the majority of cases. Of note, not all of the existing data is consistent with this theory. One case in particular reported 3 out of 4 asymptomatic children to present with chest abnormalities in computed tomography (CT) scans.[20] As such, there may be other reasons for the high prevalence of mild pediatric cases.

Severe - Critical Clinical Features

While the majority of children experience mild infection, cumulative data on North American cases indicate a rise in severe pediatric infections. At the start of April, there was 1 pediatric intensive care unit (ICU) admission and by the end of August, there was a total of 1253 ICU admissions among this demographic.[10] Furthermore, a recent study by the Centers for Disease Control and Prevention (CDC) reported that 1/3rd of children hospitalized due to COVID-19 were admitted into the ICU.[8] This mirrors ICU rates of adult cases and indicates that, in the pool of children who do get infected, the proportion of severe cases is now observed to be similar to the proportions seen in adults.[8]

Children who are particularly at a high risk for severe infection include infants and younger children as well as those with a history of congenital or acquired diseases.[4,14] The severe cases in children have typically developed into pneumonia and have involved a variety of pulmonary symptoms such as moist rales, dyspnea and cyanosis.[4,17] The further deterioration of cases are typically reflected by a progressive reduction in lymphocyte and platelet count accompanied by an increase in transaminase or creatine kinase levels.[4,17] These observations have indicated the development of acute respiratory distress syndrome (ARDS), respiratory failure, shock, coagulation disorders, and organ dysfunction and failure.[7,17] In many severe and critical pediatric cases, children have presented with gastrointestinal symptoms during the onset of their infection.[7,17] The same observation has been made with adult cases, indicating that gastrointestinal symptoms may be a marker for disease severity.[21] See Table 1 for a summary of the clinical features of COVID-19 in children.

Pediatric cases that become severe or critical can be especially difficult to treat. Until recently, experimental drug candidates for COVID-19 treatment have only been available to patients involved in the corresponding clinical drug trials, the inclusion criteria for which have mostly been exclusive to specific adult demographics.[22] Now, drugs like remdesivir have become available to those outside of clinical trials through expanded access programs and the implementation of emergency use authorization.[22,23] Clinical trials involving pediatric cohorts have also been increasing since the beginning of the pandemic, and by August 28th there were 165 registered pediatric clinical trials around the world.[24] However, compared to the 1785 total clinical trials currently occurring, the inclusion of children only account for 9.2% of ongoing trials.[24] Furthermore, only 9 of the 165 trials with pediatric inclusion have completed recruitment to date.[24] Given the current situation, the existing body of COVID-19 literature lacks published results on the safety and efficacy of drugs like remdesivir for the pediatric demographic.[23,25] Therefore, although certain drugs have become more widely authorized for use, physicians do not have a lot of guidance on how to treat the severe cases they encounter.

Peculiar Clinical Features Unique to Pediatric Cases

The following clinical features are peculiar observations which have been made in pediatric cases. Certain observations with no identified cause warrant further investigation which may help to elucidate a better understanding of COVID-19 in children.

Lower Rates and Milder Infection in Children

The main difference between viral infection in children when compared to adults, is the significantly lower rates of infection and milder cases in the pediatric demographic, especially during the beginning of the pandemic.[7] These are perplexing observations because children are considered to have greater vulnerability to respiratory tract infections due to their developing immune systems.[4] Children even account for the largest portion of influenza infection rates annually.[26] However, as with the previous coronavirus epidemics, SARS and MERS, children appear to be the demographic that is least affected by COVID-19.[12] In current literature, there are a handful of postulations which may provide an explanation for this. It is important to note, however, that the following theories may evolve in the coming months as more cases of greater severity emerge in the pediatric demographic.

1. Children are less mobile than adults and generally have less exposure to virions.[14] In fact, most children are infected through intrafamilial transmission.[14] Furthermore, ribonucleic acid (RNA) viruses including those in the coronavirus family, are prone to mistakes in replication and mutation which decreases their virulence.[16] Therefore, infection from a family member via a second or third generation virus may be less likely.[16]
2. Children may have immune systems that are better equipped to fight the virus. The hypothesis is that children have more active innate immune systems which are more effective in producing early responses to fight off infection from COVID-19.[16] This observation was made with the two previous coronavirus outbreaks, SARS and MERS, and may explain why the symptoms of many pediatric patients are observed to remain in the upper respiratory tract.[16] There is, however, an opposing theory that children have weaker innate immune systems which induces less of a response to infection.[6] This results in less systemic inflammation and subsequent organ damage.
3. Viral entry may occur less often with lower effectiveness in children when compared to adults. SARS-CoV-2 gains entry into host cells primarily through angiotensin-converting enzyme 2 receptors.[15] The expression of this receptor may be lower in children as they are still developing, and this decreases the potential for viral entry.[6,16] These receptors may also be less developed in children and may not function as well for viral entry as the corresponding receptors in adults.[6,16]
4. Children have healthier and stronger bodies than adults. They are less likely to have risk factors for COVID-19 including underlying diseases, smoking tendencies, and exposure to pollutants.[14] This means that their chance of catching infection is lower than that of adults, and children that do get infected can fight off the virus with more ease.
5. Co-infections appear to be more prevalent among children when compared to adults.[4,14] The presence of other viruses may create competition and keep SARS-CoV-2 from proliferating as abundantly when compared to those without co-infection.[14] Furthermore, antibodies formed against concurrent infections may provide additional defenses against SARS-CoV-2.[6]

Delayed Onset of Symptoms and Prolonged Viral Presence

In a study comparing COVID-19 in children to their adult family members, it was reported that symptoms took longer to appear in 5 of the 6 children compared to adults in the same family.[16] Moreover, the same 5 children tested as COVID-19 positive for a longer duration than adults.[16] These children, who were discharged after 2 negative reverse transcription-polymerase chain reaction (RT-PCR) nucleic acid tests, were even recalled when stool samples tested positive, while no adults were recalled.[16] It is not understood why the onset of symptoms were delayed in the same children that presented with prolonged viral presence.[16] However, this phenomenon supports the hypothesis that the virus has a different pathogenesis in children compared to adults.

Prevalence of Asymptomatic Cases in Children

There are varying reports presenting on the frequency of asymptomatic children. A meta-analysis with case reports mainly from China indicated that 17.4% of children presented as asymptomatic while a study in France involving 438 children found that 45% of patients were asymptomatic.[27,28] Furthermore, in the study comparing infection in children to that of their adult family members, results indicated a predominance of asymptomatic cases in children.[16] Additionally, 66% of children were asymptomatic while only 28% of adults lacked symptoms.[16] With a range between 17.4% and 66%, asymptomatic COVID-19 cases in children are considered to be prevalent and may have even contributed to the reason why infection rates in children are recorded to be so low. Moreover, data reporting a higher frequency of asymptomatic cases in children suggest that the virus may act differently in children when compared to adults.

See Table 1 for a summary of the peculiar clinical features of COVID-19 that are unique to children.

Kawasaki Disease and Multisystem Inflammation in Children

The understanding of COVID-19 is further complicated by the surge of Kawasaki disease (KD) and similar multisystem inflammatory conditions observed in children during the pandemic. The timing of this influx in cases draws concern over its relation to COVID-19 and calls for the reevaluation of disease severity and post-viral complications in pediatric cases.

Prevalence of inflammatory Conditions During the Pandemic

Following the first diagnosed COVID-19 case in Italy, hospitals reported 30 times more Kawasaki-like, multisystem inflammatory conditions in children than in previous years.[29] France reported similarly, with 17 KD cases in 11 consecutive days between the end of April and beginning of May.[30] This showed a significant increase from their average of 2 cases per month for the past 2 years.[30] In April, American researchers documented the first case study of diagnosed KD concurrent with COVID-19 infection in a 6-month-old infant.[19] By the end of May, however, there were 186 child-related multisystem inflammatory conditions in America.[31]

Clinical Features of Multisystem Inflammatory Conditions

Kawasaki disease is a rare but severe condition which causes multisystem vasculitis, predominantly in previously healthy infants and young children under the age of 5.[11,19,29] The disease is characterized by persistent fevers lasting over 5 days, accompanied by

rash, conjunctivitis, cracked or dry lips, strawberry tongue, cervical lymphadenopathy, and swelling in the hands and feet.[19,32] When intervention occurs early enough in the development of the disease, children often make a full recovery.[11] However, without intervention, coronary-artery aneurysms will develop in 25% of KD patients, which poses a great risk for myocardial infarction.[11]

It is important to note that many of the cases resembling KD which have emerged during the pandemic have not been identical to classical KD cases observed pre-pandemic.[33] To distinguish between the similar conditions, cases which did not fulfill the criteria of the classically known KD have been termed Kawasaki-like disease, multisystem inflammatory syndrome in children (MIS-C), pediatric inflammatory syndrome (PID), or pediatric inflammatory multisystem syndrome temporally associated with SARS-COV-2 infection (PIMS-TS).[33] These pseudo-Kawasaki cases are different because they typically involve children and young adults over the age of 5, and the severity of the condition is often greater.[32,34] For example, MIS-C is diagnosed in adolescents under the age of 21 and presentation may include classical KD symptoms in addition to hypotension, shock, myocardial dysfunction, coagulopathy, and gastrointestinal involvement.[32,35] MIS-C also shares a similar clinical presentation to multisystem inflammatory conditions in adults; however, these cases remain more prevalent in adults for the time being.[35] Nonetheless, the presence of these severe cases in children frequently leads to pediatric ICU admissions and may be a large contributing factor to the high ICU rates among this demographic.[36]

These clinical features shed new light on the range of severity that pediatric COVID-19 cases can exhibit when complicated by multisystem inflammation, in particular the potential for cardiovascular involvement. See Table 1 for a summary of the clinical features associated with multisystem inflammatory conditions in children.

Cause of Multisystem Inflammatory Conditions

The cause of KD and the newly emerging multisystem inflammatory conditions in children are currently unknown.[11,19,29] For KD, infectious triggers like coronaviruses have been implicated as possible causes in the past and given the current data, it is likely that COVID-19 is responsible.[29] Viral infection from SARS-CoV-2 is known to induce powerful inflammatory responses and mediate endothelial injury which is postulated to provoke the development of KD or similar conditions in children.[32] However, while many of the inflammatory conditions have been associated with a positive RT-PCR nucleic acid test for SARS-CoV-2, there have been cases involving negative tests as well.[32] This indicates the possibility for other infectious triggers or distinct causes all together.

Possible Post-Viral Complications

The rising rates of multisystem inflammation and pediatric ICU admissions are likely to be accompanied by an increase in children experiencing post-viral complications similar to those observed in severe adult cases. Findings from SARS and MERS as well as limited data on COVID-19 cases indicate that reduced lung function, greater risk for heart conditions and psychological trauma are likely to occur.[37] These consequences have the potential to severely alter quality of life in children and produce long-term negative health outcomes. Therefore, it is imperative to establish widely accepted treatment guidelines for these severe cases and elucidate the effectiveness of aspirin and other interventions against long-term complications.[32]

Conclusion

Children can exhibit a range of clinical features when infected with COVID-19 and most symptoms resemble those observed in adults. However, children tend to exhibit milder forms of infection with many cases involving symptoms limited to the upper respira-

Table 1. Summary of the clinical features of COVID-19 in children

Category	Description
Mild – Moderate Clinical Features	• Fever • Cough • Sore throat • Rhinorrhea • Sneezing
	• Diarrhea • Vomiting • Dyspnea on exertion • Myalgia
	• Fatigue • Co-infection
Severe – Critical Clinical Features	• Pneumonia with moist rales, dyspnea and/or cyanosis
	• Reduced lymphocyte and platelet count
	• Elevated transaminase and creatine kinase levels
	• ARDS* • Respiratory failure • Shock
	• Coagulation disorders • Organ dysfunction and failure
	• Gastrointestinal symptoms during onset of infection
	• Kawasaki disease
	• persistent fever, rash, conjunctivitis, cracked or dry lips, strawberry tongue, cervical lymphadenopathy, swelling in hands and feet
	• Other multisystem inflammatory conditions
	• classical Kawasaki disease symptoms, hypotension, shock, myocardial dysfunction, coagulopathy, gastrointestinal involvement
Clinical Features Unique to Children	• Lower rates of infection and milder infection
	• Delayed onset of symptoms and prolonged viral presence
	• High prevalence of asymptomatic cases

*ARDS = Acute respiratory distress syndrome

tory tract. Co-infection of a bacterial or viral nature is also commonly observed in this demographic. While severe pediatric cases and child mortality associated with COVID-19 are still considered to be rare, the rate of severe cases is on the rise. With the proportion of pediatric ICU admission rates equal to that of adults, it is becoming clear that children may not be as resilient against COVID-19 as initially thought. Although data now indicates that children may have a similar likelihood of developing severe infection to adults, there is an underrepresentation of children in clinical research. Most clinical trials regarding drugs for treatment against COVID-19 have been limited to adult patients. More pediatric-focused research on the efficacy and safety of remdesivir and other interventions is necessary to help guide clinicians through the management of severe pediatric cases.

During the investigation of COVID-19 in children, many studies have reported discrepancies from the typical clinical features of infection observed in adults. Currently, there exist explanations for some features while others lack understanding. Literature suggests that lower susceptibility to infection and milder cases in children are likely due to the smaller epidemiological footprint, superior physiology, and higher likelihood for co-infection in children. Still unknown, however, is the mechanism responsible for a delayed onset of symptoms followed by prolonged infection, though this phenomenon was detected in a small case study with limitations. Therefore, larger, multi-centre case studies involving patients with diverse backgrounds may help to determine if these features reflect the pathogenesis of SARS-CoV-2 in the entire demographic. Further observation on asymptomatic cases in the pediatric population may also be useful in elucidating how COVID-19 develops in children.

Finally, the rise in multisystem inflammatory conditions further demonstrates the increasing prevalence of severe child-related infection. Viral infection complicated by acquired inflammatory conditions can significantly increase the severity of pediatric cases, putting young patients at a risk of cardiovascular damage. These associated conditions even have the potential to induce post-viral damage similar to those seen in adults who recover from severe COVID-19 infection. The negative implications of these complications on the quality of a child's life make it vital to apply research efforts towards establishing widely accepted therapeutic guidelines and validating the effectiveness of interventions against long-term complications.

From the pediatric perspective, a better representation of children in research and literature is needed. An improved understanding of disease pathogenesis and validation of clinical treatments can significantly help in managing severe pediatric cases and it all starts by establishing the ABCs of the clinical presentation of COVID-19 in this younger demographic.

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Review, analyses, and comparisons of interventions in active and completed clinical trials of Alzheimer's disease

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Abstract

Alzheimer's disease is an incurable neurodegenerative disorder causing deteriorating cognitive function and memory loss. The purpose of this paper is to create a comparable landscape of completed and current clinical trials and therapeutic interventions for Alzheimer's disease, identifying future hallmarks of neurodegenerative research. In the status quo, the urgency for new drugs and interventions surges as the aging population and cases of cognitive impairment grow. Current FDA-approved drugs have only decreased disease progression slightly; these drugs last for brief periods and are useful for symptom management rather than reversing pathogenesis. Through the data compilation, intervention analysis, and the corresponding figures that provide a visual perspective of the respective trends, this review article effectively identifies the developments and gaps for intervention in Alzheimer's disease clinical trials. The methodology follows the specific guidelines and reporting standards of the Methodological Expectations for Cochrane Intervention Reviews (MECIR) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Moreover, inclusion and exclusion criteria were centered upon publication date, trial results, and a multitude of keyword searches pertaining to Alzheimer's disease and cognitive impairment. Based on the review of clinical trials and literature precedent, descriptions of advancements are provided. Examples of these developments include the new interventions of stem cell therapy and declining trend of active immunotherapeutics. Trial details about the specific interventions were compiled using the ClinicalTrials.Gov database. Analysis of pending and completed trials are discussed based on advancements in Alzheimer's disease research and the progression of drug development.

Introduction

Alzheimer's disease (AD) is an irreversible neurodegenerative disorder that causes neuron degeneration, synaptic dysfunction, and cognitive impairment. As life expectancy and the aging population grow, the percentage of the aging community with cognitive dysfunction and impairment consequently rises. The World Alzheimer Report asserts that by 2050, the number of people affected will triple to approximately 152 million people, while the economic cost will double to two trillion dollars by 2030.[1] Expenditures for AD continue to rise (alongside worsening symptoms and rising mortality rates) due to pharmaceutical needs for aging symptoms, caregiver burdens, insurance premiums, and high out-of-pocket costs.[2,3] Even with the abundant research currently conducted, the Food and Drug Administration (FDA) has yet to approve a drug since 2003. Clinical trials have empirically failed due to limited recruitment that can be attributed to concerns of invasive procedures, exclusion criteria for underrepresented minorities, and lack of caregivers and study partners able to track daily functioning.[4] Many trials reaching Phases 2 and 3 status have had poor results for patients with dementia, some of which are discussed in subsequent sections. The four FDA-approved drugs (donepezil, memantine, rivastigmine, and galantamine) failed to show positive results for reversing pathogenesis and have only slowed symptoms for patients.[5] Each of these drugs has presented treatment-emergent symptoms, and branded drug Namzaric, a combinatory therapy of donepezil and memantine, reported adverse clinical symptoms such as seizures, ulcers, and muscle spasms.[5] 2011 guidelines of the National Institute on Aging and Alzheimer's Association (NIA-AA) Research Framework conclude that AD is normatively defined by the pathological processes that can be documented by biomarkers or post-mortem examination.[79] This focus on biomarkers posits two major protein deposits seen as major markers of AD: amyloid-beta (Aβ) and phosphorylated tau. These abnormal protein deposits are key to understanding AD as these protein deposits, while not necessarily causal, are the unique, defining marker of AD that differentiates it from other neurodegenerative disorders.

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The amyloid hypothesis proposes that the amyloidogenic cascade that leads to abnormal Aβ deposition begins with the improper cleavage of the amyloid precursor protein (APP). Secretases cleave APP in an amyloidogenic pathway, producing Aβ protein-peptide fragments that aggregate as neuritic plaques; major biomarkers of cognitive impairment and AD. This dysregulation produces 42-amino acid chain peptides, better known as Aβ-42. Additionally, Aβ-42 has been hypothesized as the cause of neurofibrillary tangles (NFT) composed of tau.[6] This hypothesis proposes that Aβ-42 is a precursor to plaque deposition in the brain along with NFT linked to AD pathogenesis, as concluded by the NIA-AA framework results. However, after 20 years of support, failing clinical trials and therapies question the amyloid hypothesis. Post-mortem reviews of patients with dementia noted that the linkage between tau-based NFTs and AD pathogenesis was stronger in relation to amyloidogenic plaques, along with evidence of NFT formation without plaque deposition; potentially representing independent relations of tau and cognitive impairment.[7,8] The tau hypothesis, in recent trials, seems more relevant in the progression of cognitive impairment presented in patients with AD. The hyperphosphorylation of tau protein causes microtubule disassembly, leading to NFT aggregation and neuron degeneration. The NFT formation blocks synaptic function and causes cell death; one proposed mechanism of cognitive dysfunction.[9] Investigations of the tau hypothesis present it as a prime focus for future drug development. Additionally, experts agree that AD drug development should move beyond mainstream hypotheses like tau and amyloid.[10] Many of these hypotheses work in conjunction with pending research based on literature precedent. Microglia-mediated phagocytosis successfully cleared amyloidogenic plaques, supporting evidence of microglial inflammation as a potential cause of AD. Additional evidence explains that glial cells are more abundant near plaques and NFTs.[11] Dysfunctional bio-metal homeostasis presents strong linkage to plaques and NFTs in patients with AD.[12] The cholinergic system hypothesis (acetylcholine degradation) is the theory with the most successful trials; donepezil, galantamine, and rivastigmine are cholinesterase inhibitors.[5] Elevated calcium levels with astrocytic inflammation are proposed as a biomarker of AD pathogenesis; memantine is a FDA-approved drug focused on calcium homeostasis and regulation.[13,14] The myriad of listed hypotheses have made investigational interventions critical in understanding AD and cognitive impairment. The 2011 NIA-AA framework encourages focus on the biomarkers through the lens of these hypotheses; essentially, rather than associating the potential hypotheses to the displayed clinical symptoms, the hypothesized pathways should be associated with the primary biomarkers of Aβ and abnormal tau.

Due to this framework, neuroimaging and biomarker tracing remain a major research focal point, as researchers attempt to find ways to diagnose patients before reversing pathogenesis. Past trials indicate that multiple imaging studies classified as "Procedural intervention" use technology, such as positron emission tomography imaging (PET).[15-17] PET focuses on in vivo structural imaging in preclinical studies and can identify NFT accumulation.[18,19] Other procedural interventions and imaging studies are discussed in the *Results* section.

This review report discusses the differences between active and completed trials while identifying gaps within the current development pipeline. This interventional review exemplifies the current differences in clinical trials and the potential pipelines for drug development, symptom management, and other ways to mitigate the main biomarkers seen in AD. Additionally, novel therapies are discussed based on ClinicalTrials.Gov data, classified based on the type of intervention. Details regarding the selection of overarching categories are described in the Methods section.

Objectives

The primary objectives of this review article are to improve systematic understanding of AD research through the lens of clinical trial registry review.

1. Through interventional analysis, the differences in pending and active trials can support new scientists and clinicians in identifying potential therapies, novel solutions, and cross-applicable molecules (e.g. using medications for other disorders).
2. Using this information supports cross-collaboration by researchers interested in studying similar therapeutic methods, leading to improved standardization of protocols; protocol standardization alleviates issues with study design differences and result comparisons.

Methods

Search strategies

The holistic review process of clinical trials began in May 2020. Using the "Advanced Search" tool on ClinicalTrials.Gov, restrictions were applied regarding dates, status, keyword searches, and additional details described in the various exclusion and inclusion criteria below. The World Health Organization's International Clinical Trial Registry Platform (ICTRP) was initially planned to be used, but has been temporarily unavailable due to heavy traffic caused by the COVID-19 pandemic; ICTRP is a future direction that researchers may consider to analyze results in this study. Due to the specific consideration of clinical trials, only trial registries were utilized to find information; the benefits from research conducted on other registry platforms other than ClinicalTrials.Gov were minimal. The distinct requirements between clinical trials registries could lead to major disadvantages in trying to analyze the trends for the clinical trials listed. Examples include the search interfaces for major registries, including ClinicalTrials.Gov and ICTRP, which could lead to different search results using the same key terms.[76] As ClinicalTrials.Gov is the most expansive registry offered, a focus on one specific registry was essential to support the accuracy of an interventional review in a specific clinical trials registry. Including multiple registries would have complicated the analysis and caused further discrepancies due to differences in reporting standards, search interfaces, and other registry-specific information. The search protocol was based on guidelines and strategies described in the Methodological Expectations for Cochrane Intervention Reviews (MECIR) Manual created by the Cochrane Library.20 The following paragraph describes the specific protocols and criterions applied to the systematic registry review.

Date restrictions were applied from 2005 onward, as the International Committee of Medical Journal Editors (ICMJE) ruled that clinical trials must be cited in public trial registries before

publication opportunities in July 2005.[21] The following keywords were utilized in searches in the "Conditions or Disease" search bar on the ClinicalTrials.Gov database: "Alzheimer Disease", "Alzheimer Disease, Early Onset", "Alzheimer Disease, Late Onset", "senile dementia", "cognitive impairment", "cognitive decline", "cognitive dysfunction", "cognitive deterioration", "Dementia", "Dementia Alzheimers", and "Dementia of Alzheimer Type". AND/OR operators were not available while searching in the clinical trial registry, thus justifying the wide keyword search. In order to separate active and completed trials, status filters were chosen while searching for trials ("Active, not recruiting" trials represented active trials with pending results and "Completed" trials represented completed trials since July 2005). Figure 1 describes the screening and selection process for clinical trials after the initial search. Phase I included the initial search on the ClinicalTrials.Gov database, along with the removal of duplicate studies or separate data entries for existing trials. Phase II incorporated the various exclusion and inclusion criteria, and Phase III finalized trials along with the data extraction, categorization, and appraisal processes.

Inclusion Criteria

Clinical trials were included based on dates (starting July 2005 to May 2020, the time of the screening process) and limited to trials published in English. No criteria were applied to the specific locations of the trials to access as much reliable information from across the globe. The use of a United States-centric trial registry could possibly exclude trials from other regions unintentionally due to language and cultural barriers.

Exclusion Criteria

All observational studies were excluded during the screening process to investigate specific interventions associated with the purpose of the study. Studies published prior to July 2005 were excluded. For the search of completed trials, trials were required to have detailed, reported results to determine the reliability, accuracy, and quality of the provided information about investigational trials.

Data Extraction

The following information was extracted per trial: the full title, location, study design, interventions, outcomes, and website hyperlink. All data was checked for errors in characterization of intervention and outcome measures. Further information regarding standardization is provided in the Categorical definitions subsection and describes how various therapies were categorized based on the type of intervention used in each study. Figure 2 was created based on the data extraction and categorization processes in Phase III (Figure 1).

Critical Appraisal

Critical appraisals are essential for determining accuracy and relevance of results and analysis during systematic reviews and other research methods. In this study, the Critical Appraisal Skills Programme (CASP) checklist tool was used to ensure the quality of each trial. The checklist was adopted based on the CASP randomized clinical trial checklist rather than the systematic review checklist to specifically cater towards the purpose of this study.[22] The study used a modified version of the CASP trial checklist to consider sample size, sample demographics, thoroughness of the trial, and reported results. Each study was ranked on a scale for assessment accuracy and bias, based on numerical assignment; another modification from the original checklist released by CASP. As mentioned previously, each completed trial was required to have detailed outcome measures as well as results, which could additionally be classified under the critical appraisal for each trial. Through all the appraisal steps in Phase III, the list of trials was finalized. Information regarding the search results is described in the *Results* section below. This search protocol has not been pre-registered due to the ongoing prioritization of COVID-19 and public health-related review protocols.

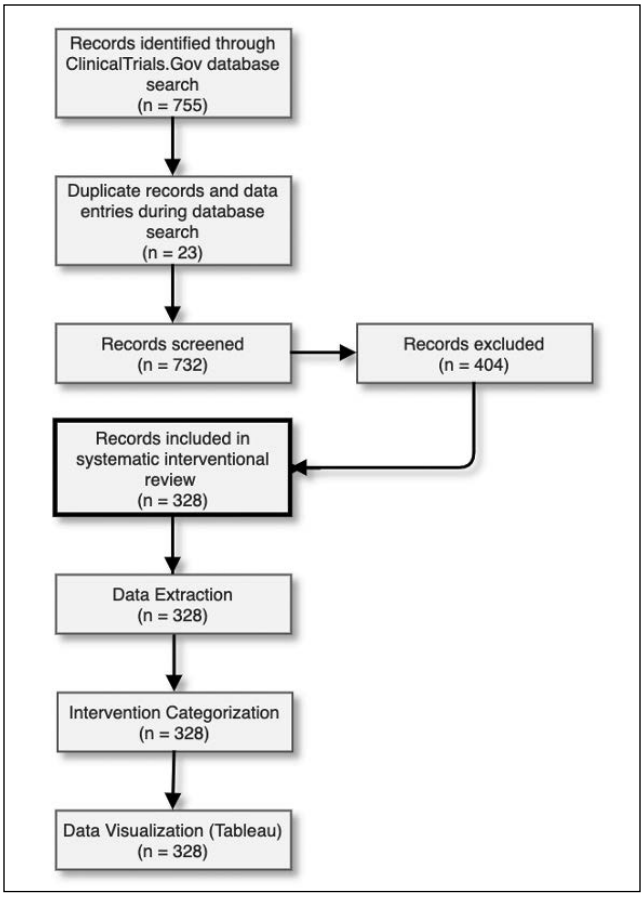

Figure 1. Screening flow diagram based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A total of 328 active and completed trials were analyzed

Results

Search Results

The main focus of this review article is the comparisons and analysis of interventions, relevant details, and gaps and developments in AD clinical trials. The screening process was adapted from the PRISMA selection process (Figure 1).[23] 220 completed trials with reported results and 108 active trials pending results meeting the requirements of the criteria and critical appraisals were chosen for review as of May 28, 2020. Trials added subsequently were not considered. Various intervention-outcome combinations in clinical trials isolated by status (active or completed) were also analyzed (Table 1). Table

Table 1. Systematic compilation of intervention-outcome relationships in current and past clinical trials and therapeutic interventions in Alzheimer's disease

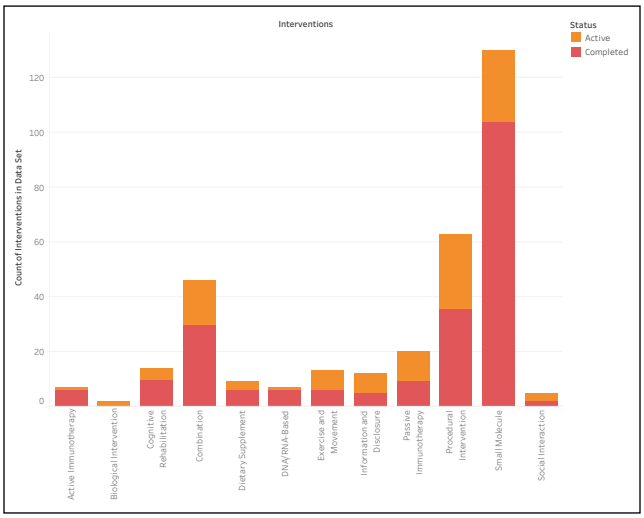

Figure 2. Intervention comparisons between past and current clinical trials and therapeutic interventions in Alzheimer's disease

1, the "evidence map", identifies gaps and developments within the interventions and their relationships to common outcome measures, such as cognitive assessments or pharmacokinetics. Intervention categories were also compared, based solely on the Categorical definitions subsection (Figure 2). Due to the quantitative difference between pending and completed denominators, percentages were contrasted throughout the study for the specific intervention types. Each of these percentages were documented in individual sections of intervention comparisons. Figure 2 was created through the Tableau Public, a desktop software for data visualization.

Categorical Definitions

Intervention categorizations were conducted through definitions from ClinicalTrials.Gov, The Agency of Healthcare Research and Quality (AHRQ), and the AlzForum Therapeutics Database.[24,25] AlzForum's updated therapeutics database provided most information for pharmaceutical and procedural intervention types in dementia, cognitive impairment, and AD. Specific drugs and molecules were classified under the pharmaceutical interventions listed below. Three overarching sections for interventions were chosen, based on the guidelines presented by the references listed above: pharmaceutical and biological, procedural, and behavioural.

The various behavioural interventions included "Exercise and movement", "Information and disclosure", "Cognitive rehabilitation", and "Social interaction" (Table 2).

The categories of pharmaceutical and procedural interventions followed the therapeutics database of AlzForum, an information-based website to support researchers, in terms of drug discovery and treatment. These categories were "Combination", "DNA/RNA-based", "Active immunotherapy", "Passive immunotherapy", "Small molecule", "Biological intervention", "Dietary supplement", and "Procedural intervention" (Table 3).

Table 2. Categorical definitions for behavioural interventions

Exercise and movement	Activity-based interventions that support stabilization of neuropsychiatric symptoms, such as anxiety, aggression, or depression. Examples include dancing or cardio-based exercises every morning over a sample time period.
Information and disclosure	Disclosure of Alzheimer's disease (AD)-related symptoms or risk factors and education platforms for patients and families. This category usually directs the information and disclosure towards patients rather than caregivers, who are already informed regarding the function of the individual with cognitive impairment.
Cognitive rehabilitation	Cognitive rehabilitation therapy (CRT) is a psychological therapy for thought patterns, memory, and relaxation. CRT has been demonstrated to combat cognitive deterioration through non-invasive methods in individuals with neuropsychiatric disorders and/or criminal behaviours, pregnant mothers, and elderly adults.[26]
Social interaction	Communication through clinical trials with caregivers, other patients (with or without dementia), and professional support to improve social skills, quality of life, and neuropsychiatry for patients with AD.

Intervention comparisons

Active and Passive Immunotherapy

The diminished size of active trials describes the failures of active immunotherapy (Figure 2). The last active immunotherapeutic intervention, AN-1792, consisted of a synthetic Aβ peptide and showed varied promise through the trial's initial phases. However, it was terminated in Phase 3 due to treatment-emergent cerebral inflammation in 6% of patients.[37,38] Three active immunotherapies (AD02, ACC-001, and CAD106) were shut down by pharmaceutical corporations due to treatment-emergent symptoms, tolerability and safety, or minimal cognitive success.[39]

Table 3. Categorical definitions for pharmaceutical and procedural interventions

Combination	Two or more interventions tested in one clinical trial. Examples include pairings of behavioural and pharmaceutical interventions to combine invasive and non-invasive approaches or cross-over and factorial study designs to interchange intervention assignment. This category was not analyzed due to minimal developments and relevance of combinatorial therapy.
DNA/RNA-based	Personalized medicine is the synthesis of precise molecules based on specific genomic sequences. Examples include antisense oligonucleotides (ASOs) and RNA interference (RNAi), which target specific mRNA strands and control protein production.27 This has shown extensive potential for tau protein and even other neurodegenerative diseases, such as Huntington's.[28]
Active immunotherapy	Methods engaging the host's immune system (in this case, the patient's) through molecular stimulation that amounts to an eventual response.[29]
Passive immunotherapy	Immune system-related molecules without activation or engagement of the immune system. Passive and active immunotherapy differ based on immune system involvement.[29]
Small molecule	Targeted small molecule therapies, organic molecules with low molecular weights actively targeting specific biomarkers.[30] In Alzheimer's disease trials, small molecules are synthesized to degrade amyloid-beta plaques, tau-based neurofibrillary tangles, or other biomarkers. Examples include secretase inhibitors to prevent the improper cleavage of the amyloid precursor protein.[31]
Biological intervention	Substances created from living organisms to treat neurodegenerative diseases. The only examples in the data set were mesenchymal stem cells (MSCs) derived from mesodermal embryonic regions to promote regenerative measures. MSCs are the primary focus of neurodegenerative stem cell therapy due to their multipotency rather than the regional limitations of other stem cells.[32-34]
Dietary supplement	Additions to daily routines for patients during a trial, usually in the form of pills or capsules. Examples include turmeric derivatives that contain phenolic compounds supporting disaggregation of amyloidogenic plaques.[35]
Procedural intervention	Imaging studies and device-based interventions that use energy sources to stimulate brain activity. Examples include transcranial magnetic stimulation, which conducts electromagnetic currents in patients exhibiting neuropsychiatric symptoms, or positron emission tomography tracers for plaque imaging.[36]

Passive immunotherapy demonstrates high tolerability and safety, even though only a few clinical trials have shown evidence demonstrating substantially slower cognitive decline rates.[40,41] Additional research regarding the introduction of antibodies has shown promise in Phase 1 and Phase 2 trials. Through proposed hypotheses, such as phagocytosis and toxic neutralization, synthetic antibodies are expanding current trials (Figure 2).[39]

Monoclonal antibodies (mABs) have become the focal point of passive immunotherapy in pending trials. These agents, mABs, are cloned antibodies from one unique parent immune cell, which can either be completely human or humanized. Humanized antibodies are taken from organisms and synthesized through human-adjusted variants, while complete human mABs are taken from humans or similar organisms with minimal modifications.[42] Multiple researchers hypothesize mABs could counteract Aβ oligomers through microglial activation, preventing neuronal degeneration.[43]

Eleven different passive immunotherapies are being tested for brain amyloid clearance, safety, and tolerability in pending trials. BAN2401, a humanized mAB-based drug currently in Phase 2 trials, resulted in 93% brain amyloid removal in the highest-dose group, along with 30-50% decreased cognitive decline.[44] Gosuranemab is an anti-tau mAB that decreased tau NFT formation by 67 to 97%; further drug analysis is required for tolerability, safety, and pharmacokinetics.[45] Current trials on semorinemab, another humanized tau mAB, are being conducted in Phase 2 after successful safety and hazard testing.[46] Additional passive immunotherapeutics in active trials are heavily supported by mAB precedent, including Donanemab, Gantenerumab, and Crenezumab.[40]

DNA/RNA-based therapies (precision/personalized medicine)

Precision medicine develops tailored drugs and interventions for individual patients. Past therapies included the use of albumin, immunoglobulin, and insulin in multiple trials as potential methods for slowing cognitive impairment; however, molecular cross-applicability failed to slow cognitive decline after strong safety and patient tolerability protocols.[47-50] Current research for individualized therapies revolves around gene therapy and antisense oligonucleotides. Vector-driven expression of the nerve growth factor (NGF) in the CERE-110 gene therapy trial was discontinued due to results with minimal effect on cognitive impairment.[51] Antisense oligonucleotides (ASOs) are synthesized based on nucleotide sequences; through complementary replication, ASOs can prevent gene expression and protein production. ASOs have had success with genetic neurological disorders such as Duchenne muscular dystrophy, which refers to a single DMD gene.[52] Figure 2 identifies only one ASO-based clinical trial of IONIS-MAPTRx, an anti-tau therapy in Phase 1 trials targeting specific mRNA strands involved in tau protein production causing neuropathic disorders.[53]

Personalized therapies have likely decreased due to the challenges of individualized medicine. The examination of genetic variation is critical to understand and innovate personalized medicine.[54] Currently, the clinical knowledge of genetic causes of AD are unknown, making DNA/RNA-based therapies difficult. While the one-size-fits-all models hold disadvantages, they have the potential to slow cognitive decline in multiple patients compared to in a single individual. Additionally, the costs associated with DNA sequencing, hyper-specific molecular development, third-party medical premiums, and medical regulatory guidelines discourage pharmaceutical interest in precision medicine.[55]

Specific mutated genotypes associated with AD and cognitive impairment continue to offer promise for individualized medicine. As genetic analysis grows, the expansion of causal relationships between genotypes and AD is imminent, offering affordable methods for pharmaceutical companies.[56]

Biological Intervention

As described in the Categorical definitions subsection, mesenchymal stem cell(MSC) therapy is the primary focus of the biological interventions developed in only pending trials (Figure 2). MSC therapies focus specifically on neurodegenerative diseases through production of growth factors for neural regeneration in the host patient.[57] Both Phase 1 clinical trials are currently investigating safety and tolerability protocols.[32,33] Neurodegenerative stem cell

therapy remains to be heavily researched due to the complexities of neurologic pathways. Preclinical studies have found that the translation from animal to human models in stem cell therapy, especially considering neurological conditions, has been inaccurate. Transgenic models present different genetics with homogeneous populations based on hypotheses, whereas humans affected by AD span a spectrum of heterogeneity in terms of race, gender, ethnicity, and other genetics-related factors.[34] Exogenous and endogenous methods of stem cell therapy present simultaneous limitations. Endogenous reparation in AD fails due to minimal neural regeneration.[59] AD is associated with major neural degeneration of the CA1 subregion in the hippocampus, and stem-cell-induced hippocampal regeneration fails to restore neural connections in CA1. Exogenous introductions of stem cells risk tumour formation because of nonnatural stem cells.[58] Specific cell therapies, such as embryonic stem cell therapies (ESCs), present ethical challenges due to different donor cells; however MSCs and induced pluripotent stem cells (iPSCs) have potential to circumvent concerns due to regenerative multipotency, including neurotransmission and neuroprotection.[59,60]

The multipotency of MSCs remains the most enticing development in AD clinical trials, but also encourages research into specific stem cell therapies targeting specific brain structures, such as the dentate gyrus in the case of brain-derived neural stem cell therapies (NSCs).[34]

Procedural Intervention

Procedural interventions slightly increased in trial popularity, likely due to safe, inexpensive, and non-invasive methods regarding stimulation, brief energetic repetitions controlling action potentials in neurons, and manipulating brain activity in tested patients (Figure 2).[61] The focal points of device-based and procedural interventions are neural and brain region-based stimulation. Neural stimulation includes energy sources, such as airway pressure, light waves, radiation, and magnetic fields.

Continuous positive airway pressure (CPAP) is used for sleep-related and neuropsychiatric conditions, which are extensively linked to AD pathogenesis.[62] Mixed results regarding CPAP and cognitive impairment have been reported; however the quality of life, mood, and sleep assessments associated with CPAP interventions are positive, with decline in obstructive sleep apnea.[62] Ongoing investigations are likely to develop studies and technologies temporarily managing symptoms to improve living standards for patients with AD.

Transcranial stimulation is another research focus for device-based interventions and has shown potential modulation and regulation for neuropsychiatric diseases.[63] AD research presented in this interventional review regarding transcranial stimulation has focused on the non-invasive brain stimulation techniques. Of the seven trials pertaining to transcranial stimulation in this review, the categories of non-invasive transcranial stimulation are transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (TDCS). Other methods such as transcranial alternating current stimulation (TACS) have also been conducted in vitro, reporting lower connectivity in neuronal function and decreased modulation; the failures during in vitro testing are presumably the reason why TACS is not represented in this interventional review's clinical trial data.[77] TMS utilizes electromagnetic stimulation in energetic bursts directed to motor and cognitive regions to reduce depression, psychosis, and neuropsychiatric symptoms associated with AD.[63] Systematic reviews identify TMS with positive results on cognitive assessments, such as the Alzheimer's Disease Assessment Scale-Cognitive Subscale.[64] Further TMS development could provide cost-effective, non-invasive approaches, maximizing accessibility. TDCS serves as a different modulatory technique that delivers constant, low-powered currents; this is almost the opposite of the energetic bursts of TMS. TDCS has improved symptoms of patients with AD, especially in task-based assessments such as word recognition and face-name association.[78]

Other forms of neural stimulation are categorized based on energy source. New energy-based methods, including infrared, gamma ray, and other energetic stimulations, can manipulate plaque deposition in non-invasive approaches, having success in preliminary in vivo trials.65 Gamma ray stimulation reduced tau and amyloid biomarkers in a small-scale human study.[66] Stimulatory methods could expand device-based interventions with minimal risk, resolving a plethora of neuropsychiatric concerns.

Behavioural Intervention

Current behavioural interventions have nearly doubled in comparison to completed trials (Figure 2). Behavioural interventions present minimal requirements for in vivo and in vitro models, which are likely associated with the expansion of the field. 80-90% of patients with cognitive impairment or AD pathogenesis present neuropsychiatric symptoms, establishing the need for behavioural methods to improve and sustain quality of life.[67] Studies continue to conclude that symptom management is best through social interaction and caregiver training compared to antidepressants and antipsychotic medications.[68] As pharmaceutical approaches are deemed ineffective and unsafe, behavioural intervention remains the safest and most tolerable method for symptom management, especially when measuring long-term outcomes post-trial (Table 1).[69] Each of the subcategories listed under the Categorical definitions subsection had percentage increases in clinical interventions. Disclosure and educational services given to families and patients, when supported with accurate assessments, have improved neuropsychiatry; resulting neuropsychiatry can vary when assessment evaluations are ambiguous and lack sufficient information for direct diagnosis.[70] With additional neuroimaging studies to identify cause-effect relationships between biomarkers, information, and AD, information and disclosure will expand as assessments are able to make accurate diagnoses. Exercise and movement are common interventions in many disorders, ranging from obesity to cognition-related disorders. Exercise is directly related to tissue oxygenation within the brain, which has been shown to improve AD symptom management in similar methods as CPAP, due to the similarities in oxygen delivery mechanisms.[71] Social interaction and cognitive rehabilitation follow similar patterns in neuropsychiatric symptom management.[72,73]

Small Molecule

Quite possibly the most important pharmaceutical therapeutic of all remains the small molecule method. Small molecule treatments have decreased significantly, possibly due to the plethora of Phase 3 trial failures (Figure 2). Much of this can be attributed to differences in transgenic models, as mentioned in Biological

interventions, causing multiple treatment-emergent symptoms. Avagacestat, a gamma-secretase inhibitor focused on the proper cleavage of APP, failed to pass safety and tolerability tests in Phase 2 due to higher doses causing progression of skin cancer along with nausea.[39] Clioquinol, a cross-applied molecule designed for the disruption between toxic metals and amyloidogenic peptides in the brain, was reported to have no evidence of safety or efficacy.[74] The AlzForum Therapeutics Database details tens of treatments that are inactive, shelved, or discontinued.[25] While the small molecule intervention section is the most populous amongst completed clinical trials, the decreased research concentration on small molecules is associated with lack of outcome standardization (Table 1), decreased focus on drug kinetics and uptake (better known as pharmacokinetics), inability to establish causal relationships between drugs, biomarkers, and AD, and transgenic inaccuracies.[75]

All in all, the trends described by the data evidently recognize the advancements and the shortcomings of certain therapies in the AD pipeline. The findings of the interventional review examined the past changes in research directions in order to establish potential research directions in the future. Moreover, the various categories each provide a snapshot of the trial analyses since 2005. The vast field of therapeutics provides opportunities for researchers to explore different aspects of AD, especially in regard to the NIA-AA framework's conclusions of biomarkers. The categorical therapies discussed all contribute to the considerable effect of AD biomarkers and the progression in plaque deposition, whether through pharmaceutical, behavioural, or procedural methods.

Discussion

Through the entire systematic review process, the study report focused on comparisons between past and current trials, analyzing differences in therapeutic categories. The development of relatively new therapeutic methods, such as behavioural interventions, passive immunotherapy, and various potent stem cell therapies, have shown promise to slow cognitive decline, and potentially manage symptoms and reverse the pathogenesis of AD. MSC therapies and mABs are currently in early trial phases for safety and tolerability, with potential to degrade commonly associated biomarkers, such as hyperphosphorylated tau and amyloidogenic peptides. The consistency of behavioural interventions is additionally noted amongst researchers, representing a non-invasive, neuropsychiatric approach to symptom management, as clinicians research potential pharmaceutical and biological methods. Precision and individualized medicine remains to be heavily researched as pharmaceutical companies look for methods to reduce biomarkers for entire experimental groups rather than individuals. As traditional treatments, such as small molecules and active immunotherapy, fail to produce substantial differences in cognitive decline and AD-related symptoms and slowly phase out, novel methods including device-based interventions could provide valuable insight into brain structures, symptom-biomarker-pathogenesis relationships, and effective therapies to improve neuropsychiatric symptoms and reverse cognitive dysfunction.

Limitations

As mentioned beforehand, the limitations regarding clinical trial registries could represent a possible impediment due to the significant issues concerning data reporting. While the ClinicalTrials.Gov registry has diverse trials from across the globe, 6% of a sample set of 347 trials were reported in ClinicalTrials.Gov; a significant example of potential discrepancies for clinical trials in AD.[76] With 24 different clinical trial registries, the lack of standardized reporting methods was a major cause of the disparities presented in the interventional review. Differences in symptoms related to ethnicity, race, and other biogeography-related factors could change the landscape of therapeutic evaluation and assessment, as the success of interventions may be affected by the presentation of genetic factors that are relevant in specific ethnicities, for example. Moreover, the exclusion of other international trials and the unavailability of the ICTRP could change the comparisons of each intervention category.

Future directions

Future directions of research could involve the investigations of clinical trials in AD in multiple international registries, such as the ICTRP and European Union Clinical Trials Register, to encompass more details, interventions, and additional categories that ClinicalTrials.Gov may have not been exposed to beforehand. Moreover, researchers could utilize this analysis to determine future projects in the therapy development pipeline for investigating biomarkers and causes of AD. Analyzing outcome measurements in AD clinical trials, the popularity of specific assessments, and the lack of standardization available could also be a future direction of research that could prove as valuable as the intervention analysis conducted within this report.

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Familial adenomatous polyposis: an adolescent with refractory iron deficiency anemia and a mandibular mass

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Abstract

Familial adenomatous polyposis is an autosomal dominant disease that results in numerous colonic polyps resulting in malignancy if left untreated. We report a case of a 15-year-old male with a strong family history of colon cancer who presented with refractory iron deficiency anemia and a mandibular mass. Colonoscopy revealed extensive large lobulated polyps and genetic testing confirmed familial adenomatous polyposis, while computed tomography scan revealed his mass to be a mandibular osteoma, a known extracolonic manifestation of familial adenomatous polyposis. The combination of colorectal and extracolonic manifestations is known as Gardner syndrome. In an adolescent with iron deficiency anemia refractory to adequate supplementation and a strong family history, the diagnosis of familial adenomatous polyposis should be considered.

Introduction

Familial adenomatous polyposis (FAP) is an autosomal dominant disease most commonly caused by germline mutations in the adenomatous polyposis coli (APC) gene on chromosome 5q21-q22.[1] In classic FAP, patients develop more than 100 adenomatous colorectal polyps, typically in the second or third decade of life with progression to colorectal cancer in 100% of untreated individuals.[1] Attenuated FAP (AFAP) is characterized by fewer colorectal adenomas (10 to 99 polyps) with a later age of onset.[1] In children and adolescents, common presenting symptoms include rectal bleeding and diarrhea.[2,3] Genetic testing can establish the diagnosis of FAP or AFAP. Diagnosis of FAP or AFAP should be considered in individuals who present with refractory iron deficiency anemia and in those with a strong family history of colorectal cancer. In addition, these diagnoses should be considered in those with a history of adenomas in combination with known extracolonic features, such as thyroid cancer, desmoid tumors, duodenal adenomas, or osteomas.[1]

Here we describe a case of a 15-year-old male who presented with refractory iron deficiency anemia (IDA) and a mandibular mass who was found to have FAP.

Case presentation

A 15-year-old male was referred to a paediatrician for pallor and fatigue despite an iron-rich diet. There were no symptoms of epistaxis, hematuria, blood in the stool, or rectal bleeding. On further questioning, he had a 4-month history of a left mandibular mass. It measured 2 by 3 cm and was hard, non-tender, and attached to bone. There were no fevers, night sweats, or weight loss.

His family history (Figure 1) revealed that his father had multiple colonic polyps and died at age 38 of colorectal cancer. His paternal uncle had FAP with 500 colorectal polyps on colonoscopy and died at age 36 over 10 years ago, also of colorectal cancer. The patient's younger brother (13 years) and sister (11 years) were healthy. Laboratory investigations ordered by the paediatrician revealed a microcytic anemia (hemoglobin [Hgb] 104 g/L; mean corpuscular volume [MCV] 71 fL) and low ferritin (6 µg/L). He had an elevated reticulocyte count (109 x 10^9/L) and his Hgb electrophoresis was normal. A fecal occult blood test was positive. A hereditary cause for gastrointestinal bleeding was suspected and he was referred for colonoscopy. In the meantime, iron supplementation (ferrous fumarate 6 mg/kg/day elemental iron) was prescribed with good compliance. Shortly after presentation he developed intermittent hematochezia. Despite two months of adequate iron supplementation, his Hgb and MCV remained unchanged and ferritin increased slightly (14 µg/L).

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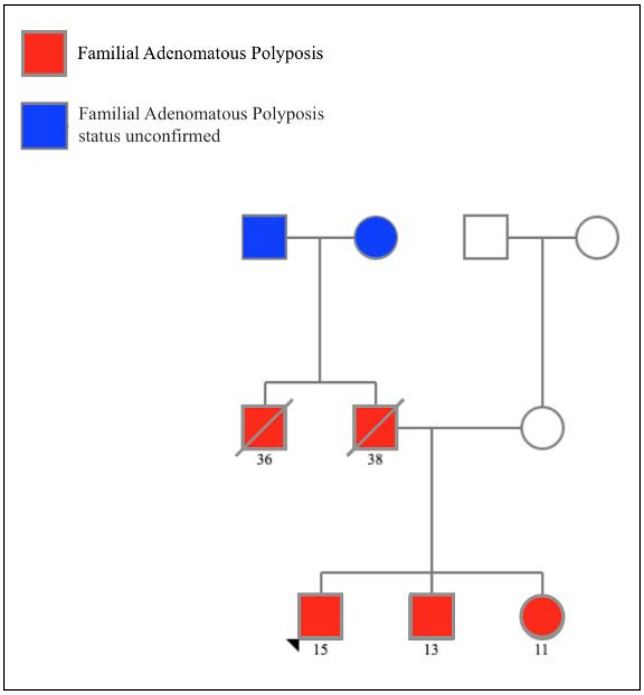

Figure 1. Familial adenomatous polyposis pedigree

A colonoscopy revealed extensive large lobulated polyps. The pathology findings confirmed adenomatous polyps, while his genetic testing for the APC gene confirmed FAP. A computerized tomography scan was done which showed an osteoma of the mandible.

The adolescent's two siblings underwent screening genetic testing and were also confirmed to have FAP. He was subsequently followed by a paediatric gastroenterologist who performed several colonoscopies and has recommended a colectomy because of the extensive polyps.

Discussion

IDA is a common presentation in adolescents; however, in this case, his IDA was atypical from that of most adolescents in that it was refractory to iron supplementation. Children under 4 years of age and adolescents are the two age groups in paediatrics who are at the highest risk of iron deficiency.[4] Iron supplementation (3-6 mg/kg elemental iron/day) should produce a Hgb rise of greater than 10 g/L within 4 weeks for those with Hgb greater than 90 g/L, or within two weeks for those with Hgb less than 90 g/L.[4] Adolescents who do not demonstrate an adequate rise in Hgb should be re-evaluated. If compliance and dosing are both appropriate then the clinician should consider other etiologies such as thalassemia, anemia of chronic inflammation, or a gastrointestinal bleed, and further investigations for IDA should be done. A thorough family history should be taken to rule out hereditary etiologies of gastrointestinal bleeding; if suspected, the patient should be referred for a colonoscopy.

In our case, the adolescent did not have diarrhea and initially did not have any rectal bleeding, which are among the most common presenting symptoms of FAP.[2,3] However, his family history included both a first- and second-degree relative who passed away from colorectal cancer at a young age, and his uncle was confirmed to have FAP. The autosomal dominant pattern of inheritance in FAP means that there is a 50% chance of passing the APC gene mutation to each child. Genetic testing for family members is offered at age 10. Unfortunately, though the uncle in our case was diagnosed with FAP, genetic testing for his family members was missed.

Screening guidelines for patients with classic FAP versus AFAP differ. Individuals with classic FAP should have flexible sigmoidoscopic examination every two years from age 12-14 years.[1] If colorectal adenomas are detected, the patient should have annual colonoscopies.[1] A colectomy is offered if polyps cannot be removed by colonoscopy alone and is eventually necessary in all patients with classic FAP.5 Patients with AFAP can be managed with colonoscopic examination and polypectomy every 2 years from the age of 18-20 years and may never require colectomy.[1] Surveillance for extracolonic malignancies for both FAP and AFAP may include upper endoscopy with side-viewing scope for gastric and duodenal polyps.[1] Surveillance may also include cervical palpation for lymph node involvement and ultrasound for thyroid carcinoma.[5] Interestingly, our patient was found to have a mandibular osteoma which is a known extracolonic feature of FAP. The combination of colorectal and extracolonic manifestations is known as Gardner syndrome.[1]

Conclusion

We report on a case of refractory IDA, a strong family history of colorectal cancer, and hematochezia. Our case reinforces that IDA refractory to adequate dosing and compliance to supplementation should be further investigated, and a family history should be taken. If hereditary etiologies of gastrointestinal bleeding such as FAP are considered, a colonoscopy should be pursued.

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Asymptomatic accelerated idioventricular rhythm in a 5-year-old girl

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Introduction

We present the case of a 5-year-old girl with an incidental finding of asymptomatic accelerated idioventricular rhythm with no history of structural heart disease. Family consent has been obtained in writing.

Case

A 5-year-old girl was referred to the community pediatrician with an incidental finding of short bursts of fast heart rate on physical examination. She was asymptomatic. There were no complaints of palpitations, chest pain, dizziness, or syncope. Her past history was unremarkable. Her electrocardiogram showed sinus rhythm with frequent consecutive premature ventricular contractions with left bundle branch block morphology (Figure 1). Her echocardiogram was normal. Her holter monitor showed predominantly sinus rhythm with very frequent monomorphic ventricular ectopics and 16% QRS complexes with fusion beats. The longest episode of the accelerated ventricular rhythm was 35 beats at 113 beats per minute. There were no pauses. The diagnosis was confirmed as an accelerated idioventricular ventricular rhythm (slow ventricular tachycardia). The child has followed a benign course without symptoms or syncope, and no treatment was required.

Discussion

Accelerated idioventricular rhythm (AIVR) is a benign arrhythmia and is often a self-limited condition, particularly in young infants.[1,2] It is an enhanced ectopic ventricular rhythm and may be confused with potentially serious rhythm disorders, such as ventricular tachycardia (VT). It has at least three consecutive premature ventricular beats, with gradual onset and termination. The usual rate of AIVR is <120 beats per minute (bpm). It is typically faster than normal intrinsic ventricular escape rate of 30-40 bpm, but slower than the rate of VT.[3-6]

AIVR is thought to be related to enhanced automaticity in His-Purkinje fibres or the myocardium. Spontaneous cell depolarization rates can be accelerated by ischemia, reperfusion, hypoxia, drugs, and electrolyte abnormalities, leading to enhanced automaticity of the ectopic focus.

Due to its slow ventricular rate, AIVR is generally a benign and well tolerated arrhythmia that resolves spontaneously without treatment.1 However, the arrhythmia should be treated in rare situations, such as sustained or incessant AIVR, or when AV dissociation induces syncope, increasing the risk of sudden death.1 In a report on 19 patients diagnosed with AIVR, 13 showed spontaneous resolution while six continued to exhibit persistent VT at their last follow-up.[7] Those who were treated appeared to respond well to all prescribed medications.[7]

AIVR can be found in patients with a structurally and functionally normal heart.8 This arrhythmia has also been associated with cardiac pathology, such as myocardial infarction in adults and congenital heart disease in children.[8-11] AIVR is often observed in the reperfusion phase following an acute myocardial infarction, drug toxicity, electrolyte imbalance, or congenital heart disease.[1,2] Treatment of underlying aetiologies may lead to complete resolution of the arrhythmia.

It is important to differentiate AIVR, which often resolves spontaneously, from pathologic VT in order to avoid potentially toxic antiarrhythmic agents.13 The characteristic gradual onset and termination of AIVR are useful in differentiating it from slow VT, which is associated with sudden onset and termination. Further criteria were proposed to differentiate AIVR from VT.8 These criteria included chance discovery, absence of symptoms, sinus isochronicity, heart rate <120 bpm, conversion to sinus rhythm with exercise, arrhythmia in short bursts, no effective drug treatment, and presence of left bundle branch block morphology. Our patient met at least 6 of these criteria. A formal exercise test was not performed, nor was drug treatment attempted.

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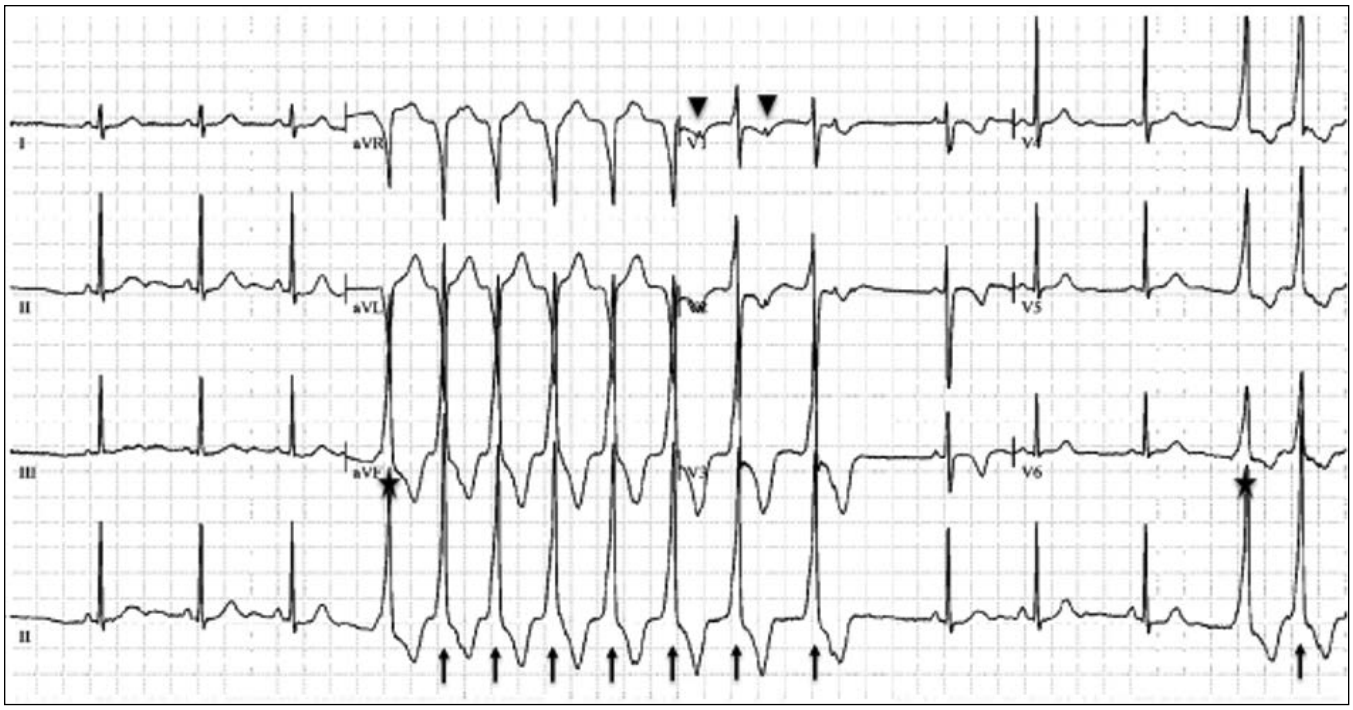

Figure 1. Electrocardiogram showing accelerated idioventricular rhythm with left bundle branch block morphology. Arrows indicate wide complex ventricular rhythm at 150 beats per minute. Triangles indicate P waves demonstrating AV dissociation. Star indicates fusion beat with a P wave, short PR interval, and narrow QRS complex. The preceding sinus rhythm is 85 beats per minute.

Conclusions

AIVR is a benign ventricular arrhythmia that requires differentiation from VT. It is generally benign and well tolerated, and most often resolves spontaneously and requires no treatment. However, patients should be followed to resolution to monitor cardiac function, as a decline in cardiac function may rarely occur in patients with frequent ventricular ectopy.13 Pediatricians can aid in differentiation from VT, emphasize the benign nature of AIVR, monitor patients, and provide reassurance.

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Acting fast on late-onset abdominal and back pain

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Abstract

Blunt abdominal trauma can cause insidious liver injury and laceration. In particular, a subcapsular hepatic hematoma may result from bleeding in the parenchyma that is contained by the liver capsule. In some circumstances, a hepatic laceration may result in delayed blood collection. A growing body of evidence has also reported the occurrence of liver hematoma associated with abdominal trauma. We describe a 13-year-old female with a late-onset subcapsular hepatic hematoma after abdominal injury. She presented with worsening abdominal and lower back pain. Her management was conservative with fluid resuscitation and in-hospital monitoring. Our case highlights the importance of close follow-up and diagnostic imaging following blunt abdominal trauma.

A 13-year-old female presented to the community physician's office with abdominal and back pain. Her past medical history was relevant for a head-on motor vehicle collision at approximately 60km/hr four days prior. She was a passenger, seated in the rear with a seatbelt. Airbags were deployed and there were no fatalities. Following the collision, she had generalized abdominal and back pain, but no other symptoms. She was taken to hospital by ambulance. Her vitals were normal, and Glasgow Coma Scale was 15. Upon examination 3 days following the collision, there were no overt signs of trauma, bruising, or injury. Her abdomen was soft, but mildly tender. The rest of her examination was normal. Focused assessment with sonography in trauma (FAST) scan was negative and cervical spine x-rays ruled out any fractures or displacements. No other radiological imaging was performed. She was provided analgesic medications and instructed to follow-up with her primary care provider.

At presentation, she complained of worsening abdominal and lower back pain. She was afebrile, tachycardic (heart rate 103 beats per minute) with a stable blood pressure (90/60 mmHg). Her respiratory rate was 20 breaths per minute with 100% oxygen saturation in room air. Her abdomen was not distended, generally tender with peritoneal signs and diminished bowel sounds. She appeared uncomfortable and was transferred to the emergency department.

Her initial hemoglobin was 64 g/L and she received a transfusion of two units of red blood cells. An abdominal computerized tomography (CT) scan revealed a non-expanding, subcapsular hepatic hematoma measuring 12x7x13 cm (Figure 1). It was classified as a grade 3 liver injury as more than 50% of the liver capsule surface area was involved. She was admitted for observation and serial abdominal examinations. Her pain improved and she remained clinically stable throughout her five-day hospital admission. Her hemoglobin at discharge was 92 g/L.

Case diagnosis: subcapsular hepatic hematoma

A subcapsular hepatic hematoma is defined as bleeding from vessels within the liver parenchyma that is locally contained by

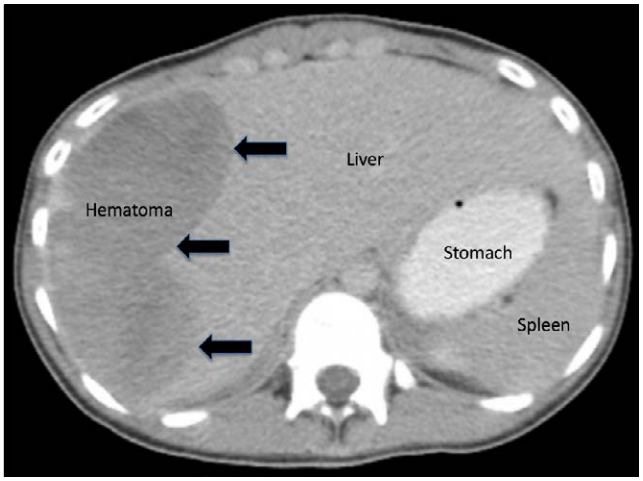

Figure 1. Abdomen computed tomography with contrast demonstrating Grade III liver injury. Note: Right subcapsular parenchymal hematoma approaching 50% of surface area without extravasation.

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Table 1. Liver Injury Scale

Grade	Injury Type	Injury Description
I	Hematoma	Subcapsular, <10% surface area
	Laceration	Capsular tear, <1cm
		Parenchymal depth
II	Hematoma	Subcapsular, 10%-50% surface area
		Intraparenchymal, <10 cm in diameter
	Laceration	Capsular tear, 1-3cm parenchymal depth, <10 cm in length
III	Hematoma	Subcapsular, >50% surface area of ruptured subcapsular or parenchymal hematoma; intraparenchymal hematoma > 10cm or expanding
	Laceration	>3 cm parenchymal depth
IV	Laceration	Parenchymal disruption involving 25% to 75% hepatic lobe or 1-3 Couinaud's segments
V	Laceration	Parenchymal disruption involving >75% of hepatic lobe or >3 Couinaud's segments within a single lobe
	Vascular	Juxtahepatic venous injuries; ie, retrohepatic vena cava/central major hepatic veins
VI	Vascular	Hepatic avulsion

Note: Adapted from Drexel et al. 2017.

the liver capsule.[1] The patient experiences abdominal pain and may have unstable hypotension and tachycardia suspicious for intraabdominal hemorrhage or shock. Most hematomas occur at the time of trauma. However, in rare cases there may be a delayed collection of blood within the liver from a continuous bleeding hepatic laceration. This may present as worsening right-upper-quadrant pain over several days with systemic signs of anemia or shock, despite negative initial investigations.[1] Due to the high vascularity of the liver, unmonitored hemorrhage can result in severe anemia, cardiac dysrhythmia, shock, and sudden death.[2]

General trauma-induced liver injury, known as liver laceration, represents some of the most common abdominal injuries. Small lacerations or intrahepatic hematomas are usually able to be managed without the use of a laparotomy.[3] This has shown to be common predominantly where rapid evaluation and potential treatment are available. Prolonged delay of evaluation and diagnosis puts the patient at higher risk of laparotomy. Outcomes in these patients have improved through direct suture ligation of bleeding parenchymal vessels, advent of damage control, and total vascular isolation with repair to venous injuries.[4]

Pliable ribs and caudally extended upper abdominal organs in pediatric anatomy contributes to a greater number of splenic and hepatic injuries from blunt abdominal trauma in children, as compared to adults.[2] A FAST scan is conducted early in all blunt trauma cases to assess intraperitoneal hemorrhage requiring immediate surgical exploration. The sensitivity of FAST scans for injuries requiring surgical intervention or blood transfusion is 87.5%.[5] In a clinically stable patient without major hemorrhage, contrast-enhanced CT is the primary modality to assess solid organ injury, including liver lacerations, hematomas, and hepatic vessel injuries.[5] The degree of liver trauma is graded based on international trauma care guidelines (Table 1). The liver injury grading is used to standardize the reporting of the degree of injury. However, it is not used as a guide for management.[6]

Subcapsular hepatic hematomas are largely managed non-operatively with fluid resuscitation and close monitoring.[7] Admission under general surgery service is recommended. Surgical management is based on hemodynamic status or worsening progress.[6-8] For general practitioners, careful re-examination of abdominal pain and transfer to a surgical centre for abdominal CT should be considered, especially if the patient presents with abdominal pain for a week or longer following blunt abdominal trauma. Positive FAST may determine if intraperitoneal hemorrhage is present, which might require surgical management.

Clinical pearls

- Following blunt abdominal trauma, symptomatic patients require close follow-up.
- Consider contrast-enhanced CT scanning to diagnose hepatic laceration when suspicion is high or symptoms persist.
- The vast majority of subcapsular hepatic hematomas can be managed conservatively but may require admission for observation.

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Primary extranodal laryngeal lymphoma: description of two cases

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Abstract

The larynx is a delicate organ which functions not only to vocalize, but more importantly for airway protection. Its structural integrity is comprised of a musculo-cartilaginous framework and an overlying epithelium, with a broad spectrum of pathologies ranging from benign mucosal retention cyst to rare soft tissue tumours. Primary haematological malignancy involving the larynx remains a rare phenomenon due to its limited lymphatic supply. The authors present two cases of primary non-Hodgkin lymphoma of the larynx which manifested with non-identical symptoms and clinical findings. Clinicians should be aware of the various forms of localized throat symptoms as well as the gross tumour appearance in a primary haematological malignancy of the larynx.

Introduction

Primary laryngeal lymphoma represents a rare entity, constituting less than 1% of all laryngeal neoplasms.[1-3] Fewer than 100 cases of primary laryngeal lymphoma have been reported worldwide to date.[1-5] Its rare occurrence can be attributed to the low lymphoid content in the larynx compared to other areas along the respiratory tract.[1,5] Non-Hodgkin lymphoma within the larynx is presumed to originate from the submucosa, which contains an abundant aggregation of predominantly B-cell lineage lymphoid tissues, as well as mucosa-associated lymphoid tissue (MALT).[4,5]

Primary laryngeal lymphoma may present with various forms of localized throat symptoms that range from just foreign body sensation to difficulty in breathing due to airway obstruction, similar to any other laryngeal neoplasm. The tumour characteristics may appear benign with smooth overlying mucosa or malignant with fungating mass: thus histopathology examination is the only avenue of confirming a diagnosis of laryngeal lymphoma. Herein, we report two cases of primary non-Hodgkin lymphoma of the larynx which manifested with non-identical symptoms and clinical findings.

Case 1

A 54-year-old male was brought to the emergency department for worsening foreign body sensation in the throat and shortness of breath for the past two weeks. He denied other associated symptoms such as changes of voice, odynophagia, dysphagia, or neck swelling. Further history did not reveal preceding foreign body ingestion, laryngeal trauma, previous intubation, recent upper respiratory tract infection, or constitutional symptoms. Upon physical examination, he appeared well-built with no clinical evidence of anaemia. There was a striking feature of intermittent inspiratory stridor with the usage of accessory respiratory muscles, indicative of impending airway obstruction. A complete head and neck examination, along with lung auscultation, were unremarkable. A flexible nasoendoscopy (Figure 1) revealed a smooth-surfaced mass occupying the laryngeal surface of the epiglottis. The mass was partially obstructing the laryngeal inlet, hindering a complete visualization of the vocal folds.

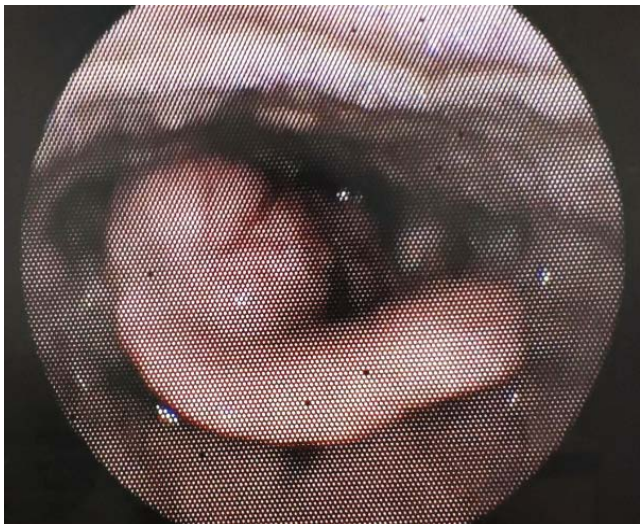

Figure 1. Flexible nasoendoscopic view of the laryngeal inlet of case 1 reveals a mass over the laryngeal surface of epiglottis (arrow). Its smooth glistening surface with a well demarcated border deceptively resembles a benign lesion, masking its true malignant nature.

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Following informed consent, the patient was brought to the operating theatre, with the purpose of airway security under a controlled setting. An attempted awake fibreoptic nasotracheal intubation was futile, so a tracheostomy under local anaesthesia was performed. The mass was seen originating from the laryngeal surface of the epiglottis upon direct laryngoscopy. It was yellowish, smooth, and hard on palpation. Other subunits of the supraglottic, glottic, and subglottic region were normal. The mass was excised and sent for histology analysis. A telescopic study of the trachea showed normal finding. Histopathological examination revealed grade 3 Non- Hodgkin follicular lymphoma with a high proliferative index (Ki-67 of 50%). The tumour sample was positive for CD20, CD23, and B-cell lymphoma-2 (BCL-2) while negative for CD3, CD5, CD15, and CD30 (Figure 2). Computerized tomography (CT) staging unveiled disease confined within the larynx (Figure 3). Bone marrow aspiration and trephine (BMAT) showed absence of lymphomatous infiltration. The patient was referred to the tertiary haematological disease centre and was treated with six cycles of chemotherapy of RCHOP regime (rituximab, cyclophosphamide, doxorubicin hydrochloride, vincristine and prednisolone). He was successfully decannulated at one-month post-treatment, with flexible nasoendoscopy surveillance showing a patent airway with mobile vocal folds. A subsequent follow up at six months post-treatment revealed no clinical evidence of recurrence.

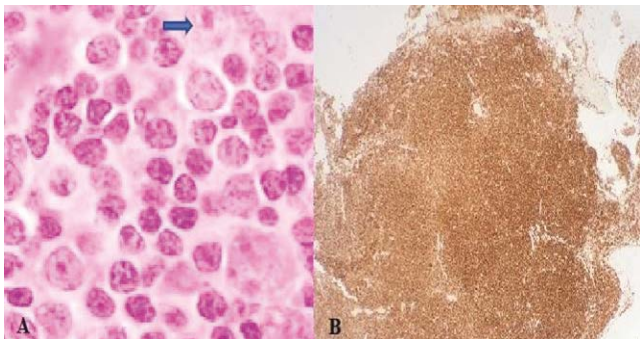

Figure 2. (Panel A) Hematoxylin & eosin (H&E) image of case 1 in high power shows homogenous infiltration of small to moderate mononuclear cells with centroblasts (arrow in blue). The small cells are mostly cleaved with hyper-chromatic, inconspicuous nucleoli and scant cytoplasm, while the centroblasts are non-cleaved with round to oval vesicular chromatic, peripherally located nucleoli. (Panel B) Immunohistochemistry staining of case 1 with a positive result for B-cell lymphoma-2 (BCL-2).

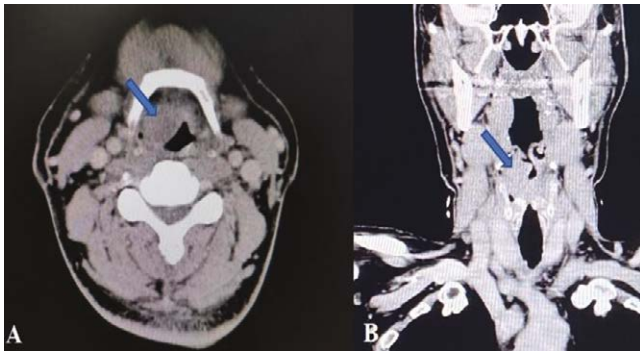

Figure 3. Axial view (panel A) and coronal view (panel B) of a contrast-enhanced CT of the neck of case 1 showing homogenous enhancing lesion at the right side of the epiglottis (blue arrows).

Case 2

A 28-year-old male chronic smoker was referred to the otorhinolaryngology department for further evaluation of a suspicious laryngeal mass following an ineffectual endoscopic transoral biopsy. He presented with worsening sore throat and odynophagia of three months duration. He also noticed a new onset of left otalgia of one-month period. He denied voice changes, dyspnoea, dysphagia, and constitutional symptoms. Further history suggested neither recent foreign body ingestion nor neck trauma. His past medical and family history was unremarkable. On examination, he spoke with a normal voice and appeared comfortable with stable vital signs. Oral cavity examination and neck palpation were normal. A flexible nasoendoscopy showed an exophytic lesion along the left aryepiglottic fold, with lateral extension to the medial wall of the left pyriform sinus (Figure 4). The vocal fold movement remained normal. He underwent contrast CT of the neck, which revealed a homogeneously enhanced lesion involving the left aryepiglottic fold and pyriform sinus (Figure 5).

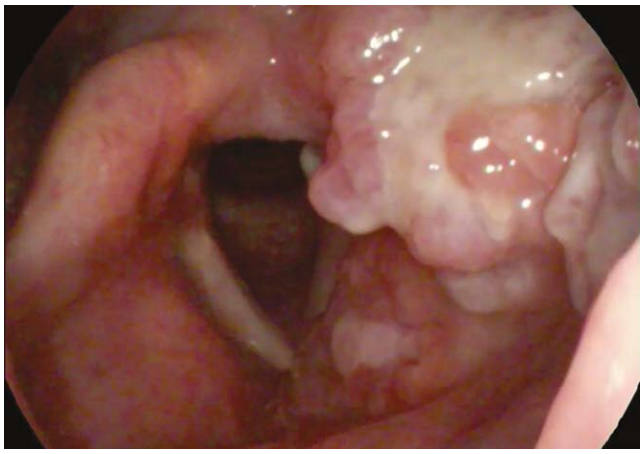

Figure 4. Videoendoscopic view of the laryngeal inlet of case 2 showing a diffuse fungating mass along the left aryepiglottic fold and arytenoid.

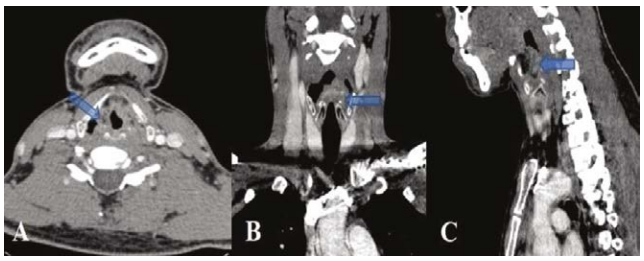

Figure 5. Axial (panel A), coronal (panel B) and sagittal view (panel C) of a contrast-enhanced CT of the neck of case 2 showing homogenous enhancing lesion on the left aryepiglottic fold. It has extended laterally into the left pyriform sinus (blue arrows).

A transoral examination of the larynx under general anaesthesia showed a friable fungating tumour from the left aryepiglottic fold and the pyriform sinus. The mobility of the cricoarytenoid joints were normal on palpation. The glottis and subglottic remained free from disease. Biopsy of the lesion confirmed the diagnosis of a NK/T cell laryngeal lymphoma with high proliferative index (Ki-67 of 60%). The specimen revealed malignant lymphoid cells

with prominent nucleoli, which were positive for immunostaining of Epstein-Barr encoding region (EBER), CD3, CD5, T-cell intracellular antigen 1 (TIA1), and CD56, while negative for CD20, CD4, CD8 and anaplastic lymphoma kinase (ALK). A subsequent positron emission tomography/computerized tomography (PET/CT) and BMAT showed localized laryngeal disease. He was planned for six cycles of chemotherapy of GELOX regime (gemcitabine, L-asparaginase, and oxaliplatin) with radiotherapy.

Discussion

The age of diagnosis of primary laryngeal lymphoma ranges widely from 4 to 81 years, with an average age of diagnosis at 70.1,[5] Reports show varied gender predominance.6 The most frequent site of involvement remains within the supraglottis, comprising 47%, followed by the glottis, of 25%.[5] The paraglottic and subglottic area, on the other hand, has been rarely reported.[5]

The clinical manifestation of a laryngeal lymphoma is indifferent from other laryngeal pathologies. Localized symptoms that have been described are namely hoarseness, odynophagia, dysphagia, and foreign body sensation, which may mimic squamous cell carcinoma.[1,5,6] Similar to the first presenting case, catastrophic presentations of an impending airway obstruction which requires immediate surgical intervention has also been reported.1 Azzopardi et al. described two cases of laryngeal lymphoma with different clinical manifestations, of which one presented with progressive hoarseness while the other presented with respiratory distress secondary to an obstructed airway that necessitated an emergency tracheotomy. On the other hand, both cases reflect how systemic symptomatology such as loss of weight and night sweats is rather uncommon.[1,2,5] The literature suggests that most reports of lymphoma involving the larynx report limited stage disease.[5,6] The first presenting case gave a history of a short duration of foreign body sensation, which turned out to be laryngeal lymphoma. Contradictory to its deceiving benign-looking appearance, the final histology examination confirmed the diagnosis of haematological malignancy. The laryngeal mass in the second case, however, appeared fungating in a cauliflower-like cluster, implicating a possible malignant pathology. Various macroscopic features of the tumour have been described in the English-language scientific literature. These include a smooth submucosal mass, papillomatous lesion, and laryngeal ulcer.[1-3] Therefore, laryngeal appearance may not serve as an ideal diagnostic indicator in laryngeal lymphoma.

Histopathological examination remains the gold standard to diagnose a primary laryngeal lymphoma.[5] A generous and deep biopsy should be undertaken as the lesion is originated from the submucosa layer.[1] Imaging modalities remain imperative in delineating its regional infiltration as well as distant metastasis. The radiological features of a laryngeal lymphoma include the presence of a homogenous mass, which enhances with contrast during CT.[4,6] Magnetic resonance imaging (MRI) may aid the diagnosis of a submucosal mass.[6] PET/CT is invaluable in the diagnosis, staging, and assessing the response to therapy in laryngeal lymphoma, especially in high grade lymphomas.[7] The management of lymphoma is largely dictated by the histopathology, rather than the anatomic location. Due to the limited number of reported cases, there is no definite consensus in the treatment of laryngeal lymphoma. However, radiotherapy or in combination with chemotherapy appears to be the emerging preferred modality of treatment.[1,2,5,6] The role of surgical intervention is merely for diagnostic purpose and airway security in the event of impending airway obstruction.[3]

Conclusion

Despite its rare occurrence, primary laryngeal lymphoma should be contemplated when generating a differential diagnosis of a laryngeal mass. A high clinical suspicion index amongst physicians is imperative as overlooking this entity may result in catastrophic consequences.

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Peripheral edema in an individual with treatment resistant major depressive disorder treated with olanzapine/fluoxetine combination

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Abstract

Olanzapine/fluoxetine combination therapy is a widely prescribed antipsychotic-antidepressant regimen for treatment resistant depression and is reported to have a side effect of peripheral edema. The theoretical underpinnings of peripheral edema in association with olanzapine/fluoxetine combination therapy are still unclear. Although peripheral edema associated with olanzapine/fluoxetine combination is rarely reported, the mechanism of drug interaction and effect on cytochrome P450 enzymes may induce it. We review the case of a middle-aged patient, who presented with peripheral edema after the administration of olanzapine/fluoxetine combination therapy.

Introduction

Treatment resistant depression (TRD) is a debilitating condition that can be perpetuated by a failure of efficacy in antidepressant monotherapy of adequate dose and duration. Remission response rates to antidepressants tend to decrease as the number of failed treatment courses increase.[1] Patients who fail two or more initial trials of adequate antidepressant monotherapy are often started on alternative treatments to control their depression symptoms. One common approach is to use a combination therapy of an antidepressant with an atypical antipsychotic as an augmentation agent. A widely prescribed antipsychotic-antidepressant drug for the treatment of TRD is olanzapine/fluoxetine combination (OFC) therapy.[2] Many studies have advocated for its increased efficacy, as it demonstrates higher remission rates and improvement in depressive symptoms when compared to monotherapy. Although OFC therapy is considered a superior treatment for TRD, it has demonstrated a variety of aversive side effects. The most common side effects of OFC therapy are increased appetite, weight gain, dry mouth, somnolence, fatigue, headache, and metabolic changes.[1,3,4] Peripheral edema can also present secondary to a medical condition, medication side effect, or idiopathic cause. In this article, we aim to present the case of a patient with TRD, who developed drug-induced peripheral edema after the administration of OFC therapy, to highlight the relationship between the two.

Furthermore, a literature search was conducted using key terms, such as "Treatment Resistant Depression", "Olanzapine Fluoxetine combination therapy", "Edema", and/or other combinations, to assess whether similar cases were described within the current literature on peripheral edema. No cases were found that assessed the development of peripheral edema in individuals with TRD on OFC therapy.

Case presentation

A 36-year-old, university-educated male twin with TRD exhibited symptoms of low mood, anhedonia, difficulty in managing activities of daily living (ADLs)/instrumental activities of daily living (IADLs), disturbed sleep, social isolation, apathy, amotivation, reduced energy, diminished concentration, reduced appetite, and passive suicidality. He had had a diagnosis of major depressive disorder for 16 years. Initially, he was exhibiting mild to moderate depressive symptoms, which progressed to severe depression with a recurrent episode that had worsened within the past year. He was referred to Ontario Shores Centre for Mental Health Sciences to receive electroconvulsive therapy (ECT) and to stabilize his symptoms. Previously failed drug class trials included antidepressants (almost all selective serotonin reuptake inhibitors, SSRIs, and serotonin and norepinephrine reuptake inhibitors, SNRIs), mood stabilizers, anxiolytics, hypnotic medications, intranasal ketamine, and ECT without continuing benefits.

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Medication on admission to Ontario Shores was brexpiprazole (1.5 mg), fluoxetine (40 mg), and gabapentin (1200 mg). A trial OFC therapy was recommended. The patient had a previous trial of olanzapine (12.5 mg) monotherapy, and combination therapy of olanzapine (7.5 mg) and divalproex (1000 mg). Fluoxetine dose was increased to 60 mg, and an olanzapine-brexpiprazole cross taper was initiated. On day one, olanzapine was started at 5 mg and brexpiprazole was reduced to 1 mg. After 6 days, olanzapine reached 15 mg dosage and brexpiprazole was discontinued. The patient indicated improvements to his mood and appetite after medication changes were made.

Within a month after the commencement of OFC therapy, the patient had an onset of pedal edema. He was ambulatory and experienced no pain associated with edema. Blood pressure was stable, and peripheral pulses were palpable 2+ and symmetrical. He had good perfusion, however his feet were warm upon examination. There was 1+ to 2+ pitting edema to the mid-tibia bilaterally. There was mild symmetrical, non-tender swelling on the calves and ankles, and Homan's sign was negative. There were no signs of erythema, ulceration, or colour change on the edematous area. He had no significant past medical history or other chronic medical co-morbidities of congestive heart failure, cirrhosis, renal failure, nephrotic syndrome, or any other systemic disease. No abnormalities were found in complete blood count, renal function, hepatic panel, thyroid function test, or basic metabolic panel.

The patient had been on gabapentin (1200 mg) since 2018 and did not experience any side effects during his continuous use. Gabapentin was tapered by 300 mg every 3 days until discontinuation 9 days later to account for its possible confounding effect on the patient's peripheral edema. Following gabapentin discontinuation, the patient presented with the same findings. The swelling was more prominent with leg-dependent activities, such as standing or sitting. The patient used various techniques to reduce the peripheral edema, including elevating or changing leg positions to alleviate the swelling, not wearing constricting socks, and wearing sandals if the swelling notably worsened.

The patient reported a substantial reduction of his depressive symptoms on OFC therapy. He also reported associated symptoms of fatigue and weight gain of approximately 9 kg. The doses of fluoxetine and olanzapine at the time of discharge were 80 mg per day and 20 mg per day, respectively. No reductions to OFC therapy were made since the patient noticed improved changes in his mood. The patient was advised to weigh the benefits of continuing OFC treatment with the side effects.

Discussion

Patients with TRD are at a higher risk of increased morbidities, which include a greater risk of suicide, substance abuse, and social impairment, than patients with depression treated to full remission.[1] As patients accumulate more unsuccessful treatment trials, there is an increase in demoralization and hesitancy to adhere to alternative pharmacotherapy as well as an increase in reduced remission rates.[5] The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) treatment trials have displayed that the use of OFC therapy can result in remission rates of 25.5% for those with TRD.[3] Other studies have also revealed that participants on OFC treatments experience a rapid onset of action and a sustained improvement of depressive symptoms. Such outcomes are displayed through higher remission rates and lower relapse rates than participants on olanzapine and fluoxetine monotherapies.[1] OFC-treated patients also demonstrate significant improvement in Montgomery-Asberg Depression Rating Scale (MADRS) scores.[3]

Reports in the current literature demonstrate mixed findings on aversive side effects related to OFC therapy when compared to olanzapine and fluoxetine monotherapies. Peripheral edema is reported in ≥ 5% of patients as a result of OFC therapy; additionally, peripheral edema presents at a rate significantly higher than fluoxetine and olanzapine monotherapies.[6] Luan et al. reported that even though OFC therapy did not demonstrate higher adverse events in their study, when compared to monotherapies, it had a higher discontinuation rate due to undesirable outcomes.[6] There is no evidence of clinically significant risk of extrapyramidal symptoms while using OFC therapy in comparison to olanzapine or fluoxetine monotherapy.[3,4] Long-term use of OFC therapy, however, resulted in weight gain and metabolic changes, including increased glucose, increased total cholesterol, increased triglycerides, and decreased high-density lipoprotein cholesterol.[1,3]

This patient's genetic assay revealed extensive metabolizing across the cytochrome P450 system. There is a possible pharmacokinetic interaction when both olanzapine and fluoxetine are combined due to the inhibition of CYP2D6 and other cytochrome P450 enzymes by fluoxetine.[7] Olanzapine undergoes extensive Phase I and Phase II metabolism, achieving maximum plasma concentration after 6 hours and forming inactive metabolites in the liver. Fluoxetine is metabolized by CYP2C9 and CYP2D6, and it does not follow a linear pharmacokinetic profile like olanzapine. With dose increments, the plasma concentration of fluoxetine does not increase in a dose-proportional pattern.

Fluoxetine appears to increase serum olanzapine levels. Healthy non-smoking adults were given fluoxetine (60 mg per day) in addition to olanzapine (5 mg) and were found to have an olanzapine plasma concentration 18% higher in comparison to the same dose given in the same subjects without the combined fluoxetine.[7] In addition, OFC-treated rats showed an increase in extracellular serotonin (338%), dopamine (332%), and norepinephrine (260%) in the prefrontal cortex after 4 hours of administration of OFC therapy.[8] These findings may suggest that olanzapine could enhance the psychotropic activity of fluoxetine through additive or synergistic effects by increasing the inhibitory effect on the presynaptic serotonergic reuptake transporter.

Conclusion

This case looks at the use of OFC therapy in TRD resulting in the side effect of peripheral edema. Interestingly, the patient was previously trialed on olanzapine monotherapy in 2012 as well as a combination therapy of olanzapine and divalproex in 2015, and peripheral edema did not ensue with either trial. Furthermore, fluoxetine with brexpiprazole combination therapy was trialed in 2019 and peripheral edema was not evident. Current literature shows olanzapine monotherapy can cause peripheral edema.[9,10]

Since the initial use of olanzapine did not prompt the onset of edema in our case, we can suggest the presentation of peripheral edema was due to the combination of olanzapine and fluoxetine therapies. Gabapentin is another medication known to cause peripheral edema, however the patient had been taking it for one year prior and peripheral edema was only noted after OFC therapy initiation. After gabapentin was discontinued, symptoms of peripheral edema persisted. Lastly, this patient was found to be an extensive metabolizer across the cytochrome P450 system, which plays a significant role in the metabolism of both fluoxetine and olanzapine. The lack of remission in TRD is associated with an increase in morbidity and greater chance of impairment. Given this alternative, some may choose to make lifestyle modifications to cope with associated side effects in order to alleviate the symptoms associated with psychiatric illness.

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Inflammatory myofibroblastic tumour of the urinary bladder: a rare entity

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Abstract

Inflammatory myofibroblastic tumour (IMT) is a type of neoplasm composed of myofibroblast and fibroblastic spindle cells, with presence of inflammatory aggregates of plasma cells, lymphocytes, and eosinophils. However, IMTs rarely occur in the urinary bladder. We report a 20-year-old man who presented with haematuria for two days. Cystoscopy revealed a solitary tumour arising from the dome of the urinary bladder. The patient underwent trans urethral resection of bladder tumour (TURBT). The tissue histopathology examination (HPE) of the bladder tumour was suggestive of IMT of the urinary bladder. IMTs in the lower urogenital tract are special type of IMT. They are usually associated with surgical trauma and have been proposed to be an exuberant reparative reaction. Some IMTs are very aggressive, spreading locally, recurring, and requiring pharmacotherapy. A typical IMT can be locally aggressive and may require radical surgical resection (radical cystectomy) with close follow-up.

Introduction

Inflammatory myofibroblastic tumour (IMT) is a tumour of fibroblastic and myofibroblastic spindle cells associated with inflammatory infiltration of plasma cells, lymphocytes, and eosinophils.[1,2] Urinary bladder IMT is a rare entity.[1,2] It is important to differentiate this tumour from malignant spindle cell tumours.[1] The histopathological examination for IMT routinely shows proliferation of spindle-shaped cells with infiltration of plasma cells and lymphocytes. Immunohistochemical staining of the tumour will be positive for anaplastic lymphoma kinase (ALK), smooth muscle actin, and vascular endothelial growth factor (VEGF). If the immunohistochemical staining is positive, it is indicative of an IMT and it is suggested to use the inhibitors of ALK and VEGF as pharmacotherapy.[1]

The first case of IMT of urinary bladder was reported in 1980.[3] It was characterized by atypical spindle cell proliferation and inflammatory cell infiltrates primarily involving lymphocytes and plasma cells. Although it has been associated with trauma, surgery, and infection, the majority of IMT cases occur spontaneously. IMT is classified as intermediate (rarely metastasizing) tumour according to the WHO classification of soft tissue tumours.[1] Common involvement of IMT tumours are omentum, retroperitoneum, pelvis, and abdominal soft tissues in 73% of cases.[3] It is highly unusual to occur in the bladder.[2]

Case report

A 20-year-old man presented with gross haematuria with blood clots for two days. He had no abdominal pain or other bleeding tendencies. He had no history of taking any traditional medications, anticoagulant, or antiplatelet agents. He was a non-smoker. The patient had no past medical history. He denied any previous history of hospitalization. He also denied any urinary tract symptoms. Clinically the patient was pink with normal vital signs. No abdominal mass was palpable. Ultrasound abdomen done after haematuria resolved noted the presence of a urinary bladder mass (Figure 1). Computed Tomography (CT) scan staging revealed a 3.6 cm x 3.2 cm well-defined, macrolobulated lesion arising from the right anterolateral aspect of the urinary bladder with no evidence of metastasis (Figure 2). Cystoscopy demonstrated a solitary tumour arising from the dome of the bladder with query involvement of detrusor muscle (Figure 3). The patient underwent trans urethral resection of bladder (TURBT) on the same setting. The tissue histopathological examination (HPE) of the bladder tumour was suggestive IMT with no muscle involvement (Figure 4). Thus, he was planned for surveillance cystoscopy every 6 months for the first 3 years. No additional therapy was administered for this patient.

Discussion

IMTs range from benign to locally invasive and they have been proposed to be caused by chronic infection, an immune or autoimmune condition, trauma, surgery, or other malignancies. Commonly these tumours are found as isolated nodular lesions in the lungs, mesentery, retroperitoneum, or omentum.[5] They rarely occur in the genitourinary tract. IMTs in the lower urogenital tract

may be a special type of IMT associated with surgical trauma and have been proposed to be an exuberant reparative reaction.[6] We were unable to determine the likely cause of the IMT in our patient. Von Recklinghausen disease has also been reported to be associated with bladder IMT, but other typical characteristics of this disease such as orbital pseudotumour and thyroid lesions were absent in our patient.[2]

From the literature review, IMT is characterized histologically by an inflammatory infiltrate, and various microbes have been isolated from lesions (such as mycobacteria, corynebacteria, the Epstein-Barr virus, and human herpes virus). Infection has long been suspected to play an important role in IMT pathogenesis.[7] Although some IMTs are very aggressive, spreading locally, and recurring after successful excision, the IMT lesion in our patient

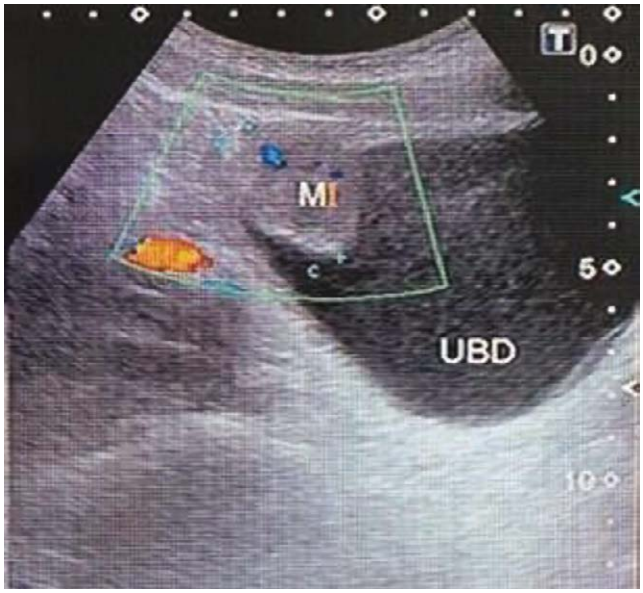

Figure 1. Ultrasound showed presence of urinary bladder mass

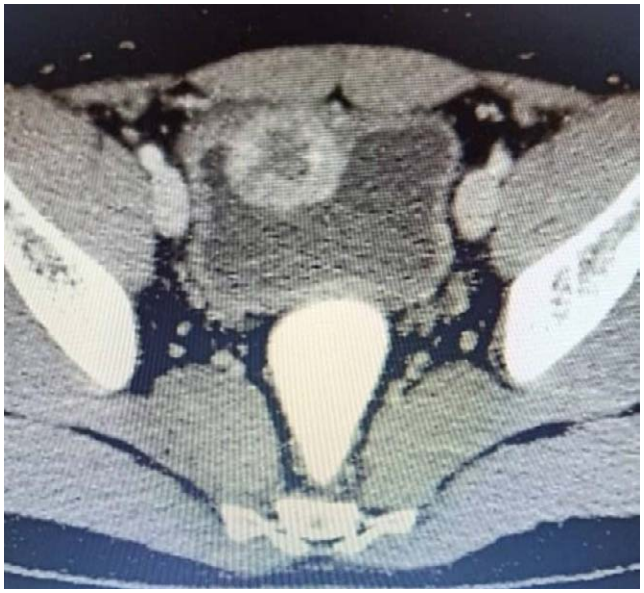

Figure 2. CT scan staging revealed a 3.6 cm x 3.2 cm well-defined, macrolobulated lesion arising from the right enterolateral aspect of the urinary bladder

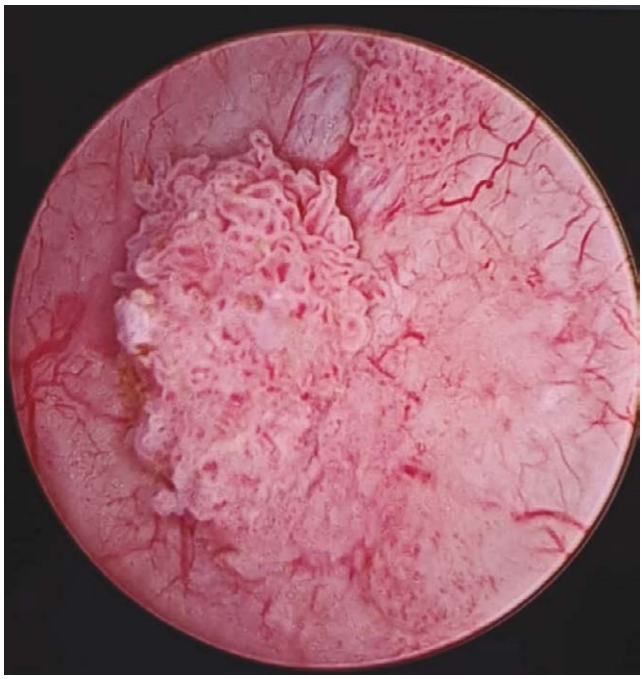

Figure 3. Cystoscopy showed solitary tumour arising from the dome of the urinary bladder

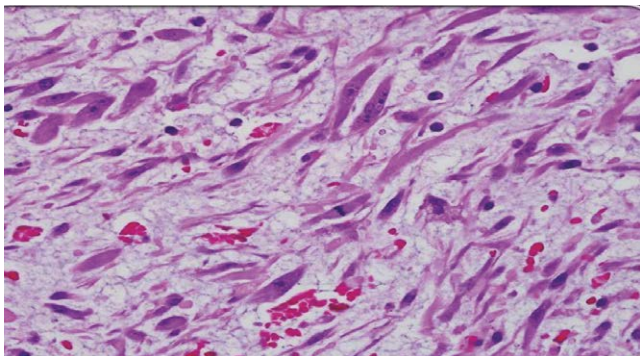

Figure 4. Microscopic features of markedly pleomorphism, plump spindly hyperchromatic to vesicular nuclei and coarse chromatin. Some with prominent macronucleoli. Elongated eosinophilic cytoplasm. Mitoses are present

appeared to be inflammatory rather than malignant. This is based on the tissue histopathological examination (HPE) of the bladder tumour which was suggestive IMT with no muscle involvement. The detrusor muscles of the bladder were preserved, which are usually involved when a bladder tumour is aggressively malignant like in sarcomatoid.[8] IMTs resemble malignant spindle cell tumours, such as sarcomatoid carcinoma, leiomyosarcoma, or rhabdomyosarcoma, making diagnosis difficult.[8]

Recent reports have indicated that ALK, which was originally identified as a protein overexpressed in anaplastic large-cell lymphomas, was overexpressed in a substantial proportion of IMTs of various anatomic location including urinary bladder.[9] A positive finding of ALK by immunohistochemistry in up to 87.5% of IMTs can be useful for the differentiation of IMTs from other spindle cell tumours in urinary bladder.[1] In this case, ALK immunohistochemistry was positive and useful for a definite final diagnosis.

Surgical resection is the initial therapy recommended for IMT of the bladder; complete surgical resection is important to avoid local recurrence.[9] In a systematic review undertaken in 2014 with total 120 patients, most patients underwent TURBT (60.8%), others had partial (29.2%) and radical cystectomy (9.2%). During follow up, 5 of the 73 patients who underwent previous TURBT experienced local recurrence.[6,10] Partial or radical cystectomy can ensure complete resection of the IMT, but in view of its benign disease course TURBT remained as an option for those patients who are reluctant to undergo a major surgery; the disease course of IMT should be explained thoroughly and the form of treatment should be highly individualized and tailored according case by case scenario. For locally aggressive or malignant IMTs, pharmacotherapy can be considered.[1] Cyclooxygenase-2 (COX-2) and VEGF expression have been detected in IMTs and may present therapeutic targets, thus enabling the use of COX-2 inhibitors such celecoxib.[1,11] An ALK inhibitor, crizotinib, has also been used in the treatment of IMTs.[1,11]

Crizotinib has been used successfully in the treatment of ALK-driven tumours in children, particularly IMT and anaplastic large cell lymphoma (ALCL). The clinical trials conducted by the United States Children Oncology Group (COG) demonstrated a complete response (CR) in 36% and partial response (PR) in 50% patients treated with crizotinib in ALK-positive IMT.[12,13]

Conclusion

In conclusion, IMT within the urinary bladder is a rare neoplasm of unknown malignant potential. A typical IMT of the urinary bladder can be locally aggressive and may require surgical resection (TURBT or radical cystectomy). Close follow-up with interval clinical and radiological monitoring for local recurrence and distant metastases is therefore warranted.

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Global plastic surgery case rounds: a low-fidelity global health tool to maintain trainee engagement during residency

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Significant inequities continue to exist with respect to the delivery of global surgical care. Surgically treatable conditions currently comprise 30% of the total global burden of disease and 11% of disability-adjusted life years.[1,2] A growing recognition for the significant health and economic burden of surgical disease treated by plastic surgeons has led to a newfound interest in incorporating formal global health education into surgical training. There is also increasing concern that surgical training has become dependent on tertiary institutions, with a decreasing emphasis on developing surgical skills in low-resource settings.

Traditionally, global health education during residency is administered via didactic teaching and the opportunity for international mission experiences.[3] These opportunities are effective at improving cultural competency and knowledge.[4-7] However, plastic surgery trainees continue to face barriers to engagement over the course of their residencies. Such barriers include a lack of institutional support, financial and time restrictions, insufficient mentorship, and a lack of recognition that global surgery is academically legitimate. To many trainees, these barriers are compounded by rigorous clinical and academic demands, which unfortunately put global health interests on hold over the course of their 5 to 7 years of surgical training.

In an effort to address these barriers and engage residents in a low-demand and time-flexible fashion, the authors hypothesized that online global surgery case rounds would provide a platform for cross-cultural learning and international collaboration. In 2015, the Resident Global Surgery Collaborative (RGSC) was jointly created by plastic surgery trainees in Canada and the United Kingdom. Every 3 months, 45-minute-long case-based rounds were held between plastic surgery trainees in developed and developing institutions. Meetings were typically attended by 10 trainees from 3 to 5 countries worldwide and moderated by at least one attending surgeon to ensure quality assurance. Cases were typical shared by one host institution and followed by discussions of clinical and surgical approaches specific to each resource setting. As such, trainees learned to address common plastic surgery problems using a range of diagnostic tools and surgical techniques that reflected the diverse cultural and socioeconomic backgrounds of attendees. Cases were also typically followed by the presenter distributing relevant literature around the topic to international attendees. Case round scheduling was featured on the RGSC website where residents were given the opportunity to sign up for meetings around their busy schedule.

The bidirectional exchange of knowledge and experiences through the RGSC has been invaluable in educating trainees to treat surgical disease with varying resources, tools and techniques. Trainees learn to appreciate the manner in which the social determinants of health impact the delivery of global surgical care and challenge them to find innovative ways to deconstruct the social and institutional barriers that lead to healthcare inequities. Perhaps most significantly, the RGSC has successfully provided a much-needed dialogue between like-minded surgeons-in training across the globe, hopefully inspiring long-term partnership and collaboration.

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Interview with Dr. Jeff Kwong

Huaqi Li and Raumil Patel

Dr. Jeff Kwong

Dr. Jeff Kwong is an epidemiologist, a specialist in public health and preventive medicine, and a family physician. He is the Program Leader of the Populations and Public Health Program at ICES (a research institute that houses a large array of linkable health-related databases), a Scientist at Public Health Ontario, and a Professor at the University of Toronto. As a Clinician-Scientist, he practices family medicine one day per week and devotes the rest of his time to research and teaching at the interface between primary care and public health. His research interests include infectious diseases epidemiologic research using large linkable databases, influenza vaccine and vaccination program evaluation, and assessing the health and economic burden of infectious diseases.

UTMJ: Can you tell our readers a bit more about your work and career in infectious disease and public health thus far?

JK: I'm trained as a public health physician and I'm a clinician scientist, and I do research on the epidemiology of respiratory viruses including influenza. I also work as a family physician 1 day per week at the Toronto Western Family Health Team. For my research, I work at ICES and also at Public Health Ontario. At ICES, we link many large health-related databases at the individual level to do epidemiologic research studies.

UTMJ: With COVID, what does your day-to-day look like?

JK: We're doing lots of analyses of laboratory COVID testing data, generating estimates like percent positivity at different levels of geography, providing these data to the Ministry of Health and local public health units to inform their decision making. I've also been involved in research studies looking at predictors of COVID testing and diagnosis, doing some media interviews to help with the pandemic response, and seeing patients in clinic.

UTMJ: Many countries, such as Canada and the US are experiencing a second or third wave of COVID. What are your thoughts on this in general and what do you think we could have done better to prevent this?

JK: There is a lot we could have done: greater adherence to public health measures (wearing masks, hand-washing, physical distancing), because all of these things definitely help prevent local transmission. I think we could have done more for travelers coming in, such as enforcing quarantine. Some countries have made it mandatory for travelers to quarantine in hotels for 14 days before going anywhere. That is something we could have done more of in Canada in my opinion. I think we could have been more aggressive in our testing, although I do appreciate that we were limited by laboratory capacity. More investments in public health for both laboratory testing and contact tracing probably would have been helpful as well. So, all of these are things we wish we could have done earlier, but now it's a lot harder that we're seeing so many cases. Other things we can still be doing are ensuring that everyone has paid sick leave, especially essential workers who often have no choice of staying home if they're sick—they have to go to work to provide income for their family. Or providing isolation centers for individuals who can't adequately isolate, such as a crowded family of 7-8 people in a 2-bedroom apartment. It's very hard to properly self-isolate under such circumstances, so providing isolation supports would be helpful. I think these are some of the things that could be done to try and mitigate the second wave.

UTMJ: Especially with the holidays coming up, do you think there's anything we can do regarding airline restrictions?

JK: They've been talking about requiring testing for people who are flying. I think that would be helpful, but not the only solution to the problem as you could still be incubating at the time you get tested. I've heard of some places where, when you arrive, you get tested and then go into quarantine and then get tested 5-7 days later and then you're released, so that could be one solution. In the Atlantic provinces, now you can't quarantine with anyone or if you do quarantine with somebody, then everyone in the entire household needs to go under quarantine for the entire period. I think we just need to take the lessons learned from these places and apply them everywhere else.

UTMJ: How has your practice changed during the pandemic? How do you counsel patients on topics like herd immunity and the role of vaccination?

JK: We're trying to do as much virtually as we possibly can, so I do lots of phone calls and video calls with patients. We only bring people in for essentials, such as vaccines or when we need to examine patients. We do standard counseling around minimizing social contacts and following physical distancing and masking recommendations. When people do come in, everyone is masked up, clinicians wear PPE (mask, face shield) and are washing hands frequently, and we wipe down surfaces after seeing each patient. So, it hasn't been a huge change. I think in a way it has accelerated the move towards virtual care, which is probably a good thing. It's generally not efficient for patients to take half a day off work, drive to the doctor, and then sit in the waiting room, all for a 10-minute appointment. A lot of people are actually much happier with virtual care because they can be at home and just wait for the doctor to call them. I think there is a lot of good that has come out of this in terms of healthcare delivery, at least in the out-patient setting.

UTMJ: What are your thoughts on "The Great Barrington Declaration", a statement written by public health experts from Harvard, Stanford, and Oxford urging government officials to lift lockdown measures and let the virus run its course to promote herd immunity?

JK: I don't think it's a good idea. There are a lot of vulnerable people and it's not possible to separate them entirely from everyone else. Bottom line is if we tried this, we'd see a lot of deaths as a result and we certainly do not want that. There's also a lot of uncertainty about how long immunity lasts for, so even for people who have been infected, we don't know how long until they can be re-infected. There hasn't been any country that has tried this and proven it will work, and I think for good reason. I don't think they'd want to suffer the number of deaths that would result if they proceeded with that route.

UTMJ: How can we address anti-vaccination especially now when the issue has seemed to have shifted away from vaccine safety to patient autonomy and civil liberties - is science losing the battle against the anti-vaccination movement?

JK: I would say no—there is a small but vocal minority who are truly anti-vaccine, but what we should pay more attention to is vaccine hesitancy. There are a lot of people who may have some hesitations about getting vaccines, but I think it's about understanding the risks and burden of the disease and the safety and effectiveness of the vaccine. When most people are presented with the facts on any disease and the accompanying vaccine, most choose to get vaccinated. In the context of COVID, I think mostly everyone is aware that COVID can cause serious illness and right now we don't know how safe and effective the vaccines are. In the news of the past week or so though, a couple of candidate vaccines seem to be highly effective. Hopefully these and the other vaccines that complete the clinical trials are shown to be effective and safe. When people know a vaccine against a serious disease is safe and effective, I think vaccine hesitancy won't be a huge problem. I actually think vaccine supply will be a bigger problem – how many doses of vaccines will we have available as we try to roll out vaccination campaigns. So, I'm not as worried about vaccine hesitancy as I am about vaccine supply.

UTMJ: How can we provide equitable supply of the vaccine if some may require special storage facilities (such as extremely cold temperatures) that are not available in all areas?

JK: For storage, the Pfizer vaccine has to be kept at -70C and you'd need specialized freezers, but they can stay at standard fridge temperatures for 5 days. If you can ensure that you can get them into people's arms quickly, then that would be okay. There is the Moderna vaccine that can be stored at regular fridge temperatures for 30 days, so perhaps you have the Pfizer vaccines for urban centres where they may have those specialized freezers and then use the Moderna vaccines in rural settings where there is a longer time to transportation and they might not go through as many doses as urban centres.

UTMJ: How do we decide which vaccine is safe to use?

JK: The process is undertaken by Health Canada. They approve each vaccine and review effectiveness and safety data to decide which vaccines to approve.

UTMJ: How can we improve our communications to the general public, especially those without expert knowledge or who don't have a scientific background?

JK: I think this is where you have to get people specialized in communications to prepare materials to communicate the message effectively. There are some obvious things like translating the materials into as many languages as possible so people can understand what is being said, and then also making the messages accessible to people at a level they can understand and coming up with messages that they will react positively to. The latter aspects are easier said than done.

UTMJ: How do you navigate information that seems potentially contradicting? For example, early on in the pandemic, wearing masks was discouraged whereas now they are essentially seen as a necessity and have been mandated in many areas.

JK: I think that's a reflection of the evolution of our understanding of COVID and also the reality that initially we were facing a shortage of masks and other PPE, so we initially wanted to reserve them for healthcare workers. Now there is more supply and we can also use cloth masks. We know now that wearing masks both protects the wearer and is a form of source control as it prevents spread from someone who may be infected but is not aware they're infected. If we all wear them, we can reduce overall transmission, and if you do get exposed while wearing a mask, we think there is less viral inoculum, which may lead to a milder infection, so that's why we now encourage everyone to wear masks. I think we have to accept that sometimes we don't know and we have to make decisions based on the best evidence available at the time and that these recommendations can change as we get more knowledge. So, I don't think we should think of them as contradictory guidance, but more as an evolution of guidance as we gain more knowledge.

UTMJ: Pandemics build sudden interest and new plans for our health systems that seem to be ignored after the pandemic subsides. How can public and global health physicians and scientists take advantage of the window of opportunity provided by the COVID-19 pandemic?

JK: That's a really tough question. I was a PGY-1 during SARS in 2003. After the SARS pandemic, there was a lot of investment and they created Public Health Ontario and the Public Health Agency of Canada. Since the 2009 H1N1 pandemic, there has been slippage in ongoing investment in public health resources and capacity. It's hard because the politicians are looking at the next political cycle, so their horizon is much shorter, so they may say, "well, we can use this money to invest in public health and pandemic preparedness that may not happen during our time in office, or we can use this money in other areas that have a more immediate impact." That is why there is a natural tendency for public health resources to wax and wane in between pandemics. I think the lesson to be learned from it is to not allow that to happen and to maintain a higher level of preparedness because we don't know when the next one will be. We don't know what will happen in the future, but having preparedness is vital. I think we are seeing the consequences of not having adequate laboratory and public health capacity at this time with COVID.

Interview with Dr. Andreas Schleicher

Monish Ahluwalia and Sabrina Campbell

Dr. Andreas Schleicher

Dr. Andreas Schleicher is Director for Education and Skills at the OECD. He initiated and oversees the Programme for International Student Assessment (PISA) and other international instruments that have created a global platform for policy-makers, researchers and educators across nations and cultures to innovate and transform educational policies and practices.

UTMJ: Could you tell us a bit about yourself and your work?

AS: I am the director for Education and Skills at the Organization for Economic Cooperation and Development (OECD). We pursue international comparisons by looking at the experiences of global education systems and their successes. Our most well-known effort is the Program for International Student Assessment (PISA) where every three years we assess the quality of learning among students. We know how long students spend in classrooms and how much money is spent, but we know little about how students can apply their knowledge creatively. We're not only interested in cognitive skills, but also social and emotional development. These are often hard to measure with traditional tools, so at the OECD we design and develop new tools to conduct these comparisons.

UTMJ: Is it reasonable to say that COVID-19 has created an educational crisis worldwide?

AS: I think so. Young people are least vulnerable to the virus itself, but conversely, they suffered among the most from public policy responses. About 1.5 billion students are locked out of schools. School closures not only impact learning, but also social interaction, engagement with an organized environment, and connection with teachers. At the OECD, we're trying to determine how we can reconcile this health situation with education. There are no clear-cut answers nor precedence, so we try to help countries learn from each other.

UTMJ: Which groups are most impacted by this crisis?

AS: Well, remote learning works well for high school students, but it's difficult for early years and primary grades. Early childhood education is all about social-emotional development, and a tablet can't help much there. Second, those from disadvantaged backgrounds, especially those without access to digital resources or home support, have suffered greatly. These kinds of social disparities exist both within and between countries.

UTMJ: Where should we focus our efforts to target specifically these populations?

AS: I think the first step is to re-establish education, and this is a prerequisite to rebuilding and restructuring learning. The crisis has taught us that we need to rethink what we focus on in school. What matters most now is your capacity to be resilient and work together despite differences. We must think harder about what knowledge, skills, attitudes, and values education needs to provide to make people fit for the future. The second thing is doubling our efforts toward disadvantaged students. Some countries have responded well by planning for students to learn during holidays and receive additional support, but more needs to happen. From experience, disparities that exist in school only grow wider throughout life, and public policy can make a difference. We also need to be smarter about integrating technology and learning. Learning is not a place, it's an activity, and we need to capitalize on development of, for example, augmented reality, learning analytics, and big data.

UTMJ: What are some of the other short-term impacts of school closures?

AS: Violence at home for children has been an issue. As a teacher, when you see a student with bruises on their face you can call social workers and parents. Similarly, child obesity is increasing with decreased activity and there are many other issues around the child well-being. Some of these are hard to measure and generalize, but there are many reports of this nature.

UTMJ: What are some of the long-term impacts of school closures?

AS: Well, if you learn less in school, you will be a less productive worker. We think that Canadians affected by this CO-

VID-19 school generation will see approximately 3% less lifetime earnings. This translates to hundreds of billions of dollars lost due to less opportunity. It's a large price to pay, and it's very inequitably distributed. This is not even mentioning the social costs. What about students who have lost their connection to learning? Maybe you didn't like school before and during COVID-19 you turned elsewhere. Are we going to get those people back? I don't know.

UTMJ: Noting all the negative impacts of school closures, how do we reconcile the health situation with education?

AS: I think the biggest question is how we make trade-offs between the present and future. As an individual, you think about how much spend today and how much to invest in the future. As a country, you make the same decisions. Education means you invest in people today to have a more cohesive and productive environment for tomorrow. In a way, your schools today will be your society tomorrow.

This link is most notable in East Asian countries, who have been very successful in improving their education systems because they're willing to invest their last resources, effort and finances on them. In the western world, we've already spent those resources on ourselves. I think it's a very difficult trade-off that greatly impacts our future.

UTMJ: In the Western world, what are some of the issues with our education system?

AS: One of the biggest challenges I've seen in the last 10-15 years is a growing trend of commodification of education. Students became consumers, schools became passive, teachers became service providers, and parents became clients. This has created a distance that isn't conducive to education. Learning is not some service industry, it's a society-wide project. COVID-19 has helped with this. I think parents are paying more attention to the education of their children and teachers are paying more attention to how individual students learn differently, especially in the online environment.

I also believe the education industry needs to draw on other experts and professions. This is not the time for instructors, rather coaches, mentors, facilitators, and evaluators. I think a lot of people with different skills can come together. This is also the time for public to work with private, instead of competing. Especially with technological solutions, there are many synergies we can build with these partnerships.

UTMJ: This seems like an educational revolution.

AS: I think you have revolutions in many different places, but whether they will scale up is unclear. There's a risk they slip back into a worse status quo. We could end up with complete fragmentation of education where people turn to their own solutions.

Some countries like China have seen great implementation of technology in their school systems. Teachers have collaborated in unprecedented ways to develop and design new learning environments. With the pandemic, we have seen efforts to completely reconfigure the people, spaces, technology, and time, that's quite a courageous step. You have probably seen less reform but more change in education than ever before.

UTMJ: What do you mean by more change but less reform?

AS: Often what we do in education is add another process on top, like add a new curriculum or new level of teacher education. However, very little changes in the classroom. Looking at the learning outcome scores for a country like Canada, there have been marginal improvements over the past 20 years but no transformational reform.

Now by change, I mean what happens in the minds of students: their attitudes, aspirations, knowledge, and skills. I think we've seen the emergence of new skillsets like a greater emphasis on teamwork. Before the pandemic, we talked a lot about agency and your capacity to do something. Now people talk about co-agency – how do we work with people who are different from us. For example, wearing masks carries a social responsibility. Our individual actions have implications for others and what others do has implications for us. I think this is an interesting development.

UTMJ: How might health care professionals contribute to education?

AS: Healthcare and education are tightly interdependent – you're not going to learn very well in school if you're not healthy. I think teachers need to be more aware of the emotional, social and physical well-being of their students and healthcare workers need a better sense that emotional health really depends on education. Maybe schooling in the future post-pandemic will not just be an academic institution, but also a place where healthcare professionals, education professionals, and psychologists will work closer together.

UTMJ: What are the next steps for the OECD?

AS: Our priority is to accompany countries through the recovery process economically, socially and educationally. In my Directorate, this means building better schools and universities by re-imagining what we need for the future. In a time of artificial intelligence, we need to ask ourselves what it means to be human. This is centre to our future work at the OECD.

Interview with Dr. Brian Goldman

Ryan Daniel and Grace Lee

Dr. Brian Goldman

Dr. Brian Goldman is a veteran emergency room physician at Mount Sinai Hospital in Toronto and the host of two popular CBC radio shows, *White Coat, Black Art*, and *The Dose*. He is a successful author of three published books, *The Night Shift: Real Life in the ER*, *The Secret Language of Doctors*, and *The Power of Kindness*. He has been involved in multiple high-profile speaking engagements including a 2011 TED Talk on medical errors and the culture of medicine. Dr. Goldman is a highly respected healthcare advocate and voice for Canadians from coast-to-coast, and the UTMJ was thrilled to hear about his unique insights regarding the COVID-19 pandemic.

UTMJ: How do you feel about your role as a prominent healthcare informer, especially during times of a public crisis such as COVID-19?

BG: The first thing I should say is that it's a privilege to have a platform to talk to Canadians through my *White Coat, Black Art* [podcast] and, since February, with our new podcast The Dose. They work in a complementary way. *White Coat, Black Art* tells stories about the patient experience inside the culture of modern medicine. *The Dose* gives information that people can use and is generated by questions that come from our listeners, through social media and emails. *The Dose* is "news you can use" and *White Coat, Black Art* involves stories. Not surprisingly, both shows have pivoted to COVID-19 now because that's what the public wants to know about.

It's an awesome responsibility, but not unique or different compared to our overall mandate within the CBC. We have Journalism Standards of Practice (JSP for short), which are rules and guidelines that are very much like a "code of ethics" that guide us. We want to present information that is balanced, and as far as we know, that is accurate. We're not broadcasting information that's hearsay, or [that is based in] rumours. If we have a sense that there is a vested interest in the information - that it is controlled by commercial or political interests - then we're certainly not going to present it, not without proof. That doesn't mean we won't discuss a topic such as the current demonstrations in downtown Toronto against the use of masks. We will discuss the anti-vaxxer movement, but in its context as a political statement as opposed to a factual [statement]. We did the same thing with the vaccine hesitancy movement. There's a misconception that people have about [being] a public broadcaster: that you're obliged to present both sides as if they're equal. We came to the conclusion a long time ago that the science is well in favour of using vaccines, and that the anti-vax movement is based in fear, not in fact. So, we don't feel obliged to present both sides equally.

UTMJ: As both a public health advocate and a physician, how do those two roles play off each another? Do you feel a greater responsibility to the public because of your role as a physician during these times?

BG: Let's start with hosting a radio show or podcast. There's no question that from the first moment I wrote newspaper and magazine articles in the early 1980s (for The Globe and Mail, The Toronto Star and Maclean's Magazine) to today, [when I am] hosting two radio programs, I have known that the media likes having experts. The information that experts present is considered more trustworthy, and the media knows that readers care about what physicians have to write and say on radio, television and social media. I've never had any difficulty getting my message "out there".

COVID-19 has certainly reinforced the need to be accurate based on the latest science, and to adapt with new information, so that's certainly an imperative. But, there's nothing new about COVID-19; I've always felt that awesome sense of responsibility to be as accurate as I can. This is because I want to give good information to the public, but also because people are going to come after you very, very quickly if you're expressing a point of view that's based in vested interests or if you frame information in a way that's obviously political or is a cheap shot.

The only thing that's different now with COVID-19 is that we have the public's attention like never before. When we're talking about dyslipidemia, high blood pressure or obesity, we might have people's attention, but these conditions are not going to "kill you tomorrow". They might increase your risk of dying prematurely over the next 10, 15 or 20 years, which for most people is almost never. But with COVID-19, what you do or don't do could affect your life, or your loved one's life if they live in long-term care, are over 75, or have other risk factors. So that immediate sense of danger, and the immediate engagement is something that's very different.

Now, does it affect the way I practice? Not because of COVID-19. There's no question that having a relatively

high profile in Canada makes me cognizant when I practice in the Emergency Department. A lot of people know who I am, and if they don't know who I am by looking at me, they certainly recognize my voice after a while. And that happens every shift. Clearly, I'm not going to be the guy who doesn't wash his hands. [COVID-19] probably has me on my best behaviour.

UTMJ: Has this greater responsibility as a public health advocate added further stress in addition to the stress that physicians already face during the pandemic?

BG: COVID-19 has added stress, but not because I'm a broadcaster. It's spending the entire shift wearing PPE. Being in and out of PPE every time I go into a room to see a patient. To put things in perspective, we're not inundated with patients who have COVID-19 in the Emergency Department. We weren't during the first wave at Sinai Health. We saw patients with COVID-19, but there were parts of the Peel Region, Brampton and Richmond Hill where they saw a large number of patients with COVID-19. So, we were more fortunate - but we still had precautions. You never know when the next patient might have COVID-19, and there's such a broad set of risk factors and symptoms, that you have to assume that a lot more patients have COVID-19 than appears. That means there's an increased vigilance - and that's stressful. There's an increased need for PPE – that's stressful. There's a fear that a patient who does have COVID-19 will deteriorate, and you'll have to do a protected code blue procedure - which again, is stressful.

So, I don't think it's the broadcasting. I think it's the COVID-19 aspect that's added to the stress level for all of us.

UTMJ: Is there anything about the field of medicine that wasn't on your radar prior to the pandemic, that's come to the forefront for you?

BG: Although it certainly has always been on the radar, something that has become much more urgent with the advent of COVID-19 is [our society's] disparities in income, and opportunities. We've always known about these; we've done lots of stories on White Coat, Black Art about whether marginalized populations (such as Indigenous and racialized communities) get equal access to medical care. And our stories show that they don't.

But for it to be upfront - that people who are homeless, who come from racialized backgrounds, who are Indigenous, who are older, who have disabilities, and who have dementia, are more likely to get COVID-19, be in the hospital with COVID-19 or die from COVID-19 - certainly added a layer of urgency to these stories that wasn't there before. And I'm glad we're paying attention to them. These are certainly stories that we've covered on White Coat, Black Art, and we will continue to do so.

I think another story that has become really important is the politicization of medical advice. To see masks or vaccines, for instance, become a statement of which party you vote for - as has particularly happened in the United States and to an increasingly disturbing extent in Canada - was an eye-opener. We knew it with diseases like measles, but it's different because a significant percentage of the Canadian population is vaccinated against it. COVID-19 though, is a novel coronavirus to which nobody is immune to (unless they contracted COVID-19 itself which is still a disputable way of becoming immune). The main way that we're going to combat this in the long run is to have a vaccine that is safe and effective. And the idea that in the United States, for instance, approaching 50% of the population is skeptical about whether they would get the shot is incredibly disturbing. So that's something that has more urgency because of COVID-19.

UTMJ: What's the one issue that concerns you the most about COVID-19 and its effects on neglected patient populations?

BG: There are several, but I think the one most disturbing effect of COVID-19 is its impact on long-term care homes and frail seniors. As you know, approaching 70 to 80% of the people who have died of COVID-19 in this country have died either in long-term care or were elderly patients. I think it's a black mark on our record as a Western nation with publicly funded health care - we have to be able to do better.

When we look at some of the reasons for this, it's crumbling infrastructure [and] multi-bed and multi-resident rooms in long-term care. It's treating personal support workers as if they hold a disposable occupation, when in fact they are some of the most important people [in our society]. The idea that personal support workers are supposed to get by on an income of $15/hour is absurd. They do incredibly important work, and unless and until we fix the problem of looking after some of the most vulnerable people who get COVID-19, it will be a black mark on our reputation for providing decent health care. Up until very recently, the new uptick in COVID-19 involved younger people. But we are starting to see more outbreaks in long-term care facilities, and with that, more frail seniors who are dying of COVID-19 - just as we did in the winter and spring.

UTMJ: In one of your recent podcasts on The Dose, you talked about the severe isolation, and depression that residents in long-term care homes experience. How do we strike a balance between safety and compassion with long-term care homes?

BG: Back in the first wave of COVID when we were telling people to stay home, businesses were being shuttered and long-term care homes were on lockdown, essential family caregivers were designated as visitors. They were earmarked to stay home, [and told] "you're not allowed to visit". There was a huge misconception here - which we did stories about on White Coat, Black Art - surround-

ing the notion that essential family caregivers could be labelled as "mere visitors". [For example,] my late father fed my mother (when she had dementia and was staying in a long-term care facility in North Toronto) twice a day until he could do it no longer. Then my sister came in and I came in on the weekends. When it took 15 minutes to spoon-feed my mom, it was easy. But then it was 20 minutes, 30 minutes, 45 minutes and eventually it was an hour and a half [to spoon-feed]. I can tell you there is no staff that is going to spend an hour and a half, or even 45 minutes, spoon-feeding anybody's loved one in a long-term care facility (unless you hire them privately). There just isn't enough staff to do that. So, when long-term care facilities designated intimate family members, partners, adult children or even close friends who just wanted to volunteer as "mere visitors", it completely dismissed and trivialized what they do. [These family members and friends] are, in many respects, just like personal support workers. They are the backbone of care provided in long-term care facilities and anybody who's got a loved one there long enough knows exactly what I'm talking about. So, the good news is that the system has finally recognized that essential family caregivers must have access.

The other thing you're talking about is the lack of stimulation, including the lack of other visitors, such as grandchildren, who say "hello", spend time with and cheer up their grandparents. There is no question that residents of long-term care facilities have missed this stimulation and their moods have gone down - what we don't know yet, is by how much. And this is coming from geriatricians, like Dr. Samir Sinha and Dr. Nathan Stall. We have to do better and find that balance. If you believe that you cannot train a visitor to wear PPE, wash their hands properly, screen themselves for symptoms, and have their temperature taken at the door - if the system is that strapped for cash, and infrastructure - I'd be very surprised. I just don't believe that's true.

I can understand that during the first wave, [there was] this sense of shock. There was a sense that "we have a lot of problems to solve with the novel coronavirus, so we're going to put [visitation] a little lower on the list of priorities". But we know a lot about the virus now. The idea of forbidding long-term care residents from having adequate stimulation and time spent with loved ones is, I think, absurd and tragic. We need to find a better balance this time, frankly.

UTMJ: One of your books explores the power of kindness in yourself and in those all over the world. How do you think that being kind and empathetic can help the medical community, as well as the community at large, get through this pandemic?

BG: I think that kindness and empathy can help in many different ways.

First of all, we are hardwired to be kind; it's in our brain architecture. We have "dual-purpose" neurons that are simultaneously capable of performing an action and lighting up when we observe somebody else performing this action. They allow us to experience a disgusting taste in our mouth and to look at somebody else who has the same disgusted look, which triggers the same set of neurons to light up. Neuroscientists believe that this is the seat of empathy.

[Empathy] begins in infancy, when parents bond to their children. Children, through a process called behavioural synchrony, begin to mimic one another's facial expressions, hand movements and eventually, vocalizations, words and songs. This is the beginning of attachment. Without attachment, you wouldn't have parents looking after their kids. Without attachment, you wouldn't have parents looking after other kids in a community.

In our more primitive nature, there is an instinctive capacity to recognize others as belonging to another group - which psychologists referred to as an outgroup. So, we have ingroups and outgroups; ingroups are "my people" and outgroups are "somebody else's people", and potentially "my enemy". Within the nervous system, we can look at somebody's facial expressions, their tone of voice or their turn of phrase, and begin to ascribe nasty things to [the outgroup]. If I decide that somebody belongs to my ingroup, then I will give him/her the benefit of the doubt; they're kind, charitable and ethical. So, we have these duelling capacities inside us to be empathic or kind and, on the other hand, to recognize enemies [so we can] either run away from them or gear up to fight. How do we make that decision? It turns out this "us versus them" thinking is part of our primitive brain architecture. We have giant frontal lobes and executive function that allow us to say, "That makes no sense. I'm just being prejudicial".

So, what does that have to do with COVID-19? COVID-19 is a massive stressor. There are lots of people who are stressed out by the imminent risk of dying, of losing their business, losing their social contacts or having food insecurity. The more stress we feel, the more likely we are to suspend our executive functioning and lapse into that primitive "us and them" behaviour. That's what you're seeing in the United States today, with a lot of these demonstrations in favour of Donald Trump - and I am going to get political here! I don't think he's a force for good during the pandemic. We could argue about the destruction to the economy and how much damage it's doing to people, which I think is considerable. But I think that a polarizing debate saying, "The economy or your life - choose" is a false dichotomy. I think that an enlightened approach says that the economy will do better when we take better care of people living in society, do a better job of surveying society for COVID-19 and protecting these people against it.

UTMJ: At the End-of-Life Public Forum in 2014, you talked about care at the end of life from your perspective and its importance in light of our aging population. With that in mind, how has COVID-19 impacted care at the end of life and how has the medical profession adapted?

BG: Well, there's no question that end-of-life care has been adversely affected by COVID-19. [This occurred] particularly during the first wave, when hospitals absented visitors and family members from being with their loved ones at the end of life. When a patient was deemed to be within hours of dying, family members were generally allowed at the bedside. But this didn't necessarily include the whole family; maybe one caregiver or family member would be allowed, and they would have to switch. There were different policies in different places and frankly, some hospitals defied the rules or interpreted the rules in different ways. I certainly know there were some concerns about access to medical aid in dying, which was a lot more difficult during the first wave of the pandemic. Medicine adapts and I think we're seeing adaptations in end-of-life care.

The biggest thing that we are adapting to, which is more in society than in medicine, is how to handle deaths and funerals. We've lost so many people in Canada to COVID-19 and to other causes not related to COVID-19, that [this period] has left a whole cohort of Canadians grieving silently and alone. They are unable to congregate with their extended families and friends to remember people they love and have to resort to using online platforms like Zoom to communicate. We don't know the impact of that on the psyche and mood of Canadians and it's something that I think we need to look at carefully. We need to be aware of just how difficult it is to try to grieve during the time of COVID-19. There is something cathartic about a funeral, about a remembrance in a public forum and a graveside service.

Personally, I remember that when my father died (almost exactly seven years ago today, in 2013), I was astonished by the show of love and affection, and the sheer number of people who came to his funeral in North Toronto. That's something that cannot happen today. We need those symbols. The living needs those symbols to be able to acknowledge a death and [they need] the opportunity to extend or receive sympathy - it's part of the healing process. I don't know what it feels like for people going through [the grieving process] right now. Personally, I know that one of my wife's cousins lost her husband suddenly, in September - not to COVID but to other causes - and they live in Winnipeg. As a result, aside from good friends, there was a large extended family that was not able to be there, to hold her hand or hug her and say, "we're with you". I know what it is like from that standpoint, and it is something that's very disturbing.

UTMJ: During one of your podcast episodes on White Coat, Black Art, you interviewed community paramedic Matthew Cruchet, regarding the Virtual Triage Assessment Centre (VTAC). This is a program designed to meet the healthcare needs of people in rural Renfrew County using community paramedics. With regards to returning to normal after the pandemic, Cruchet stated that, "Normal with respect to healthcare would be a step backwards". With that in mind, what are some of the positive changes in healthcare that have been implemented due to the COVID-19 pandemic, and do you envision these changes continuing post-pandemic?

BG: There are certainly some positive developments, and I'm glad you noticed that show. I think we are slowly evolving to this notion that healthcare is best for patients when they are served by a team, and not by one person. During [COVID-19], with the sheer necessity to reduce the number of people who come to the hospital to receive care, the idea that patients can receive care at home became a necessity. The [VTAC] program was wildly successful in a population, Renfrew County of the Ottawa Valley, where a lot of people don't have access to a family doctor, or they have a family doctor who has a panel of 5000 patients and can't possibly take care of all of them. These people often don't live in multi-generational families and often live by themselves after a partner has passed away. While they do have adult children looking in on them, all too often they have no means of transportation, they don't drive a car, there is no taxi service, or there's a taxi service but there is no public transit. In these situations, dialing 911 would be their only option. This [VTAC] program shows dramatically that if you align a system where a single phone call puts you in touch with a trained medical receptionist who can triage the situation, arrange a consult with a family doctor virtually or by phone, and then dispatch a paramedic for immediate care if necessary, the system works - and is cost effective if you want to do it. The program also has allied health professionals at their fingertips, including registered dieticians, nurse practitioners, social workers, physiotherapists, etc. Cruchet and Renfrew Paramedic Chief Mike Nolan have made the point that programs like VTAC should be a standard everywhere. It is in some countries, but it isn't here.

Unfortunately, all too often we have great experiments that are pilot projects that end up going nowhere. That's not to say that community paramedicine isn't making inroads - it is in other parts of Ontario, Nova Scotia, Alberta, and elsewhere. So that's one silver lining. Another silver lining is the growth of virtual health care. Does every medical complaint require an in-person visit? No, of course not. And certainly, there are people who depend on telemedicine who know that's not true. I think the provinces have been very slow to establish decent fee codes to enshrine virtual visits in the fee schedule. British Columbia was the first [province] in the country to do so and we did a show about that five or six years ago. We've [Dr. Goldman's podcasts] been on top of those developments and that is certainly something that COVID-19 has accelerated. In the future, having more point of care testing is something that is very exciting. Having disposable electrodes that can provide an ultrasound image that is connected to your smartphone, point of care blood testing or having a cardiologist be able to auscultate your heart and take your vitals without being there are all possibilities in the future. Right now, the technology we use is often 10 years out of date, it's clunky and not very user-friendly. I suspect that new medical technologies will continue to

evolve, become disposable, get cheaper and provide a wealth of information that will bridge the gap between a physical examination that occurs in person and a physical examination that can occur virtually. However, it's going to take a while for it to occur. Will COVID-19 spur that on? I hope so. But I'm not necessarily sure about that and certainly during this season on White Coat, Black Art, we will look at other innovations that are silver linings of the pandemic.

I've talked about technological advances, but how about just eradicating some of the differences in opportunity and privilege in our society and seeing what impact that can have on the general health of Canadians? I suspect the impact will be far greater than the slickest piece of medical technology at a patient's fingertips.

UTMJ: For many people, the pandemic has prompted deep self-reflection. Is there anything that you have learned about yourself during the pandemic?

BG: I've learned a lot of things during the pandemic. For one, I am not immune to stress. There have been days when I've had trouble sleeping and functioning. In the months prior to the pandemic, I got back to something that I've done most of my adult life, which is running. I run 8-10 km at least three times a week, so not a trivial amount of running. What I've discovered is that if I don't run for a certain number of days, I really start to get stressed out. I become anxious, I become more irritable, and I have to run to induce a sense of calm and well-being. Even more than that, I have to run to feel as normal as possible. What I am saying is that, very often, I don't feel normal because of the pandemic. And so that transformation [running routinely] has become very necessary for me.

Another aspect is that I'm old enough to be closer to retirement than to the beginning of my career, so the pandemic has gotten me to think a lot more about what it would look like to not practice medicine. It has also made me grateful that I have a job - actually two jobs, working at the CBC and in the hospital. I can't imagine how stressful it would be to have my job hanging in the balance by a government grant or to have a career in an industry that seems on the "endangered" list, like cinemas or managing a duty-free shop in an airport. Think about all the industries that have been decimated during the pandemic. We're maybe halfway through it now - or are we a third of the way through it? I don't know. My daughter got her first job, after graduating from university with a Bachelor's in Business Administration, working for a company that makes and supplies air filtration systems. All I'm thinking is, "thank goodness that you've got a job that's growing and not shrinking due to the pandemic!". So overall, I would say the pandemic has forced me to think about the things I'm grateful for because it is so easy to lapse into complaining and moaning. Ultimately, I have no reason to do so. I think it's really important that we maintain an attitude of gratitude. And, to remind ourselves that whatever we're going through right now, things could be worse. Just look around and listen, and you'll find somebody whose story is worse.

UTMJ: Since the start of the pandemic, is there one clinical anecdote that stands out to you?

BG: Yes, this is a personal one. Early in the pandemic, we'd [emergency medicine physicians] been doing a lot of training in protected code blues with stringent forms of protection, including wearing N-95 masks, face shields, two sets of gloves, and special gowns. We'd practiced the donning and doffing procedures routinely because it's during the doffing procedure when, if you do it incorrectly during an intubation, you can expose yourself to a high dose of COVID-19. I remember practicing during SARS in 2003. That was about 17 years ago - and 17 years is a long time. I'm a lot older now and unfortunately, I'm old enough to be in more of a high-risk group so that if I got COVID-19, I might have a more serious prognosis. I remember coming to the hospital to do a night shift during the first wave. I was getting a handover from a colleague about half my age, who had just been working from 9PM to 4AM. And he offered to spend the night doing my intubations so that I wouldn't have to do an intubation and risk getting COVID-19. In our medical culture, your first impulse when you hear that is to think, "Oh, he thinks I can't do intubations?" or "Does he think I'm fragile?". However, it was quickly followed by a sense of gratitude. Here's a guy who wanted to take [a shift] off my list. I could have answered him back and said, "But, you're a young father" or "There are young people who have gotten a bad case of COVID-19 and who have died of COVID-19 too" or "Wouldn't it be better if I got COVID-19 instead of you, since I've lived a long good life and been able to benefit from the privilege of being a physician for over 30 years?". So, there was an internal debate there. But suffice it to say, that I was touched by his willingness to take one for me. His name is Paul Koblic. And he's an amazing guy. He's one of the kindest, most empathic physicians I've ever met, and I'm proud to call him a colleague.

UTMJ: You have engaged in such diverse forms of health promotion throughout your career - from being the author of three books, to having two very successful radio podcasts and many prominent speaking engagements, including a TED Talk! What advice do you have for medical students wanting to get involved in health promotion? What have you learned along the way?

BG: For me, I didn't call it health promotion - I just called it writing. There are certainly people who want to use writing exclusively for health promotion and I'm not saying that there isn't an alignment of those goals. But, when I write a book about empathy or kindness or what it's like to work in the emergency department, it may or may not be with the goal of health promotion. It's certainly to inform, enlighten, and entertain to some extent. Because

if you're not writing books for the public that entertain them, then you should be looking for a different media, unless you want to write textbooks. And even textbooks, I think have to grab you at some level. So, first of all, write about what you like. And, don't turn down opportunities to write or appear on podcasts just because they're not what you might think of as "top drawer" opportunities. I cut my teeth, if I can use that expression, or I got my 10,000 hours in the "Malcolm Gladwell" sense, writing for all kinds of freelance publications that were aimed at healthcare providers. I wrote for the Canadian Medical Association Journal, I wrote for MD Magazine and many other media outlets. And slowly but surely, I honed my craft. Then I took a shot and aimed towards some of the mass media outlets like magazines, newspapers, and ultimately public broadcasting.

If you're going to do that, you have to take it as seriously as you take your medical studies. That means taking courses, accepting feedback, accepting criticism, and being devoted to self-improvement. The first documentary I ever did on the CBC was for a show in the late 1980s, called Sunday Morning. It was a radio show and I went through nine versions of that documentary (it was only 27 minutes long!) until it was suitable to get on the air. Through that process, I'm grateful to the people who spent a lot of time helping me make my work better. If someone offers you help, take it. Don't be too proud to think you don't need it - or that if you do need it, there's something wrong with you. We are all lifelong learners.

I would also say that one thing today that didn't exist when I was getting started, is all the fellowships [for example, the Munk Fellowship in Global Health] where you can get postgraduate training to help you get a leg up on health promotion and writing. I would also say gain expertise in what you want to write about, so you can write about what you know. The more you do that, the more you will become a trusted voice in the world of media. Be respectful of the job, be grateful for the job, but also know the limits of the stories that you want to tell. It's tempting to find intimate stories, but make sure that you get permission from the people whose stories you want to tell. Professional ethics is certainly something that you have to abide by if you're going to wear both hats [physician and writer].

UTMJ: Finally, what general advice do you have for healthcare professionals in training (such as medical students, pharmacy students, nursing students, and others) in light of this pandemic?

BG: My general advice to young healthcare professionals today is to work hard, but do not let the work define you entirely. Leave yourself time to have a life outside of healthcare - to love, to be loved, and to do things that you love to do. Make sure that you keep that light on and don't sacrifice it all for your medical training. You'll find that life goes by very quickly if you do that, and you don't want to be somebody who looks back with regret at the things you didn't do. I would also say that as somebody who strived to be the best, believe me, 10 years out, nobody's going to care where you grew up or graduated from medical school. So, think about that.

And be human. Recognize that to be human is to try - but to try is to make mistakes. I think that medicine, in particular, has been very slow to embrace the concept that making mistakes is not a crime against humanity - that it's part of being human. Instead of looking for scapegoats or looking for people to blame and admonish, it'd be better if we taught others not be ashamed of themselves for making mistakes, and to find constructive ways of dealing with mistakes. All too often when somebody makes a mistake, we identify, isolate, and separate them - instead of making them part of the solution by having them teach us how not to make the same mistake in the future. These are observations that I've made over a lifetime in medicine. I did a TED Talk about that and continue to receive emails and notes from people saying [the TED Talk] has changed their career. They realized they weren't alone in making mistakes. That is probably the last thing I want to say: if you do make a mistake, you're not alone, you're part of a huge community.

Redefining leadership during the COVID-19 pandemic: an interview with John Yip, CEO of Kensington Health

Prem Nichani

John Yip

John Yip, a highly respected leader in ophthalmology and community health, is the CEO of Kensington Health in Toronto, Canada. He accrued his reputation as a leader in previous roles as the Vice-President of Corporate Services for Health Quality Ontario, a managing consultant for GCI, the IT and business consulting services giant, a senior consultant at PricewaterhouseCoopers Consulting, and a consultant at KPMG. John has made significant strides in health, reducing cataract surgery operating room turnover times from 30 minutes down to a mere seven which is integral when such a procedure has a waitlist of over a year amidst a rapidly aging population. His experiences, insights, and achievements are profoundly influential, not just for other current and future CEOs in healthcare but also for any front-line worker who is willing and dedicated to making an impact during this unprecedented COVID-19 pandemic. There is much to learn from John in terms of leading a revolution to transform and innovate within our healthcare system for the better.

PN: Why do you think health systems innovation and transformation is so important during these times?

JY: Innovation and transformation are really just buzz-words that people use to look at cost-containment in the current environment of ballooning deficits. The system is complicated by inefficiencies, tax-payer funds, and a highly political environment. One of the simplest ways to enact change is to get the media involved and that is what happened during COVID.

It takes a good crisis to move people, structural barriers, and innovation forward. I am not going to diminish the tragedy that is unfolding; lives have been lost and that damage is irreparable. This crisis has revealed our vulnerabilities, not just in health care, but also human elements including our cravings for social interaction. In the former, we saw how fragmented our system was with the inability to deal with a global pandemic.

Three examples are as follows: (1) Virtual care adoption has skyrocketed; trying to launch this pre-COVID was like pulling teeth; (2) LTC [Long-Term Care] homes are finally getting much-needed attention, funding, and advocacy. The public now understands the importance of LTC and the negative impact a lack of support can have on our patients and families; and (3) The intersectoral nature of our system is improving where LTC homes, hospitals, and primary care are more interconnected than ever and where relationships have deepened significantly.

I would not call these 'innovations.' They are not very innovative, and we have been speaking about them for decades. This pandemic forced us to enact the change we needed 20 years ago because we had no choice. I think that our focus on innovation and transformation are misnomers as they force us to think too far out of the box when the answers are clearly in front of us. Rather than thinking of new ways to solve problems, let's focus on improving quality of care by looking to other sectors, observing what works best for them, and piloting some of those ideas in health. Post-pandemic, we will have a better system. That is my hope.

PN: If you had to hire a person to take your place at Kensington Health, what qualities would you look for in this leader to improve the quality of care at your organization?

JY: Leadership does not need a title. Rather, it is about doing what is best for your organization. We have overlooked a lot of people who help in delivering bedside care. Everyone at Kensington is a front-line hero in some way. I royally screwed up on the simplest tasks while on the floor during COVID and a dietician called me out for possibly contaminating the food. It does not matter if I am the CEO or a residential aid; if I make a mistake that can impact the patients negatively, I should be called out on it. Leave no stone unturned. Erin had the grit and the 'balls' to tell off the CEO and that is commendable.

If I had to make the decision for our next hire, I would look for courage, integrity, and selflessness. Leaders need to understand the movement of the current and swim upstream when needed despite it being difficult. They also need to be true to themselves; it will garner trust. If you mean what you say and act on it, you will build strong relationships and those around you will help you in your endeavors. If you are trustworthy, you will have each other's backs; when one says, 'let's dance,' you will both dance. Finally, it is not about you. Treat others the way you want to be treated and you will get everyone to dance with you. Hopefully, this will lead to influencing someone else with your idea so that someone says it like it is their own and gets credit for it because that is when you realize that you really made an impact.

Whether you are a physician, cleaner, or nurse, there will be competing priorities for your time, clinically, financially, and personally. We are the privileged 1%, but do not forget your role in the system. Remember, you are here to put the patient first because that is a person just like you, an entity that is a part of your community.

PN: Who or what in your life do you look to for guidance when you have hit a rough patch?

JY: The whole experience during COVID was very cathartic and I had held my emotions all in. My board chair pointed out that I was burning out and I did not realize it. I could not sleep, gained a lot of weight, ate unhealthily. I unfortunately had to bag deceased bodies in transparent bags with a Sharpie to mark their names; I could not get that image out of my head. Twenty-four hours prior, I was feeding them.

I turn to mindfulness and introspection. My mornings start early with a run to see the sun and clear my mind. I also bike to work to be alone, reflect, and keep my stress on the road so that I am calm when I get to work or back home. This has helped me to obtain clarity on who I am and who I am not which helps me to better structure my actions to get to where I want.

COVID or not, dealing with stress is tough so find that outlet to release. Set goals; my new one is to run every street in the city of Toronto, and I am 6% there. I've seen so much that I have not seen before from communities, historical houses, and artwork that have changed my perspective on our diverse city. There is a theme here. I did not have to go far to explore; I was just in our backyard. Same thing goes for innovation. In short, balancing your work and personal life is imperative but reflecting will guide you to new heights. Just remember not to get ahead of yourself either; be proud of who you are but remember that you always have room to improve.

PN: What is one piece of advice you would give to yourself looking back to pre-COVID times?

JY: Stay the course. Hold the mind. Believe in yourself. It will be uncomfortable, and you will want to break and deviate from what you have to do. Bring people along for support and stick with it. Ultimately, it will always get better despite how small or foggy the light at the end of the tunnel is. When the self-doubt comes in when I am biking a longer route or in a triathlon, I talk to myself in third person and walk myself through one step at a time, "John, you can do it. John, bike to the next street, don't stop. Bike to the next, don't stop." We got through the first COVID wave and I know we are ready for the second. This sounds cliché but there are so many times I wanted to give up; I would have regretted it. Pain is temporary; glory and the success of saving lives is forever.

PN: Any final words?

JY: In short, this is a conversation greater than leadership. There are things you cannot predict will happen. How you react to those events is what will shape who you are; they are what got me to where I am today.

Nancy Schlichting's unconventional leadership: the comeback of the Henry Ford Health System

Justin Shapiro

Nancy M. Schlichting

Nancy M. Schlichting is a retired Chief Executive Officer of Henry Ford Health System, a nationally recognized $5 billion healthcare organization and recipient of the 2011 Malcolm Baldrige National Quality Award. She is credited with leading the health system through a dramatic financial turnaround and for award-winning patient safety, customer service, and diversity initiatives.

Schlichting joined HFHS in 1998 and was named President and CEO of the System in 2003. Retiring in 2017, her career in health care administration spans over 35 years of experience in senior level executive positions. Among the many awards received, Schlichting was honored as one of the 100 Most Influential People in Healthcare by Modern Healthcare magazine, as well as named to the Top 25 Women in Healthcare.

JS: How did you become a healthcare leader?

NS: I had many difficult healthcare experiences since I was young. When I was ten, my mother got sick and was in the hospital for a month. In high school, I wanted to be a doctor. However, at Duke I spent time in the ER as a pre-medical student and decided that the clinical side was not for me. I could not handle the blood and the emotional challenges of the interactions that I observed. It was then that I found a graduate program in hospital administration. As soon as I began coursework in health policy, I knew that was my calling. I am a big picture person. I loved working with clinicians, but I felt I could influence healthcare more in health administration. I never turned back and it has been my work for over forty years.

JS: What did you do before leading the Henry Ford Health System?

NS: I got an administrative residency at Memorial Sloan-Kettering in New York and then I worked towards a fellowship at the American Hospital Association and Blue Shield Association of Chicago working for the presidents of those organizations. I then went back to my hometown of Akron, Ohio and started as an assistant administrator in operations, but moved quickly to lead strategic planning for a 650-bed teaching hospital. I was appointed Chief Operating Officer of the hospital at 28. Thirteen years later, I managed eleven hospitals in two states. Then, one day, I got a call from the former Chief Operating Officer of the American Hospital Association who ran the Henry Ford Health System (HFHS) in Detroit. He was a great mentor for years. He asked if I was interested in joining HFHS, and I stayed there for eighteen years. I started there as Chief Administrative Officer, then quickly became Chief Operating Officer, and was appointed CEO in 2003. It has been quite a journey.

JS: Governor Whitmer of Michigan tasked you to co-chair the Michigan Economic Recovery Council. Describe that experience and the impact of COVID-19 in Michigan.

NS: We started two weeks after the shutdown in March and have been working for three months. It has been an amazing experience. I feel honored and thrilled to have had a chance to contribute to this crisis when I am no longer running a health system. I am privileged to help lead all the healthcare leaders in Michigan. We created robust analytic infrastructure to sort the data behind the decision-making. We are monitoring the capacity of the healthcare system and all the elements critical to ensuring we reopen quickly but safely. Michigan had the third-highest cases in the country and the third-highest deaths. We are now considered one of only three states that are on track to contain COVID. We are currently preparing for the second wave by creating a messaging campaign to keep people disciplined and initiating a public health-business partnership to ensure that businesses abide by best practices.

JS: Do you think we should implement a similar lockdown strategy if a second wave occurs?

NS: We never want to lock down again. Michigan currently has a 20% unemployment rate. Economically, we are one of the worst-hit states. We are doing contact tracing to hone in on where the hot spots are and contain them quickly.

Nothing has changed over the course of this pandemic other than our own behavior and the tools in our toolkit. We only have six: social distancing, masking, testing, quarantining, contact tracing, and hygiene. That is what we rely on. We must make sure that message is very clear so it does not become a political tool. It is about taking care of yourself and your family.

JS: Can you tell me a bit about how you created a culture of innovation and reinvention?

NS: In my book, Unconventional Leadership, I wrote a lot about innovation. Firstly, you must believe in your people. No one can create innovation at the top but you can create a culture that empowers and inspires people to believe they can do anything. My dad was an inventor and he always told me that innovation is about solving problems. We had plenty of problems to solve in Detroit. At HFHS, we went through difficult financial times. We had to reinvigorate a whole system's morale and performance. We had to drastically improve quality and service. Innovation was a key part of that because we had to be creative. Detroit was a very difficult market during the financial crisis. Michigan had a declining population and the worst unemployment rate in the country.

Detroit is a 4.5 million-person market and only a fraction were coming to HFHS. If we were going to compete, we had to be creative. The first robotic surgery for prostate cancer was done at HFHS. That helped turn around our flagship hospital and grew admissions by 35%. The other departments in the hospital saw that and said, "if they can do it, so can we." Creating that spirit of innovation and having people see that the hospital leadership believed in their creativity empowered them.

The story I used to tell is that one day a woman came to my table and said, "Nancy, have you met my new colleague who came from Colorado?" I said, "No, I have not met her. What are you doing at HFHS?" She said, "Well, I'm working on the global health initiative." I said, "I did not know we had one, but I want to learn a lot more about this. This is fantastic!" I later found out that the department of infectious diseases head had attracted talented people from around the world doing great things under the radar. People watch if leaders say yes more often than they say no. Many people have ideas that they never bring forward because they are afraid of the answer.

JS: How did you foster the next generation of healthcare leaders and innovators?

NS: Young people will invest in their health system when they believe in it and feel part of it. Innovation happens when you attract innovators, so investing in a positive culture allowed us to attract the best young people. They saw what we were doing and wanted to be part of it.

We also looked at our leadership structure and did a lot of succession planning. We worked to develop talent from within and attract talent from outside. I hired Gerard van Grinsven, who used to run hotels for Ritz Carlton, to be CEO of our new hospital in Detroit. People thought I had lost my mind, but he had a unique vision. If we had not hired him, our West Bloomfield Hospital would not have been so successful during one of the biggest recessions in our history.

JS: Why did you choose a hotel executive to lead a hospital as opposed to a well-known healthcare leader?

NS: I have known Mr. van Grinsven for years. He always demonstrated impressive leadership. He was thinking of working with another healthcare company on hospitality, but I insisted he work for us. People thought I was crazy. I initially thought he could oversee service, but we decided to appoint him CEO of our new hospital. We surrounded him with the best medical and nursing talent. He opened 27 resorts globally, while most hospital administrators have never opened one hospital.

JS: What do you think is the next big disruptor in healthcare?

NS: We are living it right now: Telehealth and the retailization of healthcare. We were doing telehealth at HFHS way before anybody else. We brought in a retail consultant because we had to learn how to be more customer-focused. This pandemic is going to drive disruption and we ought to embrace it. The data shows that telehealth improves access tremendously. If we can do things more quickly and cost-effectively, everyone in our community can access our services.

JS: What advice would you give to young and emerging healthcare leaders?

NS: Learn as much as you can as quickly as you can, including frontline work. When I graduated college, I worked as a nurse aid for $3.25/hour. Understand the roles of all healthcare workers. Get exposed to innovative ideas, read about leadership. Pay attention to everything: good, bad, and ugly. Weigh in. Get involved quickly.

JS: What is the next step in your health care journey?

NS: I serve on ten boards. I am very engaged in doing this work with the governor. I write articles and do a lot of speaking. I just want to contribute. I do not think I will take another big job. But I want to help in every way I can whether in DC, Michigan, Duke University, or the Detroit Symphony. These are some of the things that I am working on and I am enjoying myself.