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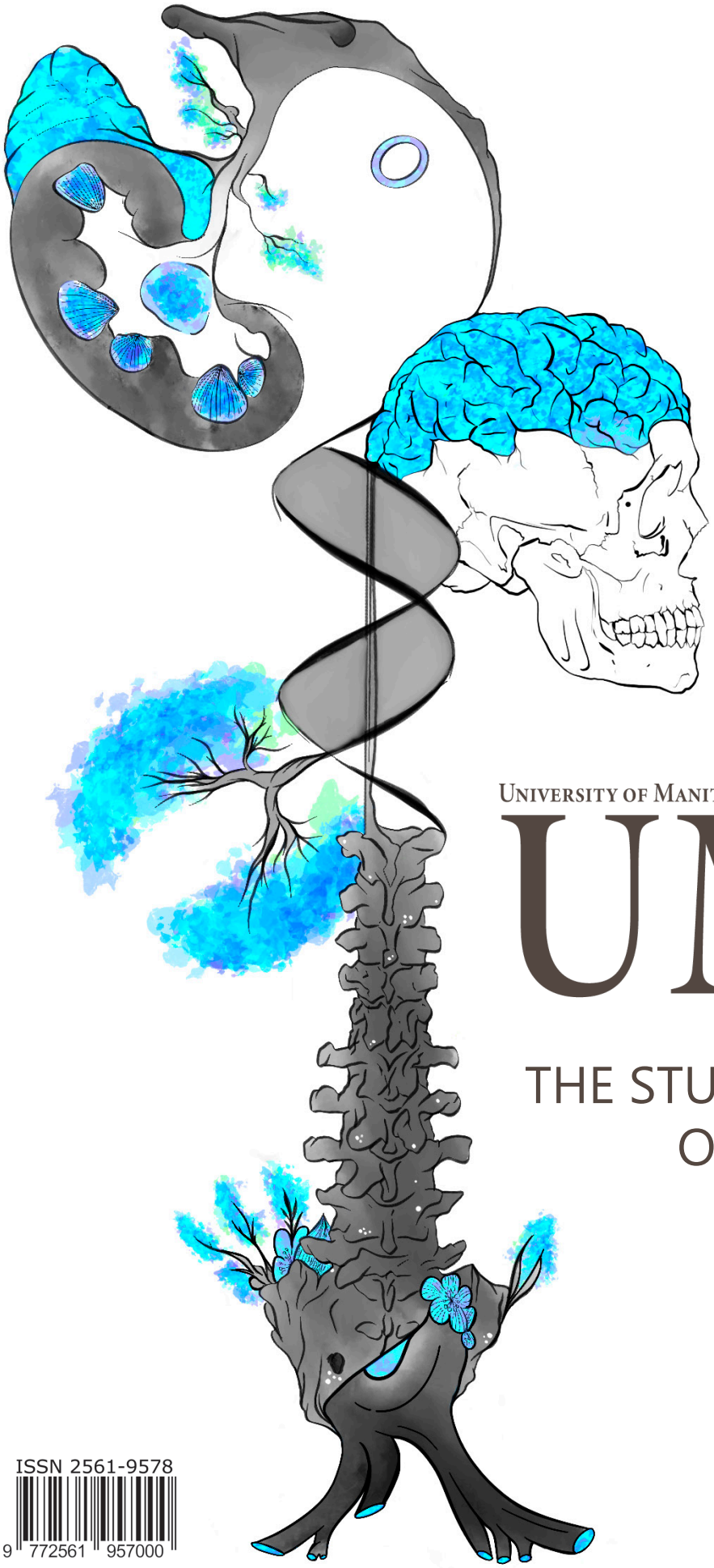

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Congratulations to the award winners of this issue!

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Learn more about how to submit your original writing at www.umjm.ca. We welcome submissions from students, residents, and faculty members from all colleges within the Rady Faculty of Health Sciences. Authors from institutions outside of the University of Manitoba are also welcome. We look forward to your submission!

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Letter from the Editors

Dear Reader,

Thank you for joining us for the fourth volume of the *University of Manitoba Journal of Medicine (UMJM)*. The theme of this issue is "The Student Experience of Medicine". It is a theme that is necessarily difficult to define. The way each of us experiences medicine is personal and unique. There is no one correct way to participate in medical school or to learn everything we need to know as physicians. We all bring our own lived-in experiences of medicine to our day-to-day learning. It is this diversity of experience that gives our communities strength and improves our ability to help one another during the pandemic.

The submissions we received for this issue certainly reflect the diverse perspectives of our students. Herein, you will find one student's original research of newborn immune deficiency screening, while another will describe their report of a notorious stroke mimic in the emergency room. This issue also contains a response to a previous *UMJM* piece outlining the relationship between interprofessional collaboration and healthcare costs. For the first time, an author presents a book review. It analyzes the memoir of one late neurosurgeon's struggle with his terminal cancer diagnosis. We are also privileged to publish the first chronology of Winnipeg's Hollenberg Clinic, a groundbreaking medical centre where students came to learn during the mid-20^{th} century. Given the COVID-19 pandemic, our authors also examine topics such as frailty in acute care assessments, novel online communication tools to combat misinformation, and responses to social isolation in older adults.

We are proud to include a submission from students outside of the Max Rady College of Medicine UGME program for the first time. It is also our first issue with an author external to the University of Manitoba community. The *UMJM* received more submissions for this volume than any other, to the point where we have divided them between two separate issues – another first for the journal. We look forward to publishing Volume 4 Issue 2 in September 2021. It will contain pieces by graduate students in the Max Rady College of Medicine, our first original research article from a PGME author, as well as a focused look at the impact of the COVID-19 pandemic from our UGME classmates.

The *UMJM* would not be possible without our strong team of students who work diligently behind the scenes over the entire calendar year to offer you this final product. It is our privilege to work and learn with each of them on an ongoing basis. Our editorial, information technology, and communications teams are among the most talented the *UMJM* has ever had. The journal would neither be possible without the support of our faculty reviewers. These faculty members donate their time to review every piece you will read. Throughout, they give our student authors invaluable feedback and commit to put students' learning at the forefront of this initiative.

We would also like to thank all of the staff, faculty, authors, and readers at the University of Manitoba and beyond for your continued support. The entire University of Manitoba community never ceases to amaze us with the generosity of time and energy that they devote to our students. In particular, we would like to highlight the commitment of our faculty supervisor, Dr. William Libich, who has mentored the *UMJM* student volunteers for all four of its volumes.

On behalf of the entire *UMJM* team, we hope that you enjoy reading about our students' experience of medicine.

Sincerely,

Lindsay Bristow & Eagan Peters

Co-Editors-In-Chief

Letter to the editor in response to: "Interprofessional collaboration and healthcare costs: a brief literature review"

Kapilan Panchendrabose MSc[†]

Conflict of Interest Statement: None to declare.

In "Interprofessional Collaboration and Healthcare Costs: A Brief Literature Review," Diaz provides strong insight into how interprofessional collaboration (IPC) in healthcare can be a cost-effective strategy in different healthcare settings.[1] Diaz should be praised for looking at IPC from a utilitarian point of view as all Canadian provinces spend most of their fiscal budget on healthcare as of 2015.[2] Manitoba's per capita health expenditure is higher than the national average, spending approximately $7000 CAD per person.[3] IPC in healthcare is a complex phenomenon with various dynamics, practice- and system-level factors, and patient needs to be considered. It is more than co-locating practitioners. Here, I underscore two considerations for determining cost-effectiveness.

First, does the composition of the IPC team matter? When establishing IPC teams, should a physician be required? These questions become critical in Canada's rural and remote areas as only a limited number of healthcare providers exist in certain communities. The studies listed in Diaz's review may be indicative of physician centredness, as all of them had a physician as part of the IPC team. However, in rural and remote areas, physicians may be scarce and nurse practitioners may often be the primary source of care for several rural communities.[4] Therefore, it is not fully elucidated whether the composition of the IPC team makes a significant difference in health outcomes and cost savings for the healthcare system and patients. It is also not clear whether these findings are limited to urban areas.

Second, IPC is not a simple, distinct intervention. There are many ways IPC can be implemented, which may impact the extent of reduced healthcare costs. For example, a health centre in Slovenia implemented IPC by having physicians make the initial diagnosis for patients with the subsequent health plan including a more diverse IPC team as part of direct patient care.[5] Whereas, a clinic in Toronto used shared patient charts and interprofessional ward rounds to benefit from interprofessional expertise where it was needed.[5] These two examples use IPC in different ways, and one may reduce costs more than the other. To the author's knowledge, there has not been any study quantitatively measuring or estimating healthcare cost reductions when using different IPC models. It would therefore be of value to determine which processes may yield the greatest efficiencies.

The inclusion of interdisciplinary teams as part of healthcare reform contributes to improved health outcomes. However, the variability and differences from one healthcare setting to another must be considered to gain a better understanding of which methods may yield the greatest cost efficiencies without adversely affecting patient care. Cost-benefit analyses require more objectively defined and measured IPC processes and structures to generate evidence of efficiency and best practices for the future.

References

[1] Diaz F. Interprofessional collaboration and healthcare costs: a brief literature review. University of Manitoba Journal of Medicine. 2019;2(1).

[2] Barua B, Palacios M, Emes J. The Sustainability of Health Care Spending in Canada; 2016.

[3] Anderson K, Wasilewski B, Farrell P, Titeu A, Callery B. Primary Care Reforms in Ontario, Manitoba, Alberta, and the Northwest Territories A Rapid Review Prepared for the Canadian Foundation for Healthcare Improvement; 2018.

[4] MacLeod MLP, Stewart NJ, Kulig JC, Anguish P, Andrews ME, Banner D. Nurses who work in rural and remote communities in Canada: a national survey. Human Resources for Health. 2017;15(1).

[5] Mickan S, Hoffman SJ, Nasmith L. Collaborative practice in a global health context: Common themes from developed and developing countries. Journal of Interprofessional Care. 2010;24(5).

*Correspondence to: panchenk@myumanitoba.ca
[†]Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada

The role of frailty in acute care assessment during the COVID-19 pandemic and beyond: A rapid review

Kevin F. Boreskie MSc[†‡§] Jacqueline L. Hay MSc[†‡] Pawel Garda BSc[§]

Abstract

Healthcare strain due to the novel coronavirus (COVID-19) pandemic has left clinicians struggling to manage patient care and identify those most at risk of COVID-19 mortality. Although chronological age-based triage strategies have been adopted, these practices have been criticized for being ageist. Improved care for each unique patient with COVID-19 may be achieved through the addition of frailty assessment in acute care. While current data demonstrates that hospitalized patients with frailty and COVID-19 are at increased risk for adverse outcomes, most data thus far has not considered patient treatment nor illness severity analyses. Therefore, frailty assessment is recommended as an adjunct tool for directing patient care in addition to factors such as acute illness severity and the presence of comorbidities. Moving forward, incorporating frailty status into patient decision-making and the analyses of COVID-19 therapies are warranted to ensure that approaches are efficacious in the most vulnerable patients. Clinicians in acute care should familiarize themselves with frailty and its assessment to improve care during the COVID-19 pandemic and beyond.

Keywords: frailty; COVID-19; ageing; prognosis; risk stratification

Conflict of Interest Statement: None to declare.

Introduction

The spread of severe acute respiratory syndrome coronavirus (SARS-CoV-2) has led to over 80 million cases of coronavirus disease (COVID-19) and over 1.7 million deaths worldwide.[1] With over 313.3 cumulative hospitalizations due to COVID-19 per 100 000 people in the United States,[2] this pandemic has taxed medical resources across the globe. Current data demonstrates an increased risk for adverse outcomes due to COVID-19 as age increases.[3–5] This trend was identified globally early in the pandemic, with data from a systematic review demonstrating increasing case fatality rates and disease severity with age.[6] In addition, patients with comorbidities such as hypertension and respiratory disease also demonstrate increased risk for adverse COVID-19 prognosis.[5] As cases increased and healthcare systems were inundated with patients requiring hospitalization, healthcare bodies such as the Italian College of Anesthesia, Analgesia, Resuscitation, and Intensive Care (SIAARTI), discussed the need to adopt triaging strategies that incorporate chronological age in the acute care setting.[7] This decision may have been based on the finding that older age and comorbidities were associated with adverse outcomes given that likely benefits from treatment have been recommended as an important consideration when allocating scarce healthcare resources.[8–11] However, some geriatricians and geriatric groups argue that resource triaging using age is "ageist" and fails to identify those at greatest risk for adverse outcomes associated with COVID-19 at the individual level due to the heterogeneity of aging.[8,9,11,12]

Frailty

Frailty is characterized by a reduced reserve to respond to health stressors induced by multisystem physiological declines.[13] While frailty is correlated with chronological aging,[14] these are not synonymous concepts.[15] Importantly, frailty is a more valuable indicator of risk for adverse health outcomes than age.[15–17] Frailty predicts a wide range of adverse health outcomes including falls,[18] hospitalization,[18] morbidity[16,18–21] and mortality.[16,20,22] Over 50 frailty assessment tools have been developed for a variety of clinical contexts, each with inherent strengths and limitations.[23,24] As such, prevalence estimates for frailty in countries worldwide range from 7–24% in those 50 years of age or older de-

*Correspondence to: kboreskie@gmail.com
[†]Applied Health Sciences, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada
[‡]Institute of Cardiovascular Sciences, St. Boniface Hospital Albrechtsen Research Center, Winnipeg, Manitoba, Canada
[§]Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada

pending on the assessment tool utilized.[25] Generally, frailty assessments can be categorized as those that are phenotypic-based or those based on a more holistic accumulation of deficits.[23,24] Two approaches to frailty include the Fried phenotype[18] and the Frailty Index (FI).[26] The Fried phenotype[18] approach to frailty examines the following criteria: grip strength, walking speed, unintentional weight loss, self-reported exhaustion and low physical activity levels. Comparatively, the FI[26] accumulation of deficits approach looks at a wide range of health deficits on a continuum and can include variables such as cognition and lab-based biomarkers.

More recently, frailty assessment has been suggested as a means to identify best care practices for older adults in the acute care setting.[8,26–28] Current triage tools in acute care often incorporate chronological age, which does not take the heterogeneity of aging into account. It may also underestimate risk, thereby leading to interventions that are unlikely to benefit a higher risk patient with frailty.[29,30] Patients with frailty are more likely to experience adverse outcomes in acute care settings including increased length of hospital stay, admission to nursing home, and mortality.[31,32] These adverse outcomes can be attributed to not only the presenting illness, but also to iatrogenic stress introduced. However, the use of the Fried approach or the FI can be cumbersome in acute care settings.[33] The subsequent Clinical Frailty Scale (CFS) was developed to address this issue.

The CFS is a simple, rapid assessment tool used in acute care settings for those 65 years of age and older. It is based on clinical judgement and functional status.[34–36] This tool assesses frailty on a 9-item scale ranging from more robust or fit (1–3), mild or moderate frailty (4–6), more severe frailty (7–8), to terminally ill (9). Placement on this scale is based on patient status of mobility, function, and cognition from two weeks prior. In the case of an intubated or obtunded patient, information can also be collected from collateral sources such as caregivers. Determination of frailty status with the CFS has shown to be highly correlated with the FI ($r = 0.80$).[35]

Frailty-aware care and COVID-19

In the community setting, two separate analyses of data from the United Kingdom Biobank database have reported on associations between frailty and COVID-19.[37,38] One analysis found that frailty status assessed with the Fried approach was not associated with COVID-19 diagnosis ($N = 502\,640$).[37] However, the second analysis found that frailty status assessed by both the modified Fried and FI were associated with a higher risk of severe infection, hospital admission, and subsequent mortality independent of multimorbidity in those who tested positive for COVID-19 ($N = 383\,845$).[38] Additionally, a large retrospective cohort study of Medicare beneficiaries in the United States ($N = 24\,367\,476$) found that advanced frailty as assessed by a FI was associated with increased COVID-related hospitalization and mortality.[39]

Interest in adopting tools to direct resource allocation has been driven by necessity during the pandemic. Age-based approaches can miscategorise older adults as they do not all have concomitant comorbidity and/or frailty.[8] Since older adults are disproportionately affected by COVID-19,[5] it is essential to develop care and triage systems with older adults in mind. Assessing frailty in critical care can elucidate the heterogeneity present in aging[15] and has garnered increased attention as a method of triaging and identifying best care practices in COVID-19 patients.[8,9,34,40] Furthermore, older adults, and specifically those with frailty, may present with COVID-19 atypically[41] (for example, with delirium).[42] This lends importance to frailty assessment when considering care management. The National Institute for Health and Care Excellence adopted the use of frailty assessment as part of their "COVID-19 Rapid Guidelines: Critical Care" and proposed assessing patients using the CFS upon hospital admission.[43] A mobile application was developed by the National Health Services to support the use of the CFS in their clinical context,[44] and additional online training resources were developed to teach clinicians how to use the tool.[45]

The CFS has previously demonstrated predictive validity for hospitalization, ICU admission, and mortality.[36,46,47] However, the predictive validity of this frailty assessment, or others, for adverse outcomes or treatment efficacy is unknown in patients with novel COVID-19. Frailty assessment should not be used alone in acute care settings, but in conjunction with assessment of illness acuity and likelihood of treatment benefit given the role of other mediators in health recovery.[48] Data is needed to support the use of frailty assessment as an important holistic assessment in acute care settings in patients with COVID-19.[40]

Rapid review of frailty as a predictor of adverse outcomes in hospitalized COVID-19 patients

The growing publications of data and expert opinion regarding the use of frailty assessments in hospitalized older adults with COVID-19 was summarized in a systematic scoping review in July 2020.[40] This review found mainly editorials and recommendations supporting the clinical role of frailty assessments in COVID-19 patients with supporting data from only four observational studies.[49–52] Of these observational studies, two found that more advanced frailty status was associated with increased hospital mortality.[49,50] Another found that advanced frailty was associated with a longer disease course.[51] In contrast, Miles et al. found high rates of mortality in more robust patients. This was attributed to potentially be a result of immunosenescence in frailty preventing COVID-19 mortality associated with immune hyperactivation.[52] The review importantly identified that many recommendations were

given with a paucity of evidence to support them.[40] Additionally, the search did not identify any trials examining the use of interventions specifically for patients with more advanced frailty and COVID-19, nor the impact of frailty status on the effectiveness of currently studied COVID-19 therapeutic interventions. These considerations are important if patients with more advanced frailty are at increased risk for adverse outcomes from COVID-19.

Published at almost the same time as the aforementioned review, Hewitt et al. reported that frailty assessment using the CFS in patients with COVID-19 showed better in-hospital and 7-day mortality prediction compared to either age or comorbidity. This study used data from the COVID-19 in Older People (COPE) study ($N = 1\,564$).[53] Letters to the editor responding to their research identified important limitations when examining frailty in this context. Specifically, the CFS was used by investigators on adults younger than its validated use[54] and the lack of information on patient treatment or illness severity make it difficult to use their data to support the findings presented.[55,56]

Since the Hewitt et al. paper, several studies examining the relationship between CFS score and mortality in COVID-19 patients have been published and summarized in a systematic review and meta-analysis by Pranata et al.[57] Their review included seven studies[41,42,53,58–61] in the final analysis and described a total of 3817 patients with a mean age of 80.3 years ($SD = 8.2$). The Hewitt et al. paper was also included in this analysis, and was the only study to include adults under 65 years of age.[53] Frailty prevalence (95% CI) in the pooled cohort was CFS 1–3 at 34% (32–36%), CFS 4–6 at 42% (40–45%) and CFS 7–9 at 23% (21–25%). Pranata et al. found that CFS score and COVID-19 mortality had a linear dose-response relationship where each increasing point on the CFS was associated with a 12% increased odds of patient mortality (OR 1.12; 95% CI 1.04–1.20).[57] Of the included manuscripts, two were prospective cohort studies[53,60] and five were retrospective cohort studies.[41,42,58,59,61] Funnel-plot analysis indicated possible publication bias. Further potential bias was introduced as most studies were retrospective. Two of the included papers found that CFS score was not associated with COVID-19 mortality.[60,61] The remaining five studies described odds ratios for mortality per one-point increase in CFS score ranging from 1.12 (95% CI 1.04–1.20)[58] to 1.75 (95% CI 1.10–3.43).[59] As identified in the Maltese et al. scoping review,[40] lack of information on patient treatment and acute illness severity in the meta-analysis make these results harder to interpret. Exceptions to this were Aw et al. and Owen et al., who both performed analyses controlling for acute illness severity.[58,61] Illness severity seemed to attenuate the observed relationship in both of these studies.[58,61]

Frailty assessment may serve an adjunct role not only in community-dwelling and hospitalized patients, but also plays an important role after discharge from the hospital.[62] Vilches-Moraga et al. found that higher frailty scores on the CFS pre-admission were associated with increased care requirements at discharge even after controlling for age and other comorbidities.[62] This finding supports the role of frailty assessment in care planning for the needs of individual patients even after discharge.[62] The importance of frailty assessment in assessing the efficacy of therapeutic interventions for COVID-19 is also true of vaccine response. To date, vaccine trials have largely excluded those with comorbidities and frailty,[63] who are the most vulnerable to COVID-19. As vaccines for COVID-19 are now being distributed globally, considerations should be made to ensure that favourable immune responses are also achieved in older adults with frailty who may have immunosenescence.[63,64]

This rapid review was completed as of January 4, 2021. New data on this topic area continues to rapidly develop, but the British Geriatrics Society has created a continually updating list of manuscripts describing frailty scores and COVID-19 outcomes in older adults to assist with keeping track of this evolving data.[65]

Future directions

The current data and expert opinions support frailty assessment as an adjunct assessment in hospitalized older adults with COVID-19, not to be used alone for purposes of directing care plans or patient triage.[11,34,57] Most data thus far have not included illness severity nor patient treatments received in their analyses. This limits the ability to examine the effect of frailty alone on patient prognosis. It is essential to understand that frailty assessments have limitations in allocating health resources, and additional factors, such as comorbidity and illness acuity, play important roles in COVID-19 patient prognosis.[48,57,66,67] Experts have encouraged the use of frailty assessment on a continuum as opposed to simplifying it to a dichotomous variable in order to better describe the patient.[48] However, assessing patients on a continuum renders decisions for patient care pathways more challenging.[57] Instead of using the knowledge of frailty status as a means of shifting who receives care, Lee et al. describes using frailty in a "3F" approach: framing goals of care, working within the framework of frailty, and as a means of directing forward conversations.[68]

There is little research examining interventions specifically for patients with more advanced frailty status and COVID-19. The mediating role that frailty status may play in current therapeutic intervention response for older COVID-19 patients is also unknown. Older adults with frailty and comorbidity should be recruited or trials to ensure that those at the greatest risk are able to benefit from researched interventions. Future research should examine these important concepts to improve patient management in hospitalized older adults during the current pandemic and beyond. Additionally, the exact mechanisms that place frail older adults at increased risk for adverse outcomes in COVID-19 cases are not known, although increased vi-

ral shedding, atypical presentation, reduced cardiorespiratory reserve and immunosenescence have all been suggested.[69] Identifying these mechanisms could allow for targeted therapeutic interventions and improved management of COVID-19 patients with frailty.

Conclusion

Preventing COVID-19 development in older adults with frailty is critical given the associated adverse outcomes, including hospitalization and mortality.[39,57] Specifically, those with advanced comorbidity and those residing in nursing homes are at increased risk.[39] The interest in tools for directing resource allocation and best care practices has been adopted out of necessity during the COVID-19 pandemic, but serves as an example of how best care practices for older adults can be aided through knowledge of frailty status.[8,34] Frailty-aware care plays an important role as an adjunct tool in all stages of the peri-hospitalization period for older adults with COVID-19.[38,57,62] These considerations will continue to be important throughout the pandemic and in the future in order to provide the best care for older adults by using global assessments of health status through frailty assessment.[8] The pandemic has brought ageist policies and discourse to the forefront.[70] Clinicians should focus on developing skills to improve care management for older adults through frailty assessment during the COVID-19 pandemic and beyond.

References

[1] COVID-19 map. Johns Hopkins Coronavirus Resource Center; 2020. [Cited 2021 Jan 4]. Available from: https://coronavirus.jhu.edu/map.html.

[2] COVIDView, key updates for week 51. Centers for Disease Control and Prevention; 2020. [Cited 2021 Jan 4]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html.

[3] Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. JAMA. 2020;323:1775–1776.

[4] McMichael TM, et al. Epidemiology of Covid-19 in a long-term care facility in King County, Washington. N Engl J Med. 2020;383:2005–2011.

[5] Zheng Z, et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. J Infect. 2020;81:e16–e25.

[6] Meyerowitz-Katz G, Merone L. A systematic review and meta-analysis of published research data on COVID-19 infection fatality rates. Int J Infect Dis. 2020;101:138–148.

[7] Rosenbaum L. Facing Covid-19 in Italy – ethics, logistics, and therapeutics on the epidemic's front line. N Engl J Med. 2020;382:1873–1875.

[8] Boreskie KF, Boreskie PE, Melady D. Age is just a number – and so is frailty: Strategies to inform resource allocation during the COVID-19 pandemic. CJEM. 2020;p. 411–413.

[9] Montero-Odasso M, et al. Age alone is not adequate to determine healthcare resource allocation during the COVID-19 pandemic. Canadian Geriatrics Journal. 2020;23:152–154.

[10] Jecker NS, Schneiderman LJ. Futility and rationing. Am J Med. 1992;92:189–196.

[11] Rockwood K. Rationing care in COVID-19: if we must do it, can we do better? Age Ageing. 2020;50:3–6.

[12] Cesari M, Proietti M. COVID-19 in Italy: Ageism and decision-making in a pandemic. J Am Med Dir Assoc. 2020;21:576–577.

[13] Morley JE, et al. Frailty consensus: a call to action. J Am Med Dir Assoc. 2013;14:392–397.

[14] Kehler DS, et al. Prevalence of frailty in Canadians 18–79 years old in the Canadian Health Measures Survey. BMC Geriatr. 2017;17:28.

[15] Mitnitski H A, E S, Rockwood K. Heterogeneity of human aging and its assessment. J Gerontol A Biol Sci Med Sci. 2017;72:877–884.

[16] Hanlon P, et al. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: A prospective analysis of 493 737 UK Biobank participants. The Lancet Public Health. 2018;3:e323–e332.

[17] Buckinx F, et al. Burden of frailty in the elderly population: perspectives for a public health challenge. Arch Public Health. 2015;73.

[18] Fried LP, et al. Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56:146–156.

[19] Veronese N, et al. Risk of cardiovascular disease morbidity and mortality in frail and pre-frail older adults: Results from a meta-analysis and exploratory meta-regression analysis. Ageing Res Rev. 2017;35:63–73.

[20] Aguayo GA, et al. Comparative analysis of the association between 35 frailty scores and cardiovascular events, cancer, and total mortality in an elderly general population in England: An observational study. PLOS Medicine. 2018;15:e1002543.

[21] Boreskie KF, et al. Frailty status and cardiovascular disease risk profile in middle-aged and older females. Experimental Gerontology. 2020;140:111061.

[22] Shamliyan T, Talley KMC, Ramakrishnan R, Kane RL. Association of frailty with survival: A systematic literature review. Ageing Research Reviews. 2013;12:719–736.

[23] Faller JW, et al. Instruments for the detection of frailty syndrome in older adults: A systematic review. PLOS ONE. 2019;14(4):e0216166.

[24] J BB, et al. Frailty assessment instruments: Systematic characterization of the uses and contexts of highly-cited instruments. Ageing Res Rev. 2016;26:53–61.

[25] O'Caoimh R, et al. Prevalence of frailty in 62 countries across the world: A systematic review and meta-analysis of population-level studies. Age Ageing. 2021;21:576–577.

[26] Brousseau AA, et al. Identification of older adults with frailty in the Emergency Department using a frailty index: Results from a multinational study. Age Ageing. 2018;47:242–248.

[27] Lewis ET, et al. Which frailty scale for patients admitted via Emergency Department? A cohort study. Archives of Gerontology and Geriatrics. 2019;80:104–114.

[28] Hogan DB, et al. A scoping review of frailty and acute care in middle-aged and older individuals with recommendations for future research. Can Geriatr J. 2017;20:20–37.

[29] Platts-Mills TF, et al. Accuracy of the Emergency Severity Index triage instrument for identifying elder emergency department patients receiving an immediate life-saving intervention. Acad Emerg Med. 2010;17:238–243.

[30] Theou O, Campbell S, Malone ML, Rockwood K. Older adults in the emergency department with frailty. Clinics in Geriatric Medicine. 2018;34:369–386.

[31] Cunha AIL, Veronese N, de Melo Borges S, Ricci NA. Frailty as a predictor of adverse outcomes in hospitalized older adults: A systematic review and meta-analysis. Ageing Research Reviews. 2019;56:100960.

[32] Jørgensen R, Brabrand M. Screening of the frail patient in the emergency department: A systematic review. Eur J Intern Med. 2017;45:71–73.

[33] Oviedo-Briones M, et al. A comparison of frailty assessment instruments in different clinical and social care settings: The Frailtools project. J Am Med Dir Assoc. 2020;22:607.e7–607.e12.

[34] Rockwood K, Theou O. Using the Clinical Frailty Scale in allocating scarce health care resources. Canadian Geriatrics Journal. 2020;23:254–259.

[35] Rockwood K, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173:489–495.

[36] Church S, Rogers E, Rockwood K, Theou O. A scoping review of the Clinical Frailty Scale. BMC Geriatrics. 2020;20:393.

[37] Woolford SJ, et al. COVID-19 and associations with frailty and multimorbidity: A prospective analysis of UK Biobank participants. Aging Clin Exp Res. 2020;32:1897–1905.

[38] Petermann-Rocha F, et al. Comparison of two different frailty measurements and risk of hospitalisation or death from COVID-19: Findings from UK Biobank. BMC Med. 2020;18:355.

[39] Izurieta HS, et al. Natural history of COVID-19: Risk factors for hospitalizations and deaths among >26 million U.S. Medicare beneficiaries. The Journal of Infectious Diseases. 2020;223:945–956.

[40] Maltese G, et al. Frailty and COVID-19: A systematic scoping review. J Clin Med. 2020;9.

[41] Rawle MJ, Bertfield DL, Brill SE. Atypical presentations of COVID-19 in care home residents presenting to secondary care: A UK single centre study. Aging Medicine. 2020;3:237–244.

[42] Marengoni A, Zucchelli A, Grande G, Fratiglioni L, Rizzuto D. The impact of delirium on outcomes for older adults hospitalised with COVID-19. Age and Ageing. 2020;49:923–926.

[43] Overview: COVID-19 rapid guideline: Critical care in adults. National Institute for Health and Care Excellence; 2020. [Cited 2021 Jan 4]. Available from: https://www.nice.org.uk/guidance/ng159.

[44] Clinical Frailty Scale (CFS). NHS Elect; 2020. [Cited 2021 Jan 4]. Available from: https://apps.apple.com/gb/app/clinical-frailty-scale-cfs/id1508556286.

[45] CFS Training. Specialized Clinical Frailty Network; 2018. [Cited 2021 Jan 4]. Available from: https://www.scfn.org.uk/clinical-frailty-scale-training.

[46] Chong E, et al. Frailty in hospitalized older adults: Comparing different frailty measures in predicting short- and long-term patient outcomes. J Am Med Dir Assoc. 2018;19:450–457.e3.

[47] Kaepelli T, et al. Validation of the Clinical Frailty Scale for prediction of thirty-day mortality in the emergency department. Annals of Emergency Medicine. 2020;76:291–300.

[48] Hubbard RE, et al. Frailty in the face of COVID-19. Age Ageing. 2020;49(4):499–500.

[49] Bellelli G, et al. Frailty index predicts poor outcome in COVID-19 patients. Intensive Care Med. 2020;46:1634–1636.

[50] Brill SE, et al. COVID-19: A retrospective cohort study with focus on the over-80s and hospital-onset disease. BMC Medicine. 2020;18:194.

[51] Turner J, Hodgson LE, Leckie T, Eade L, Ford-Dunn S. A dual-center observational review of hospital-based palliative care in patients dying with COVID-19. Journal of Pain and Symptom Management. 2020;60:e75–e74.

[52] Miles A, et al. Outcomes from COVID-19 across the range of frailty: Excess mortality in fitter older people. Eur Geriatr Med. 2020;11:851–855.

[53] Hewitt J, et al. The effect of frailty on survival in patients with COVID-19 (COPE): A multicentre, European, observational cohort study. Lancet Public Health. 2020;5:e444–e451.

[54] Laurent MR. Frailty and mortality in patients with COVID-19. Lancet Public Health. 2020;5:e579.

[55] Darvall JN, Bellomo R, Young PJ, Rockwood K, Pilcher D. Frailty and mortality in patients with COVID-19. Lancet Public Health. 2020;5:e580.

[56] Pan D, Sze S, Minhas JS, Squire IB, Pareek M. Frailty and mortality in patients with COVID-19. Lancet Public Health. 2020;5:e581.

[57] Pranata R, et al. Clinical frailty scale and mortality in COVID-19: A systematic review and dose-response meta-analysis. Archives of Gerontology and Geriatrics. 2021;93:104324.

[58] Aw D, Woodrow L, Ogliari G, Harwood R. Association of frailty with mortality in older inpatients with Covid-19: a cohort study. Age and Ageing. 2020;49:915–922.

[59] Smet RD, et al. Frailty and mortality in hospitalized older adults with COVID-19: Retrospective observational study. Journal of the American Medical Directors Association. 2020;21:928–932.e1.

[60] Knopp P, et al. Presenting features of COVID-19 in older people: relationships with frailty, inflammation and mortality. Eur Geriatr Med. 2020;11:1089–1094.

[61] Owen RK, et al. Comparing associations between frailty and mortality in hospitalised older adults with or without COVID-19 infection: A retrospective observational study using electronic health records. Age and Ageing. 2020;50:307–316.

[62] Vilches-Moraga A, et al. Increased care at discharge from COVID-19: The association between pre-admission frailty and increased care needs after hospital discharge: A multicentre European observational cohort study. BMC Med. 2020;18:408.

[63] Soiza RL, Scicluna C, Thomson EC. Efficacy and safety of COVID-19 vaccines in older people. Age and Ageing. 2020;50:279–283.

[64] Andrew MK, McElhaney JE. Age and frailty in COVID-19 vaccine development. The Lancet. 2020;396:1942–1944.

[65] Conroy S. COVID-19: Frailty scores and outcomes in older people. British Geriatrics Society; 2021. Available from: https://www.bgs.org.uk/covidfrailty.

[66] Tuty Kuswardhani RA. Charlson comorbidity index and a composite of poor outcomes in COVID-19 patients: A systematic review and meta-analysis. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020;14:2103–2109.

[67] Goodman KE, et al. Letter to the editor: setting goals or shifting goalposts: role of frailty for critical care decisions during COVID-19. Clinical Infectious Diseases. 2020;9:246–247.

[68] Lee RHX, Ho EP, Neo HY, Hum A, Lim WS. Setting goals or shifting goalposts: Role of frailty for critical care decisions during COVID-19. J Frailty Aging. 2020;p. 1–2.

[69] Smorenberg A, Peters EJ, van Daele PL, Nossent EJ, Muller M. How does SARS-CoV-2 targets the elderly patients? A review on potential mechanisms increasing disease severity. Eur J Intern Med. 2020;83:1–5.

[70] Fraser S, et al. Ageism and COVID-19: What does our society's response say about us? Age and Ageing. 2020;49:632–635.

Development of a multiplexed PCR assay to identify pathogenic variants causing severe combined immunodeficiency (SCID) in Manitoba

Catherine Giffin BSc[†] Alexandra Ciapala MSc[‡] Tamar Rubin MD[§]
Cheryl Greenberg MD[‡] Geoffrey Cuvelier MD[¶] Paul Van Caeseele MD[†]

Abstract

Severe combined immunodeficiency (SCID) is a primary immune deficiency characterized by T cells that are either low in number, absent, or non-functional. SCID is fatal without treatment and has a higher incidence in Manitoba compared to the rest of Canada. Two founder mutations in Manitoba cause a T-cell positive SCID phenotype that cannot be identified using the T-cell receptor excision circle (TREC) assay, which is the commonest method of newborn screening for SCID. These are mutations of the *ZAP70* and *IKBKB* genes and are present at increased frequency in the Mennonite and First Nations of Northern Cree ancestry populations, respectively. Currently, newborns in Manitoba are screened for inherited disorders by way of dried blood spot (DBS) specimens. We developed allele-specific real-time quantitative polymerase chain reaction (qPCR) assays for the detection of both variants using the DBS sample type. These assays were multiplexed together with the existing TREC assay (a multiplexed assay is an assay in which multiple targets are assessed within a single reaction mixture). This paper will give a brief introduction to the mutations of interest and describe the methodology and validation of this assay. We will also explore some of the implications of expanded newborn screening in Manitoba and Canada more broadly.

Keywords: severe combined immunodeficiency; newborn screening; First Nations and Inuit population; Manitoba

Conflict of Interest Statement: None to declare.

Introduction

Severe combined immunodeficiency (SCID) is an inherited primary immune deficiency characterized by low, absent, or non-functional T cells. Despite no clinical signs at birth, SCID is typically fatal by one year of age if untreated.[1,2] Hematopoietic stem cell transplantation in the neonatal period (first 28 days of life) has been associated with decreased morbidity and mortality for affected newborns.[3] This curative treatment highlights the importance of early identification of all SCID cases. Surveillance studies of SCID have found an incidence in Manitoba that is close to 3 times the national incidence.[1,4] Two founder mutations underlie this increased incidence of SCID in Manitoba: a frameshift mutation in the *IKBKB* gene and a splice site mutation in *ZAP70*.[5,6]

In patients of Northern Cree ancestry, a single base pair duplication (NM_001556.3: c.1292dupG p.Gln432fs) causes a frameshift mutation and results in deficiency of the gene product inhibitor of kappa B kinase 2 (IKK2) and a SCID phenotype.[5] In homozygotes, deficiency of IKK2 interferes with the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway by decreasing the rate of degradation of the inhibitor of κ-B (IKB). As a result, NF-κB remains inactivated, impacting T and B cell receptor signalling and causing SCID.[5,7]

Among Canadian Mennonites, a homozygous base pair substitution (NM_001079.3: c.1624–11G>A) in the

*Correspondence to: giffinc@myumanitoba.ca
[†]Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, 750 Bannatyne Ave, Winnipeg, MB R3E 0W2; giffinc@myumanitoba.ca
[‡]Cadham Provincial Laboratory, 750 William Ave, Winnipeg, Manitoba R3E 3J7; lexi.ciapala@gov.mb.ca (L.C.) paul.vancaeseele@gov.mb.ca (P.V.C.)
[§]Department of Pediatrics and Child Health, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, 715 McDermot Ave, Winnipeg, MB, R3E 3P4; cgreenberg@hsc.mb.ca (C.G.), trubin@manitoba-physicians.ca (T.R.)
[¶]Manitoba Blood and Marrow Transplant Program, CancerCare Manitoba, Health Sciences Centre, 675 McDermot Ave, Winnipeg, MB, R3E 0V9; gcuvelier@cancercare.mb.ca

acceptor splice site of intron 12 of *ZAP70* produces a new acceptor splice site and results in an mRNA transcript with 9 additional nucleotides. This transcript yields an unstable gene product and an inactivated zeta chain-associated protein 70 kinase (ZAP-70).[6] The resultant deficiency of this kinase interferes with T cell maturation and receptor signalling and causes inactivity of CD4+ T cells, an absence of CD8+ T cells, and a SCID phenotype.

For a disorder to be considered eligible for inclusion on a newborn screening panel, it must meet certain criteria. The classical criteria for evaluating newborn screening candidate disorders are the Wilson and Jungner criteria, which have since been expanded to allow for the possibility of genetic testing.[8] Two of these criteria are that the facilities for diagnoses and treatment should be available and that case-finding should be a continuous process. It is important to distinguish newborn screening from diagnosis, as both are important components in case-finding. Newborn screening involves high throughput tests designed to minimize false negatives at the expense of a higher false positive rate. A positive screening test is therefore not diagnostic but raises the index of suspicion for a given disease. In the case of a positive screening test, the sample is reflexed to a diagnostic test and the patient is referred to the appropriate health care team.

The gold standard for newborn screening for SCID uses quantitative real-time polymerase chain reaction (qPCR) to quantify T cell receptor excision circles (TRECs) in neonatal dried blood spots. Very low TREC copy levels correspond to a positive SCID screening result and reflect the absence of mature T cells characteristic of traditional SCID.[9,10] SCID patients with the above-described *IKBKB* and *ZAP70* variants, however, are often T cell positive (T cells are present but non-functioning) with TREC levels above the upper threshold of the TREC screening test.[4,11] A high-resolution DNA melting procedure of *IKBKB* and *ZAP70* PCR amplicons has previously been described as a method to genotype these mutations.[2] We developed allele-specific quantitative real-time polymerase chain reaction (qPCR) primers and probes for the identification of these *ZAP70* and *IKBKB* variants. These components have been multiplexed with the existing TREC assay to improve the efficiency and scope of newborn screening for SCID in Manitoba. By multiplexing the allele-specific assays with the existing SCID screening test, we minimized costs associated with running multiple PCR plates (as required in a high resolution melting procedure) as well as improved ease of analysis. The aim of this paper is to describe the methodology and validation techniques for this assay.

Methods

In Manitoba, newborn screening is conducted at Cadham Provincial Laboratory (CPL) in Winnipeg using dried blood spots collected from newborns in their first days of life. A heel prick is performed with a lancet to collect and spot blood onto filter paper with known physical specifications such as absorbance. The blood spots are left undisturbed to dry before transport and then sent to CPL for processing. To perform PCR analysis of these samples, DNA must be extracted from the dried blood spot specimens. In the development of this assay, a 3.2 mm disc of saturated filter paper was used for the extraction step for each sample, standardizing extractions between newborns. For the *IKBKB* and *ZAP70* assays, multiple extraction techniques were used to assess the effect of inhibitors. These extraction techniques used Biosprint 96 DNA Blood kit reagents from QIAGEN Sciences (Hilden, Germany), DBS Extracta reagent from Quantabio (Beverley, MA, USA), and QuickExtract DNA from Lucigen (Middleton, WI, USA). After extraction, 5 µL of extracted DNA along with 15 µL of the reaction mixture containing primers, probes, and TaqMan Fast MasterMix from Life Technologies (Thermo Fischer Scientific, Waltham, MA, USA) was added to each sample well of a 96-well PCR plate for analysis.

PCR amplifies segments of DNA for which the appropriate primer is present in the reaction mixture. In qPCR, fluorescently labelled oligonucleotide probes (hydrolysis probes) bind to a specific sequence and fluoresce when this segment of DNA is amplified. Relative fluorescence units (RFU) are reported for fluorophores corresponding to each probe. A baseline is set automatically and adjusted manually to differentiate a signal from background. The threshold cycle (Ct) or quantification cycle (Cq) is defined as the PCR cycle at which an amplification curve crosses this threshold, constituting a signal.

To detect *IKBKB* and *ZAP70*, the assay was originally designed to use competitive binding of probes to differentiate wild-type and mutated variants. A hydrolysis probe was designed to bind with greater affinity to the wild-type variant and a non-fluorescing or "silent" probe was designed to outcompete the hydrolysis probe for the mutated variant.[12] Locked nucleic acids were used to increase the specificity of the probes (Table 1). This method has been published for use in other contexts including the molecular characterization of tumour cells[13] and when multiplexing newborn screening for spinal muscular atrophy with SCID.[14] Through this method, the hydrolysis probe outcompetes the silent probe in the presence of the wild-type variant and a signal is produced. The absence of a signal is expected in samples homozygous for the mutated variant, while a diminished signal should be observed in heterozygous samples.

Table 1. Original primers and probes for PCR multiplex assay to selectively amplify wild-type IKBKB and ZAP70 alleles in concert with TREC amplification

Target/reagent [a]	Sequence (5'–3')	Concentration (nmol/L) [b]
TREC		
Forward primer	TGACACCTCTGGTTTTTGTAA	800
Reverse primer	GTGCCAGCTGCAGGGTTTAG	800
Probe	ATG***C***A***T***AGG***C***ACCTGC	250
IKBKB		
Forward primer	AGGAATCTCGCCTTCTTCC	500
Reverse primer	CTGGATGCTGTGCCAGAC	500
Probe (wt)	TGTGGGGCC***AG***GTCTGG	100
Blocker (mt)	GTGTGGGGG***C***CA***G***GTCTG	400
ZAP70		
Forward primer	TGAGGAGGAGGACACTGG	325
Reverse primer	TTGCCCTGCTCGATGAAG	325
Probe (wt)	CTGCCC***CG***GCTTG***A***GCA	250
Blocker (mt)	CTGCCC***CA***GCTTG***A***GCA	500

[a] Bases in bold italic font denote locked nucleic acids
[b] Final concentration in PCR reaction (MasterMix)

Table 2. Adjusted primers and probes for PCR multiplex assay to selectively amplify wild-type IKBKB and ZAP70 alleles in concert with TREC amplification

Target/reagent [a]	Sequence (5'–3')	Concentration (nmol/L) [b]
TREC		
Forward primer	TGTTTCACAGCTATCCCAAG	800
Reverse primer	CTGATCTTGTCTGACATTTGC	800
Probe	AACACACTCTAOTGATGCCAGCAC	250
IKBKB		
Forward primer	TCAAGAGCCCAAGAGCAA	500
Reverse primer	CTTCCTTCAGGGTCTGGA	500
Probe (wt)	5HEX/TG***GC***CCCC***AC***A/3IABkFQ	100
ZAP70		
Forward primer	GATGAGGAGGAGGACACT	325
Reverse primer	CCGGCCCTTTCATCTTC	325
Probe (wt)	56-FAM/CCC***CGG***CTTG/3IABkFQ	250

[a] Bases in bold italic font denote locked nucleic acids
[b] Final concentration in PCR reaction (MasterMix)

TREC copy numbers follow a normal distribution and are affected by characteristics such as low birth weight or the presence of other immune deficiencies. CPL uses a TREC level of 33 TRECs/µL of whole blood as the cut-off for a positive SCID screening result. If the level of TRECs for a given specimen is below this value, and other elements of the multiplex are detected within a normal range proving successful extraction, the specimen is retested. A subsequent positive test indicates a high risk for SCID.

Primer and probe sequences and the PCR protocol were developed and optimized in-house using concentration and temperature gradients (Tables 2–3). The initial primers and probes were adjusted during validation to increase allele specificity and negate the need for a silent probe or blocker, further reducing costs and sources of error (Table 4). Candidate sequences for the custom primers and probes were selected using NCBI Primer-BLAST. Validation was carried out using two quality control standards and three blank or "no template" controls (Tables 5–6). Since these assays were multiplexed with the TREC assay, the former served as an internal control for the latter and vice versa. Successful amplification of genomic *IKBKB*, *ZAP70*, or TRECs indicated successful DNA extraction and PCR.

Table 3. qPCR protocol for the SCID Multiplex assay

Step #	Temperature	Duration
1	95°C	10 minutes
2	95°C	10 seconds
3	63.5°C	10 seconds
4	69.0°C	30 seconds
5	Plate Read; GO TO STEP 2 39×	
6	END	

Table 4. Quality controls for TREC quantification [a]

Control [b]	Contents
TREC QC 70	Dried blood spot with 70 copies of TREC per µL of whole blood
TREC QC 35	Dried blood spot with 35 copies of TREC per µL of whole blood

[a] Materials developed at Cadham Provincial Laboratory
[b] Spiked with IKBKB or ZAP70 mutated plasmid to serve as internal controls

Table 5. qPCR controls included in the SCID assay during validation

Control	Contents
No Template Control 1 (NTC1)	Filter paper blanks, DNA extraction reagents, PCR reagents
No Template Control 2 (NTC2)	DNA extraction reagents, PCR reagents
No Template Control 3 (NTC3)	PCR reagents

Table 6. Results of CPL SCID assay when analyzing CDC proficiency testing specimens

Specimen Number	Description	CPL Result	Fraction Correct
119R1	Normal cord blood with medium TREC copy level	Normal	3/3
119R2	Uninterpretable. TREC and reference gene out of range. Prepared from leukocyte-depleted blood.	Failed extraction	3/3
119R3	Normal cord blood with low TREC copy-level	Normal	3/3
119R4	Normal cord blood with medium TREC copy-level	Normal	2/2
119R5	SCID-like sample with very low/undetectable TREC. Reference gene within range.	SCID screen positive	3/3

Results

The original and adjusted primer and probe sequences for detection of *IKBKB* and *ZAP70* were successfully multiplexed with the TREC primers and probe. When multiplexed, the clinical performance characteristics of the TREC assay were unaffected. The TREC quantification ability of this assay was validated using 5 specimens donated as proficiency testing samples by the Centers for Disease Control and Prevention. The samples were run in triplicate, with the experimenter blinded to the anticipated result and position of the proficiency testing samples. Accuracy was 100% as shown in Table 6. TREC quantification was further challenged with other immune deficiencies using affected DBS samples from the CPL archives. TREC-deficient SCID was successfully differentiated from CHARGE Syndrome, *IKBKB* and *ZAP70* SCID, Down syndrome, and other

lymphopenias causing low TREC levels.

Using the original primer and probe set, the multiplexed assay successfully amplified both wild-type genes ZAP70 and IKBKB as well as TREC. This was evidenced by the presence of amplification curves for each fluorophore when human genomic DNA was analyzed using this method (Figure 1). Melting curve analysis verified the amplification of *IKBKB* and *ZAP70*, as the curves are consistent with theoretical melting points determined by amplicon sequence.[2] The absence of small, extraneous peaks indicated a lack of primer dimer formation (Figure 2).

Primer efficiency was evaluated by performing the assay on a serial dilution of genomic DNA spiked with a serial dilution of TREC plasmid. Each dilution was run in triplicate on a plate and the linear regression equation was calculated for each primer set. The efficiencies of all three primer sets were found to be between 90–100%. The assay also performed equally well on samples from each of the three DNA extraction conditions described in the methods and was therefore robust to inhibitors.

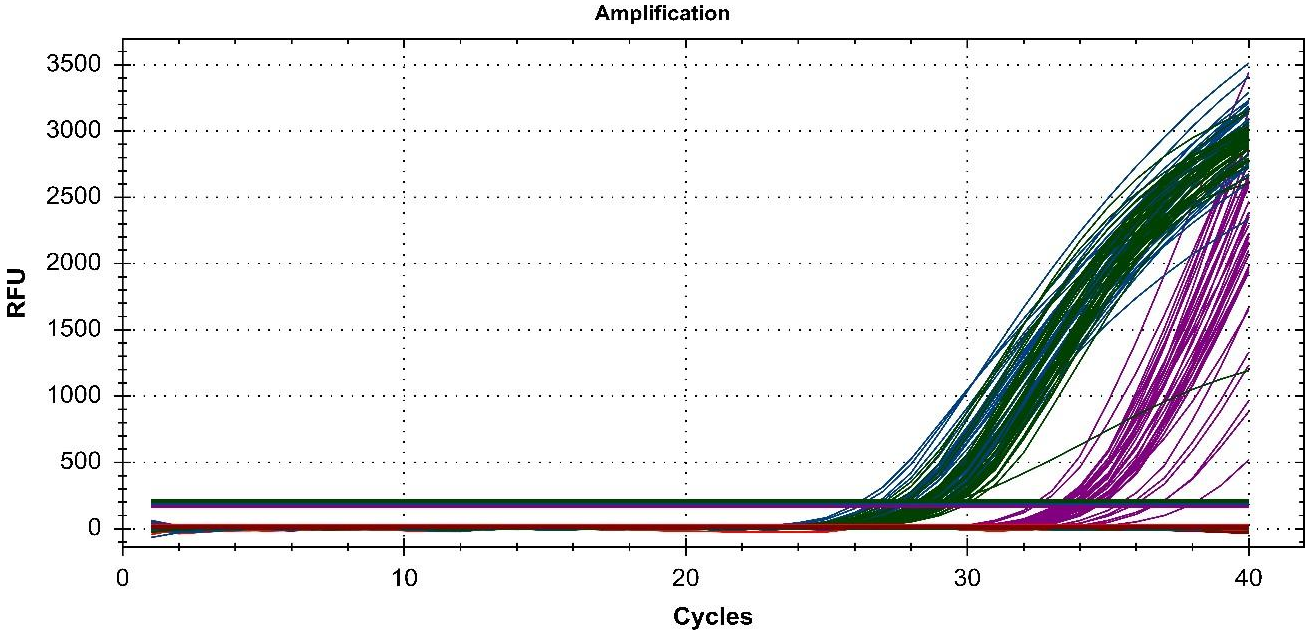

Figure 1. The amplification curves of IKBKB wild-type (Green; HEX), ZAP70 wild-type (Blue; FAM), and TREC (Purple; Cy5) for the original primer & probe (Appendix)

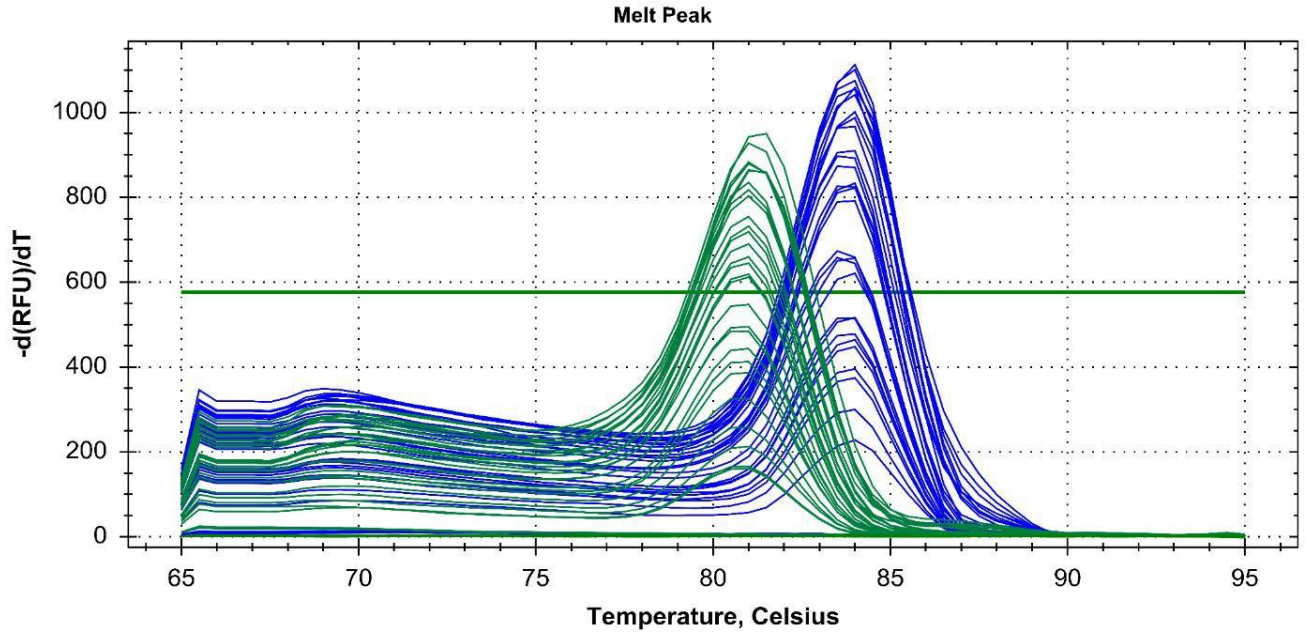

Figure 2. Post-PCR melting curves for IKBKB amplification (Green; 81°C) and ZAP70 (Blue; 84°C)

Using the second primer and probe set, the assay was able to correctly identify homozygous mutated variants of the genes in the absence of a silent probe for the mutated *IKBKB* and *ZAP70* variants (Table 7). This is evidenced by the lack of signal for the mutated allele when the assay was tested against samples from SCID patients with a known *IKBKB* or *ZAP70* mutation causing the disease (Figures 3–5).

Table 7. Quality controls for the detection of IKBKB and ZAP70 mutations [a]

Control	Contents
IKBKB and ZAP70 wild-type	The whole-blood TREC-spiked blood spots used as TREC standard curve in an independent PCR.
IKBKB homozygous mutated	Washed red blood cells with 55% hematocrit 3% bovine serum albumin spiked with ZAP70 wild-type plasmid and IKBKB mutated plasmid as blood spots.
ZAP70 homozygous mutated	Washed red blood cells with 55% hematocrit 3% bovine serum albumin spiked with IKBKB wild-type plasmid and ZAP70 mutated plasmid as blood spots.
IKBKB heterozygous	Whole blood dried blood spot spiked with TREC plasmid to 70 copies per µL and with IKBKB mutated plasmid.
ZAP70 heterozygous	Whole blood dried blood spot spiked with TREC plasmid to 35 copies per µL and with ZAP70 mutated plasmid.

[a] Materials developed at Cadham Provincial Laboratory

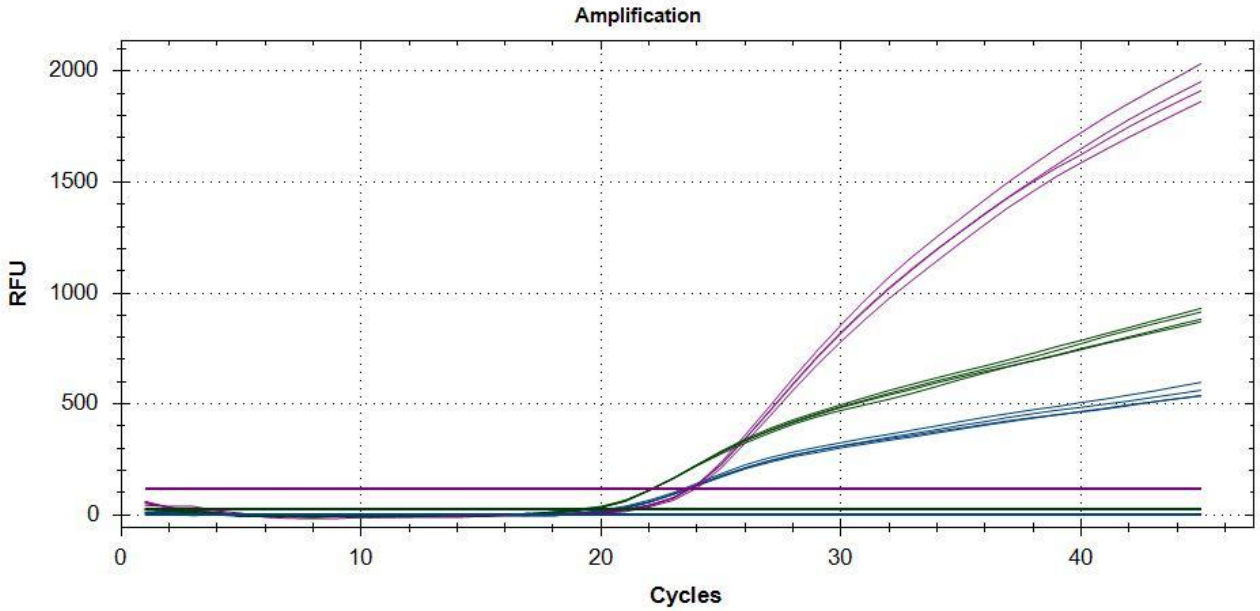

Figure 3. Commercial human genomic DNA amplification plot (purple: TREC, green: wild-type IKBKB, blue: wild-type ZAP70) using the adjusted primer and probe set

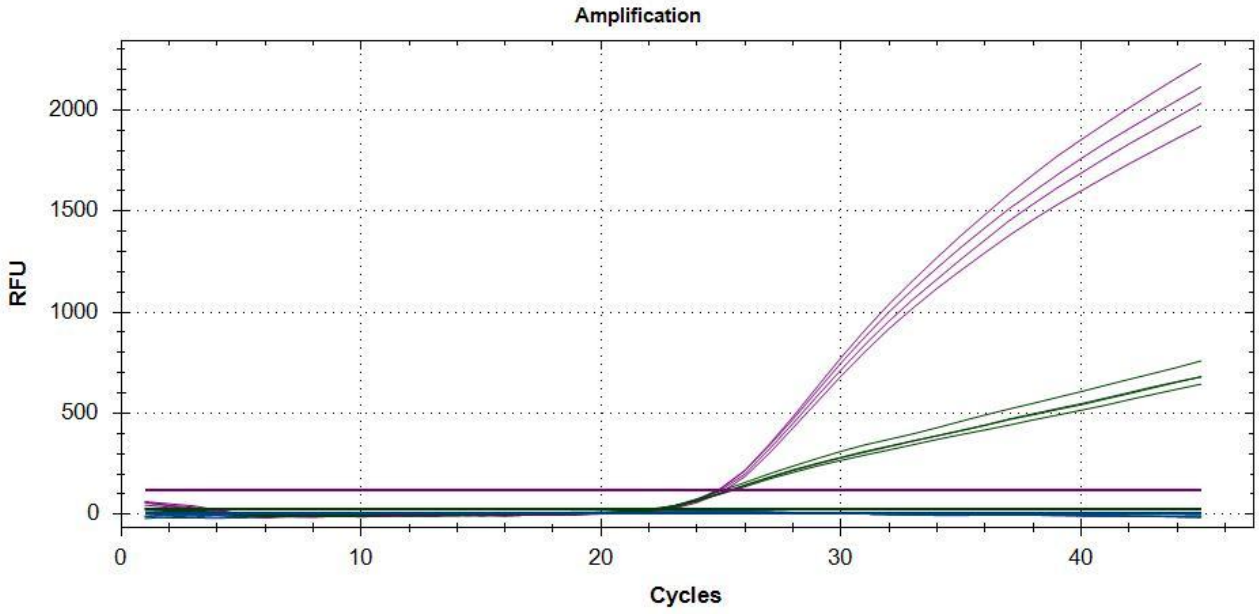

Figure 4. *ZAP70* mutated SCID DNA amplification plot (purple: TREC, green: wild-type IKBKB, blue: wild-type ZAP70) using the adjusted primer and probe set

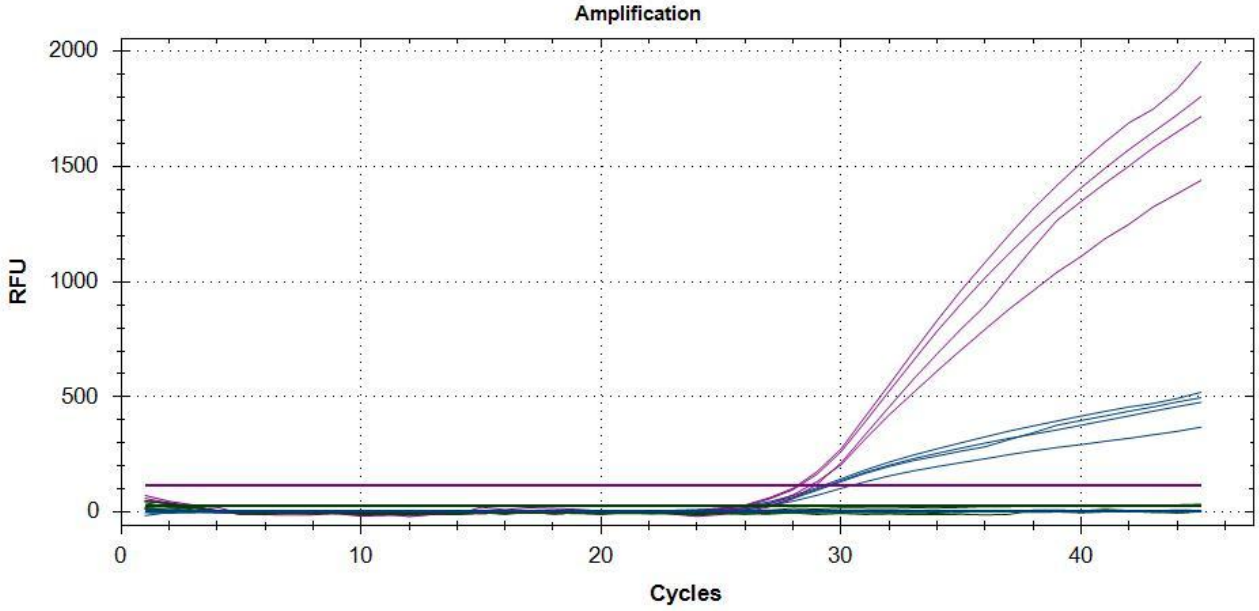

Figure 5. *IKBKB* mutated SCID DNA amplification plot (purple: TREC, green: wild-type IKBKB, blue: wild-type ZAP70) using the adjusted primer and probe set

Discussion

This assay serves as proof of concept for the use of allele-specific qPCR without a silent probe. Due to the low prevalence of SCID overall, and a resultant lack of positive control material, ongoing quality testing with in-house developed control material is required to assess the statistical power of this assay (Table 7). This will be performed in tandem with the use of the assay for newborn screening, which was implemented at CPL in September 2020. Since this time, all newborns born in Manitoba whose parents have not opted-out of newborn screening are screened for SCID using this multiplex assay.

The rollout of this assay addresses ongoing calls for a tailored SCID screening modality and provides a framework for expanded newborn screening in other provinces, particularly in the adjacent provinces of Ontario and Saskatchewan where the *IKBKB* mutation is also found.[15,16] Newborn Screening Programs for SCID currently exist in only five Canadian provinces and one territory: Alberta, Manitoba, Ontario, New Brunswick, Nova Scotia, and the Northwest Territories.[17] Although CPL receives some specimens from

births in adjacent provinces, expanded screening in Ontario and the implementation of a SCID screening protocol in Saskatchewan is needed to ensure all newborns born with SCID are identified before symptoms present. Currently, CPL only receives out-of-province samples if the newborn is either born in Manitoba, despite being from out-of-province, or if the sample is sent to CPL due to proximity. This means that robust provincial screening must be implemented to identify the greatest number of affected newborns.

Beyond the relevance of screening to decrease the direct morbidity and mortality associated with SCID, the inclusion of screening for the *IKBKB* variant has special clinical relevance because of the use of the live-attenuated *M. bovis* bacille Calmette-Guérin (BCG) vaccine in First Nations communities.[18] The BCG vaccine is contraindicated in patients with SCID and a Manitoba case series found that all IKK2 deficient infants who received BCG vaccination developed fatal disseminated mycobacterial disease.[19,20] Vaccination with BCG in the affected communities has subsequently been avoided until a negative newborn screening result is confirmed, which has been made possible through the implementation of expanded newborn screening for SCID.

To summarize, a high incidence of SCID in Manitoba is related to two founder mutations that exist at increased frequency in specific populations. We developed and validated a multiplexed qPCR assay to combine targeted, allele-specific identification of these mutations with the gold standard for screening of T cell negative SCID, TREC quantification. The implementation of this assay within the newborn screening program at CPL will decrease the morbidity and mortality of SCID in Manitoban neonates and establish a precedent for future population-specific screening programs in Canada.

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References

[1] Rozmus J, Junker A, Thibodeau ML, Grenier D, Turvey SE, Yacoub W, et al. Severe combined immunodeficiency (SCID) in Canadian children: a national surveillance study. Journal of Clinical Immunology. 2013;33:1310–1316.

[2] Thompson JR, Greenberg CR, Dick A, Jilkina O, Kwan L, Rubin TS, et al. Development of a population-based newborn screening method for severe combined immunodeficiency in Manitoba, Canada. International Journal of Neonatal Screening. 2018;4:19.

[3] Myers LA, Patel DD, Puck JM, Buckley RH. Hematopoietic stem cell transplantation for severe combined immunodeficiency in the neonatal period leads to superior thymic output and improved survival. Blood, The Journal of the American Society of Hematology. 2002;99:872–878.

[4] Jilkina O, Thompson JR, Kwan L, Van Caeseele P, Rockman-Greenberg C, Schroeder ML. Retrospective TREC testing of newborns with severe combined immunodeficiency and other primary immunodeficiency diseases. Molecular Genetics and Metabolism Reports. 2014;1:324–333.

[5] Pannicke U, Baumann B, Fuchs S, Henneke P, Rensing-Ehl A, Rizzi M, et al. Deficiency of innate and acquired immunity caused by an IKBKB mutation. New England Journal of Medicine. 2013;369:2504–2514.

[6] Schroeder ML, Triggs-Raine B, Zelinski T. Genotyping an immunodeficiency causing c. 1624–11G>A ZAP70 mutation in Canadian Mennonites. BMC Medical Genetics. 2016;17:50.

[7] Nielsen C, Jakobsen MA, Larsen MJ, Müller AC, Hansen S, Lillevang ST, et al. Immunodeficiency associated with a nonsense mutation of IKBKB. Journal of Clinical Immunology. 2014;34:916–921.

[8] Andermann A, Blancquaert I, Beauchamp S, Déry V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. Bulletin of the World Health Organization. 2008;86:317–319.

[9] Van Der Spek J, Groenwold RH, Van Der Burg M, Van Montfrans JM. TREC based newborn screening for severe combined immunodeficiency disease: a systematic review. Journal of Clinical Immunology. 2015;35:416–430.

[10] Puck JM. Laboratory technology for population-based screening for SCID in neonates: the winner is T-cell receptor excision circles (TRECs). The Journal of Allergy and Clinical Immunology. 2012;129:607.

[11] Grazioli S, Bennett M, Hildebrand KJ, Vallance H, Turvey SE, Junker AK. Limitation of TREC-based newborn screening for ZAP70 severe combined immunodeficiency. Clinical Immunology. 2014;153:209–210.

[12] Ranasinghe RT, Brown T. Fluorescence based strategies for genetic analysis. Chemical Communications. 2005;44:5487–5502.

[13] Markou A, Farkona S, Schiza C, Efstathiou T, Kounelis S, Malamos N, et al. PIK3CA mutational status in circulating tumor cells can change during disease recurrence or progression

in patients with breast cancer. Clinical Cancer Research. 2014;20:5823–5834.

[14] Gutierrez-Mateo C, Timonen A, Vaahtera K, Jaakkola M, Hougaard DM, Bybjerg-Grauholm J, et al. Development of a Multiplex Real-Time PCR Assay for the Newborn Screening of SCID, SMA, and XLA. International Journal of Neonatal Screening. 2019;5:39.

[15] Rubin TS, Rockman-Greenberg C, Van Caeseele P, Cuvelier GD, Kwan L, Schroeder ML. Newborn screening for IKBKB deficiency in Manitoba, using genetic mutation analysis. Journal of Clinical Immunology. 2018;38:742–744.

[16] Cuvelier GD, Rubin TS, Junker A, Sinha R, Rosenberg AM, Wall DA, et al. Clinical presentation, immunologic features, and hematopoietic stem cell transplant outcomes for IKBKB immune deficiency. Clinical Immunology. 2019;205:138–147.

[17] Newborn Screening for SCID [Internet]. Immunodeficiency Canada; 2020. [Cited 2021 Jan 3]. Available from: https://immunodeficiency.ca/newborn-screening-for-scid/.

[18] Faust L, Schreiber Y, Bocking N. A systematic review of BCG vaccination policies among high-risk groups in low TB-burden countries: implications for vaccination strategy in Canadian indigenous communities. BMC Public Health. 2019;19:1–32.

[19] Deeks SL, Clark M, Scheifele DW, Law BJ, Dawar M, Ahmadipour N, et al. Serious adverse events associated with bacille Calmette-Guérin vaccine in Canada. The Pediatric Infectious Disease Journal. 2005;24:538–541.

[20] Marciano BE, Huang CY, Joshi G, Rezaei N, Carvalho BC, Allwood Z, et al. BCG vaccination in patients with severe combined immunodeficiency: complications, risks, and vaccination policies. Journal of Allergy and Clinical Immunology. 2014;133:1134–1141.

Social isolation in older adults: A student-led response to fill the gap

Nebojša Oravec BSc[†] Kara Frejuk BSc[†] Kaleigh Ducas-Mowchun BSc[†]
Ann Weber BSc[†]

Abstract

While the COVID-19 pandemic forced some Canadians into "lockdown" for the first time, the experience of social isolation was already a reality for many older adults. Public health restrictions intensified social isolation during the pandemic and, while the rest of the world transitioned to using technology to meet their social needs, the older adult population was largely left behind. With focus on immediate medical and financial need, efforts to mitigate social isolation were diverted to community and volunteer agencies. The combination of inadequate action on the part of government and absence of an organized community strategy provided an opportunity for grassroots advocacy projects to address new or existing issues related to the COVID-19 pandemic. The Student-Senior Isolation Prevention Partnership (SSIPP) is one such project. It serves to connect health professional students with older adults for regular telephone visits to promote social connection and health literacy. In addition to the immediate and lasting benefits for older adults, SSIPP has expanded to become an educational tool for experiential learning and advocacy training. In this article, we describe the circumstances that led to the emergence of a national advocacy project for Canadian medical students and its potential for enhancing medical education.

Keywords: social isolation; geriatrics; advocacy; COVID-19

Conflict of Interest Statement: None to declare.

Introduction - isolation in older adults

A lack of social connection (social isolation) and the subjective feeling of being alone (loneliness) are both experienced in greater proportions by older adult populations.[1,2] Loneliness has also been identified as a major risk factor for cardiovascular disease and stroke, and has been found to increase general mortality by 26-50%.[3,4] Isolation and loneliness are both risk factors for, and consequences of, poor health. The factors that contribute to loneliness among older adults are many and diverse: gender, culture, family structure, geography, technology accessibility, and health status among others. All contribute to a complex and multifaceted social context that predisposes older adults to loneliness.[5–8] Data suggests that the life circumstances often associated with aging such as single or widowed status, living alone, having a lower household income, or functional impairment particularly increase this risk.[9]

During the COVID-19 pandemic, physical distancing and public health measures to prevent infection have also led to decreased in-person social interactions. While this is considered a necessary intervention for individual and public safety, it carries a devastating emotional impact. Older adults are already at increased risk for loneliness, anxiety, and depressive symptoms. Provincial public health orders limit access from friends, family, volunteers, and non-essential healthcare workers, particularly for congregate living such as assisted living and in long-term care.[10–12] The Canadian Frailty Network has recommended using technology where possible to mitigate the effects of social isolation and loneliness.[13] For older adults in the community this is not always possible due to limited household income, the need for in-person support to navigate electronics, lack of confidence learning new technology, and lack of infrastructure connectivity in rural settings. In the long-term care setting, barriers to enhanced social connectedness via technology are related to financial and staffing demands, as increased staffing is often needed to help manage the technology .[14] In addition, the technological dexterity necessary to operate these new programs may be a barrier for many older adults who are unfamiliar with them. The resulting lack of accessibility widens social gaps experienced by this demographic.

*Correspondence to: oravecn@myumanitoba.ca
[†]Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada

Government and community response to seniors' issues and COVID-19

As of November 24, 2020, approximately 75% of COVID-19 deaths in Canada occurred amongst Canadians living in long-term care or assisted living facilities, and almost 97% of the COVID-19 deaths in Canada were of individuals aged 60 years or older.[13,15] The government's response to issues faced by older adults during the pandemic has focused on financial resources, which have been largely inadequate.[16] A one-time refundable tax credit of $200 from the Manitoba provincial government and a second payment of a maximum of $500 from the federal government have been the only tangible economic supports for seniors in our province.[17,18] While many younger Canadians have relied on the Canadian Emergency Recovery Benefit (CERB), this program is only available to adults with a pension whose part-time work has been disrupted as a result of the pandemic.[19] Other strategies include extensions to the Guaranteed Income Supplement and Allowance payments and reducing minimum withdrawals for Registered Retirement Income Funds.[20] While addressing the financial reality of low-income seniors during the pandemic is an important step, short-term socioeconomic stability does little to address ongoing social issues.

Government response to the consequences of social isolation in older adults is lacking. This role has been informally delegated to community groups, not-for-profits, and volunteer agencies. Some of these groups existed prior to the pandemic and others have emerged to address the burgeoning crisis of loneliness in the older adult population. For example, Age and Opportunity (A&O) is an organization aimed at providing specialized programs and services to older adults in Manitoba that acknowledges a broad definition of health and well-being.[21] The organization's Seniors Resource Finders provide telephone and e-mail services that connect older adults with specialized services in their own neighborhood. Other organizations, such as the University of Manitoba Centre on Aging and the Canadian Frailty Network, have also served as sources of information about community resources that can offset social isolation for seniors and the general public.[22,23] Prior to the pandemic, A&O's Senior Centre Without Walls already provided social connection and recreation over the phone. During the pandemic, it has expanded their programming and added a Daily Hello program. Numerous seniors' councils, cultural organizations, and church groups have also started informal phone-based support. Other newly structured virtual social services include the Reach Isolated Seniors Everywhere (RISE) program and the Student Senior Isolation Prevention Partnership (SSIPP).[24,25]

As essential social services transitioned to a virtual platform, they also became less accessible for older adults. Many older adults have relied on referral to these organizations from health professionals such as physicians, nurses, social workers, mental health clinicians, home care, specialized geriatric services, and outreach teams. Healthcare represents a critical entry point for older adults to gain access to social support services. However, in the context of the pandemic there has been reduced contact with providers, delayed visits for chronic disease management, and an emphasis on virtual care. All of these can mask issues related to social isolation and loneliness. Strict visitation restrictions in hospitals, long-term care facilities, and congregate living spaces also represents a significant challenge. This has contributed to loneliness, depression, worsened cognition, and contributed to dehydration and malnutrition in the long-term care sector. With the second wave of the pandemic, Shared Health amended both its long-term care and hospital visitation policies to allow for "essential care partners," citing the Canadian Patient Safety Institute national policy guideline on the role of essential caregivers.[26] Policies are only just now being updated to reflect the essential role that caregivers occupy on the healthcare team for older adults.

The student-senior isolation prevention partnership

The Student-Senior Isolation Prevention Partnership (SSIPP) is a national collaboration of medical students seeking to address the issue of social isolation in older adults that has been exacerbated by the COVID-19 pandemic. The program pairs student volunteers with an older adult in the community who has been referred by a healthcare provider based on their risk of social isolation. The student and older adult engage in a weekly phone call with the primary goal of fostering a friendship as opposed to providing medical or mental health services. Initially founded at the University of Toronto, SSIPP quickly expanded to 12 of Canada's 17 medical schools since March 2020. Later that same year, the organization was approved as a certified non-governmental organization. Since the beginning of the pandemic, the Manitoba chapter has received more than 170 referrals from community healthcare providers, recruited over 300 student volunteers, and provided over 500 hours of volunteer phone calls. Most active student-senior pairs have engaged in weekly calls for more than four months, with the average call length of approximately 45 minutes. The individual impact has been evident in responses heard from participants and referral sources, which indicates significant changes in feelings of social isolation:

> "I got linked up... with an amazing student ... She calls on time, every time. She recorded a song on her piano and played it back to me on the phone... it was delightful and thoughtful, what an amazing program and human being. She is not only intelligent, but she is also intuitive and insightful. **My soul and spirit awakened as well as my hope.**" – SSIPP Client

> "It was our second conversation. The senior was sharing their experience of their last moment with their deceased partner and we both started crying. By the end of our conversation, we were laughing about how wild our hair was going to look when the pandemic is over. It was nice to go through this spectrum of emotions over the phone. Their demeanor at the beginning of the call and at the end was significantly improved. **This is already proving to be a rewarding experience.**" – SSIPP Volunteer

The volume of referrals as well as the responses received from participants demonstrates that SSIPP is fulfilling an essential need in the community. Its success also proves that student advocacy projects can provide meaningful improvements to community and population health. However, SSIPP also offers a unique service to medical students by facilitating experiential learning opportunities. Early contact and, in particular, contact over time have positive impacts on health profession student attitudes towards working with older adults.[27,28] Experiential learning builds on curricular teaching, adds important perspective, and can serve to fill gaps in pre-clerkship curricula. In September 2020, SSIPP was approved as an official Service Learning organization through the University of Manitoba Max Rady College of Medicine. This allows students to earn curricular recognition for their role as volunteers. To date, 25% of the first-year class and 20% of pre-clerks at the University of Manitoba have met their volunteer requirements either in part or entirely through SSIPP. We are hopeful that exposure to programs like SSIPP will inspire students to pursue careers in the field of geriatrics. We plan to focus on this as an area of future research.

SSIPP as a tool for experiential learning

The proportion of older adults in Canada is growing rapidly. In 2012, one in seven Canadians were over the age of 65. By 2030, the same figure is projected to increase to one in four.[29] Interest in the field of geriatrics among medical students has not kept pace with the anticipated needs of our population. A systematic review examining the reasons behind this lack of interest demonstrates that lack of exposure to geriatrics is a key factor.[30] Relevant teaching in the preclinical years focuses on the Geriatric 5Ms, a communication framework that describes the core competencies in Geriatrics. These include: Mind (dementia, delirium, depression), Mobility, Medication (including polypharmacy), Multi-Complexity (referring to multimorbidity and the biopsychosocial holistic approach) and Matters Most (individual goals of care). While the 5Ms help to guide clinical approaches, they are unlikely to teach students about the lived-in experiences of older adults if they are presented without the personal context and perspectives of these patients. Examples of important considerations include the impact of medication dosing for a patient with polypharmacy, impacts of sensory and cognitive impairment on medication management, and the intersection between social isolation and cognitive decline. These topics are difficult to address in a two-year pre-clerkship curriculum, and even more difficult to illustrate without the patient context.

SSIPP provides a unique experience for medical students to learn first-hand about the lived-in experience of older adults. They gain meaningful exposure to difficult-to-teach concepts such as the impact of losing a spouse, social isolation, cognitive decline, medication management, and how these challenges can be further compounded by sensory impairment or mobility issues. SSIPP provides students with the opportunity to understand these challenges on a personal level. Students receive standardized training through SSIPP to help guide older adults toward supports available within the community. This experience educates students on the challenges faced by older adults and supports available to them. Furthermore, it can also help students identify gaps in community supports and in the healthcare system where older adults may be falling through the cracks.

Medical students as health advocates

Medical students are taught early on that one of the roles of a physician is to be a health advocate. However, health advocacy is a skill. Like any other skill, it requires practice. Programs like SSIPP provide opportunities for students to practice advocating for older adults at the individual level, as well as how to engage in large-scale advocacy work. Advocating for the individual can transform into population-level advocacy efforts. This can ultimately inspire medical students to carry health advocacy for older adults forward into their future careers.

Conclusion

Though there is much work yet to be done, SSIPP has helped to mitigate some of the isolation felt by older adults during the COVID-19 pandemic. The program sets an example for how health professional students can contribute to meaningful change in their communities, thereby complementing government and community initiatives to provide essential services to populations in need. SSIPP is also an important example of how experiential learning can enhance medical education and contribute to skill development in health advocacy. These opportunities allow health profession students to affect change now and give them the skills they need to advocate for their own patients in the future.

References

[1] Fancey P, Keefe J, Andrew M, Hall M. Final Report: A Profile of Social Isolation in Canada.

Nova Scotia Centre on Aging; 2006.

[2] Havens B, Hall M, Sylvestre G. Social isolation and loneliness: differences between older rural and urban Manitobans. Can J Aging. 2004;23(2):129–40.

[3] Valtorta NK, Kanaan M, Gilbody S. Loneliness and social isolation as risk factors for coronary heart disease and stroke: systematic review and meta-analysis of longitudinal observational studies. Heart. 2016;102(13):1009–16.

[4] Rico-Uribe LA, Caballero FF, Martín-María N. Association of loneliness with all-cause mortality: A meta-analysis. PloS One. 2018;13(1).

[5] Menec VH, Newall NE, Mackenzie CS. Examining individual and geographic factors associated with social isolation and loneliness using Canadian Longitudinal Study on Aging (CLSA) data. PLoS One. 2019;14(2).

[6] Harasemiw O, Newall N, Shooshtari S. From Social Integration to Social Isolation: The Relationship Between Social Network Types and Perceived Availability of Social Support in a National Sample of Older Canadians. Res Aging. 2018;40(8):715–39.

[7] J JG, Pas S V, N K. Loneliness of Older Immigrant Groups in Canada: Effects of Ethnic-Cultural Background. J Cross Cult Gerontol. 2015;30:251–68.

[8] Nowland R, Necka EA, Cacioppo JT, Tilburg T, Havens B, Jong Gierveld J. Loneliness and Social Internet Use: Pathways to Reconnection in a Digital World? Perspect Psychol Sci 2018;13(1):70-87. Can J Aging. 2004;23(2):169–80.

[9] Norris S, Parliament L. Long-Term Care Homes in Canada – The Impact of COVID-19;. Available from: https://hillnotes.ca/2020/10/30/long-term-care-homes-in-canada-the-impact-of-covid-19/.

[10] National Institute on Ageing. Pandemic Perspectives on Ageing in Canada in Light of COVID-19: Findings from a National Institute on Ageing/TELUS Health National Survey; 2020. [Cited 2021 Jan 3]. Available from: https://www.nia-ryerson.ca/s/PandemicPerspectives-oct13-3hw8.pdf.

[11] Armitage R, Nellums LB. COVID-19 and the consequences of isolating the elderly. Lancet Public Health. 2020;5(5).

[12] Gardner W, States D, Bagley N. The Coronavirus and the Risks to the Elderly in Long-Term Care. J Aging Soc Policy. 2020;32(4-5):310–15.

[13] MacCourt P, Social Isolation FPTWG, Innovation S. Social Isolation of Seniors - Volume 1: Understanding the issue and finding solutions; 2020. [Cited 2021 Jan 2]. Available from: http://www12.esdc.gc.ca/sgpe-pmps/servlet/sgpp-pmps-pub?lang=eng&curjsp=p.5bd.2t.1.3ls@-eng.jsp&curactn=dwnld&pid=55837&did=4964.

[14] Canada S. Census Dictionary. Catalogue. 2011;(98-301-X). [Cited 2021 Jan 2]. Available from: https://www12.statcan.gc.ca/census-recensement/2011/ref/dict/98-301-X2011001-eng.pdf.

[15] of Canada G. COVID-19: Resources for seniors and their caregivers; 2020. [Cited 2020 Aug 14]. Available from: https://www.canada.ca/en/public-health/services/diseases/coronavirus-disease-covid-19/resources-older-adults-caregivers.html.

[16] Employment, Canada SD. One-time tax-free payment for seniors; 2020. [Cited 2020 Dec 28]. Available from: https://www.canada.ca/en/services/benefits/publicpensions/notice-covid-19/one-time-payment.html.

[17] Plan MP. Seniors Economic Recovery Credit; 2020. [Cited 2020 Dec 28]. Available from: https://manitoba.ca/covid19/protection/seniors.html#commonquestions.

[18] Employment, Canada SD. Canada Emergency Response Benefit (CERB; 2020. [Cited 2020 Dec 28]. Available from: https://www.canada.ca/en/services/benefits/ei/cerb-application.html.

[19] Canada's COVID-19 Economic Response Plan. Seniors; 2020. [Cited 2020 Dec 28]. Available from: https://www.canada.ca/en/department-finance/economic-response-plan.html.

[20] A&O Support Services for Older Adults;. [Cited 2021 Jan 3]. Available from: https://www.aosupportservices.ca.

[21] Matters F. Additional Resources: COVID-19 and Older Adults Living with Frailty; 2020. [Cited 2020 Dec 28]. Available from: https://www.cfn-nce.ca/frailty-matters/additional-resources-covid-19/.

[22] Community resources for older people. COVID-19 resources for older people in Manitoba; 2021. [Cited 2020 Dec 28]. Available from: https://umanitoba.ca/centres/aging/coa_community-socialresources.html.

[23] Reach Isolated Seniors Everywhere (RISE); 2021. [Cited 2021 Jan 3]. Available from: http://rise-cisa.ca.

[24] Student Senior Isolation Prevention Partnership (SSIPP); 2021. [Cited 2021 Jan 3]. Available from: https://www.ssipp.info.

[25] Employment and Social Development Canada. Canada Recovery Caregiving Benefit (CRCB); 2020. [Cited 2020 Dec 28]. Available from: https://www.canada.ca/en/revenue-agency/services/benefits/recovery-caregiving-benefit.html.

[26] Canadian Foundation for Healthcare Improvement, Canadian Patient Safety Institute. Policy Guidance for the Reintegration of Caregivers as Essential Care Partners; 2020. [Cited 2020 Dec 28]. Available from: https://www.cfhi-fcass.ca/docs/default-source/itr/tools-and-resources/policy_guidance_en.pdf?sfvrsn=292a980e_4.

[27] Reilly J, Stevens G, et al HA. Interprofessional, older adult, team-based home visits: A 6-year prospective analysis. Gerontology and Geriatrics Education. 2020;.

[28] Wilkinson T, Gower S, Sainsbury R. The earlier, the better: the effect of early community contact on the attitudes of medical students to older people Medical Education; 2020.

[29] Wong A. Government of Canada — Action for Seniors report; 2014. [Cited 2021 Jan 3]. Available from: https://www.canada.ca/en/employment-social-development/programs/seniors-action-report.html.

[30] Meiboom AA, De Vries H, Hertogh CMPM. Why medical students do not choose a career in geriatrics: A systematic review Career choice, professional education and development. BMC Med Educ. 2015;15(1):1–9.

A case of stroke mimic in the setting of metastatic melanoma

Quinn Robertson-Stovel BSc[†]

Abstract

In the emergency setting, brain tumours can present as "stroke mimics", which are a category of non-vascular pathological conditions that can present with a stroke-like clinical picture. Ischemic stroke presentations are heterogenous with a wide variety of presenting symptoms and signs depending on the area of the brain affected. Distinguishing between stroke mimics and ischemic strokes is an important challenge that requires a thorough work-up. Due to the time-sensitive nature of ischemic stroke treatment and the potentially disastrous consequences of not receiving proper treatment for an ischemic stroke, accurately identifying an ischemic stroke or stroke mimic is of utmost importance. Accurate diagnosis of stroke mimic also allows for the mimic to be accordingly investigated and treated appropriately. This report presents a case of stroke mimic due to a metastatic brain tumour. The case illustrates one of the causes of stroke mimic, the work-up required to arrive at the correct diagnosis, and why distinguishing between an ischemic stroke and stroke mimic can prevent unnecessary treatment and lead to proper follow-up.

Keywords: ischemic stroke; stroke mimic; brain tumour; melanoma

Conflict of Interest Statement: None to declare.

Introduction

Stroke mimics often present with similar acute neurological deficits to ischemic stroke and can correspond to many different vascular regions of the brain. This can complicate proper assessment on initial presentation.[1] Stroke mimics can have a wide variety of etiologies, including cardiovascular, neurological, metabolic, infectious, or psychiatric causes.[2] Brain tumours can present like strokes due to "tumour attacks", a multifactorial phenomenon that can create an acute stroke-like presentation.[3] Accurate diagnosis of a stroke mimic requires one to take note of features on history and physical exam that make stroke mimics more likely, laboratory investigations, and diagnostic brain imaging, such as computed tomography (CT) or magnetic resonance imaging (MRI).[1] This report presents a case of melanoma that metastasized to the brain and created a stroke-like presentation in a patient.

Case history

A 75-year-old man presented to the Selkirk Regional Health Centre Emergency Department (ED) with left-sided facial weakness. Approximately two hours prior to presentation, the patient experienced a sudden onset of difficulty swallowing, chattering teeth, slurred speech, left-sided drooling, and left facial droop. These symptoms gradually resolved by the time the patient presented to the ED. The patient denied any headaches, blurred vision, dizziness, and numbness or tingling.

The patient was vitally stable: temperature 37°C, heart rate 70 beats per minute, blood pressure 147/72mmHg, respiratory rate 16 breaths per minute, oxygen saturation 99% on room air). On physical exam, the patient was alert and oriented to time, place, and self. He was speaking clear, full sentences without any slurred speech. Cranial nerves II to XII were intact with no facial droop appreciated on exam. There were no motor or sensory deficits in the limbs, and reflexes were intact bilaterally. Tone in the upper and lower extremities was normal. The coordination exam was normal. Cardiovascular, respiratory, and abdominal exam were normal and unremarkable.

Further evaluation revealed that the patient's medical history included hypertension and malignant melanoma. In 2019, he had a right axillary and cervical lymph node dissection due to metastatic spread of the melanoma. He had no known allergies, did not smoke cigarettes, and consumed 1-2 alcoholic beverages per week.

Initial laboratory investigations revealed an elevated urea, creatinine, urea/creatinine ratio and decreased estimated glomerular filtration rate. Other parameters were unremarkable. Although the physical exam revealed no neurological deficits, the history given by

*Correspondence to: robertsq@myumanitoba.ca
[†]Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada

the patient was concerning for transient ischemic attack (TIA) or ischemic stroke. This prompted an uninfused CT scan of the brain to be ordered.

The CT scan showed a new right posterior-lateral frontal lobe lesion, with vasogenic edema. The interpretation was that this was related to a metastatic lesion given the patient's history of metastatic melanoma, and that the appearance of changes on the scan were not consistent with infarction. Based on the CT and cancer history, a new diagnosis of central nervous system metastasis of melanoma was considered over ischemic stroke or TIA. In consultation with Neurology, it was suspected that the most likely cause of the patient's resolving symptoms was a seizure caused by the metastatic lesion. A loading dose of intravenous phenytoin was started. Oncology was consulted and an MRI of the brain was ordered.

The MRI showed an enhancing right frontal lobe lesion with surrounding edema. The clinical impression (considering the patient's history of metastatic melanoma, the acute development and resolution of symptoms, and the presence of a new brain lesion that explained the left-sided facial symptoms) suggested that the patient likely suffered a seizure. Oncology suggested that the patient be given a prescription for dexamethasone 4mg to be taken twice a day until a scheduled follow up appointment. Neurosurgery was then consulted, who suggested a referral for Gamma Knife radiosurgery. The patient was discharged from the ED with plans to follow up with Neurosurgery and Oncology.

Discussion

The frequency of stroke mimics observed in the ED ranges from 15-43% of suspected ischemic stroke cases.[4–6] A single-centre retrospective analysis of 950 consecutive patients presenting with suspected stroke from 2012-2013 in a Canadian ED showed that 43% of those patients had stroke mimics.[6] In the largest study of stroke mimics to date, it was found that, of 8187 patients referred to the ED for suspected stroke, 30% were stroke mimics.[5] Some common etiologies of stroke mimics are epileptic seizures, metabolic abnormalities (hypoglycemia, hyperglycemia, and hepatic encephalopathy), migraines, psychogenic causes, and infections.[1]

Brain tumours account for 6-8% of stroke mimics.[2,7] Brain tumours can present with a sudden onset of stroke-like symptoms due to the aforementioned "tumour attacks".[3] However, the pathophysiology of "tumour attacks" is not fully understood. Mechanisms thought to contribute to these attacks include: acute intracranial pressure changes that result in decreased blood flow, vascular steal phenomenon, acute hemorrhage, and vascular compression with resultant infarction.[3] In addition to "tumour attacks", brain tumours can precipitate seizures, likely due to the changes in neurotransmitter homeostasis in the brain parenchyma surrounding the tumour.[8] A resulting Todd's paralysis can occur in the post-ictal period of the seizure, mimicking an ischemic stroke (as occurred in this case).[9] Seizures are especially common in metastatic brain tumours due to melanoma versus other primary cancers with one retrospective study estimated a seizure incidence of 67%.[10] One systematic review of 18 studies (N = 2012) examining seizure incidence due to intracranial metastatic disease determined that a metastatic brain tumour where melanoma was the primary site had the highest seizure rate compared to other primary cancers, including ovarian, lung, colorectal, hepatocellular, and prostate.[11]

Correctly diagnosing an ischemic stroke or stroke mimic can be challenging for even the most experienced clinician. However, there are certain features on history and physical exam that are more suggestive of stroke mimic. An absence of hypertension, dyslipidemia, or atrial fibrillation favor stroke mimics.[5] Classically, ischemic strokes present with sudden-onset focal neurological deficits, whereas seizures can evolve over seconds and are associated with positive neurological symptoms such as excessive motor activity or sensory symptoms.[12] Headache, or seizure at symptom onset, are also features associated with brain tumour-stroke mimics.[13] On physical exam, the absence of neurological signs is suggestive of stroke mimic rather than an ischemic stroke.[14] In addition to the history and physical exam, initial tests such as rapid glucose testing, electrocardiography, complete blood count, blood urea nitrogen, creatinine, electrolytes, troponins, and coagulation studies can rule out other common causes of stroke mimics.[12]

In the case presented, the patient had a history of hypertension. In the history of presenting illness, he endorsed a sudden onset of symptoms, facial droop, and slurred speech, all of which would favor ischemic stroke. However, the absence of neurological signs was more suggestive of stroke mimic. Laboratory testing was also unremarkable, indicating that other causes of stroke mimic such as metabolic abnormalities, infection, and drug or alcohol intoxication were less likely.

Although the history and physical exam can provide suggestive features of a stroke mimic, diagnostic imaging is the most essential tool to distinguish between an ischemic stroke and brain tumour-stroke mimic. Non-contrast CT head and MRI are the two most important imaging modalities for the evaluation of ischemic strokes.[3] Non-contrast CT scan is the most readily available imaging modality, and is often the first imaging modality used in the work-up of strokes and stroke mimics. On non-contrast CT, evidence of multiple lesions, mass effect, edema, and a lack of vascular distribution are features that are more suggestive of a brain tumour-stroke mimic as opposed to an ischemic stroke.[3,15] Brain tumours are expected to enhance on contrast CT.[3] The patient presented in this case had an uninfused CT scan that revealed there was a new area of low attenuation with associated mass effect and vasogenic edema. Although these features would be indicative of a brain tumour, it was recommended to further evaluate with MRI. This ultimately served to support

the diagnosis of metastatic melanoma. MRI is more sensitive and specific than non-contrast CT head scan for detecting ischemic strokes, and MRI with diffusion-weighted imaging is even more sensitive than standard MRI.[12,16] Smaller tumours, those not causing mass effect, or those that are iso-attenuating can be missed on non-contrast CT.[3]

It is imperative to distinguish between an ischemic stroke and brain tumour-stroke mimic because it prevents unnecessary treatment. If there are no contraindications, intravenous tissue plasminogen activator (tPA) administered within 4.5 hours of symptom onset is first-line therapy for most acute ischemic strokes.[16] Many physicians have a very low threshold for diagnosing and treating ischemic strokes due to the time-sensitive nature of the treatment and potentially catastrophic side effects of missed diagnoses. In some instances, stroke mimics are inadvertently treated with thrombolytics. Rates of stroke mimics treated with tPA vary from 1.4-16.7%.[17] Exposing patients to unnecessary treatments can have adverse psychological effects, add unnecessary risks, use resources improperly, and delay the correct diagnosis for a patients.[14] With respect to brain tumours, delayed diagnosis may allow the malignancy to spread further in the brain and result in increased morbidity and mortality.[15] Whereas, timely excision of brain tumours can improve survival and quality of life.[15]

Conclusion

The case in this report demonstrated a case of a 75-year-old man presenting with resolving stroke-like symptoms. This was determined to be the result of seizure caused by metastatic melanoma to the brain. The case illustrates the importance of distinguishing between an ischemic stroke and stroke mimic so that patients can receive proper management. A thorough history and physical exam can help to reveal some features that might be suggestive of a stroke. Laboratory testing and imaging modalities are crucial in differentiating between a stroke and stroke mimic.

References

[1] Vilela P. Acute stroke differential diagnosis: Stroke mimics. Eur J Radiol. 2017;96:133–144.

[2] J NB, RT Z, MP K. Stroke Mimics Transported by Emergency Medical Services to a Comprehensive Stroke Center: The Magnitude of the Problem. J Stroke Cerebrovasc Dis. 2018;27(10):2738–2745.

[3] Liu X, Almast J, Ekholm S. Lesions masquerading as acute stroke. J Magn Reson Imaging. 2013;37(1):15–34.

[4] Moulin S, Leys D. Stroke mimics and chameleons. Curr Opin Neurol. 2019;32(1):54–59.

[5] Merino JG, Luby M, Benson RT. Predictors of acute stroke mimics in 8187 patients referred to a stroke service. J Stroke Cerebrovasc Dis. 2013;22(8):397–403.

[6] J NB, RT Z, MP K. Stroke Mimics Transported by Emergency Medical Services to a Comprehensive Stroke Center: The Magnitude of the Problem. J Stroke Cerebrovasc Dis. 2018;27(10):2738–2745.

[7] Gibson LM, Whiteley W. The differential diagnosis of suspected stroke: A systematic review. J R Coll Physicians Edinb. 2013;43(2):114–118.

[8] Chen DY, Chen CC, Crawford W JR, G S. Tumour-related epilepsy: epidemiology, pathogenesis and management. J Neurooncol. 2018;139(1):13–21.

[9] Okano Y, Ishimatsu K, Kato Y. Clinical features of stroke mimics in the emergency department. Acute Med Surg. 2018;5(3):241–248.

[10] Oberndorfer S, Schmal T, Lahrmann H, Urbanits S, Lindner K, Grisold W. The frequency of seizures in patients with primary brain tumours or cerebral metastases. An evaluation from the Ludwig Boltzmann Institute of Neuro-Oncology and the Department of Neurology, Kaiser Franz Josef Hospital, Vienna. Wien Klin Wochenschr. 2002;114(21-22):911–916. [Cited 2021 Feb 28]. Available from: https://europepmc.org/article/med/12528323.

[11] Chan V, Sahgal A, Egeto P, Schweizer T, Das S. Incidence of seizure in adult patients with intracranial metastatic disease. J Neurooncol. 2017;131(3):619–624.

[12] Long B, Koyfman A. Clinical Mimics: An Emergency Medicine-Focused Review of Stroke Mimics. J Emerg Med. 2017;52(2):176–183.

[13] Arakawa A, Mitsutake A, Hideyama T, Sato T, J K, Seki T. A central nervous system metastasis of melanoma with stroke-like onset of left-lower quadrantanopsia. J Gen Fam Med. 2020;21(3):77–9.

[14] Liberman AL, Prabhakaran S. Stroke Chameleons and Stroke Mimics in the Emergency Department. Curr Neurol Neurosci Rep. 2017;17(2).

[15] Morgenstern LB, Frankowski RF. Brain tumour masquerading as stroke. J Neurooncol. 1999;44(1):47–52.

[16] Jauch EC, Saver JL, Adams HP. Guidelines for the early management of patients with acute ischemic stroke: A guideline for healthcare professionals from the American Heart

Association/American Stroke Association. Stroke. 2013;44(3):870–947.

[17] Nguyen PL, Chang JJ. Stroke mimics and acute stroke evaluation: Clinical differentiation and complications after intravenous tissue plasminogen activator. J Emerg Med. 2015;49(2):244–252.

Science communication: A tool against misinformation

Toby Le PhD[†] Jasmine Rae Frost PhD[*]

Abstract

As the world continues to mitigate the effects of the COVID-19 pandemic, it is also facing an overabundance of information. This is referred to as an "infodemic", which has rendered misinformation indistinguishable from accurate information. Misinformation poses detrimental effects to the public health response against COVID-19. It has perpetrated violence against healthcare workers and vandalism of property. Misinformation has also promoted unsafe regimens including the digestion of bleach as a treatment against SARS-CoV-2. Fortunately, efforts have increased to develop science communication projects that promote accurate information about COVID-19. Projects that have been selected for this commentary include: the Manitoba COVID-19 Report, COVID-Alerts, COVID MythBusters, and several independent initiatives. The Manitoba COVID-19 Report was an initiative organized by staff and students from the Max Rady College of Medicine to provide health professionals with weekly research updates about COVID-19. COVID-Alerts is a graduate student-led science communication project that utilizes Short Message Service and WhatsApp to disseminate information about COVID-19 to populations in Kenya. COVID MythBusters, another graduate student-led project, is an Instagram initiative that provides up-to-date information about COVID-19 to over 500 subscribers. Together, these projects illustrate the accessibility and feasibility of applying science communication as a tool against misinformation.

Keywords: science communication; SARS-CoV-2; COVID-19; misinformation

Conflict of Interest Statement: The authors of this paper are the creators of COVID Alerts, and @Covid_mythbusters. These projects are not-for-profit, and there is no revenue gained from them.

Introduction

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19) has had momentous impacts worldwide. As this pandemic continues to claim lives, it is also fueled by the spread of misinformation - also known as an "infodemic". The World Health Organization (WHO) describes an infodemic as a surplus of information that overwhelms the public by rendering misinformation indistinguishable from accurate information.[1,2] Health misinformation is defined as a health-related claim that is untrue based on current scientific knowledge. If left unaddressed, health misinformation can undermine the general public's trust in their healthcare workers and scientists. Unfortunately, health misinformation has been shown to disseminate faster than accurate information.[3]

At the start of the 2020 pandemic, a systematic analysis revealed that, while 38% of misinformation on social media was completely fabricated, the largest proportion of misinformation (59%) was accurate information manipulated to be misleading.[4] As a result, researchers are beginning to witness the harmful effects of misinformation on public health. For example, the false notion that alcohol intake can help prevent or treat COVID-19 has so far been linked to more than 800 preventable deaths and 5800 hospital admissions around the world.[5–9] Even worse, this misinformation has further transpired into violence against frontline healthcare workers. News stories published throughout 2020 describe healthcare workers being threatened, physically assaulted, spat on, pelted with eggs, stoned, and doused with bleach.[10–13] One international study even found that high susceptibility to misinformation was linked with increased vaccine hesitancy and decreased compliance to COVID-19 public health measures.[14]

Some of the most harmful effects involving misinformation occur when scientific uncertainties are exploited to promote toxic narratives. Since the start of the COVID-19 pandemic, there has been a surge of misinformation related to the origin, transmission, and treatment of SARS-CoV-2. One popular myth suggests that Microsoft founder Bill Gates created the virus to profit from a mandatory vaccine, which would contain digital trackers for mass surveillance.[15–17] There are

[*]Correspondence to: let6@myumanitoba.ca

[†]Department of Medical Microbiology and Infectious Diseases, Max Rady College of Medicine, University of Manitoba, Winnipeg, Canada

also conspiracy theories that implicate 5G, a new generation of wireless technology for broadband cellular networks, as a transmission agent of SARS-CoV-2.[18,19] This has resulted in mass vandalism and illegal destruction of over 80 cell phone towers across the UK.[20–23] Another myth promotes drinking methanol or bleach as a form of self-treatment for COVID-19.[24] This misinformation was further propagated by former President Donald Trump at a press briefing on April 23, 2020, when he speculated about the use of disinfectant injections to treat COVID-19.[25–27] Following that press briefing, the American Association of Poison Control Centers reported a 121% spike in accidental poisonings from disinfectants compared to the same month the previous year.[28,29] Misinformation has also been shown to be perpetuated by other famous figures: one study found that 20% of the false claims in their sampling were shared by public influencers. However, this 20% ended up accounting for 69% of social media engagement.[4] While the examples listed here are not comprehensive, they nevertheless illustrate the unpredictable and proliferative nature of misinformation.

Responding to misinformation is challenging. One effective strategy is to offer accurate information directly to those exposed to misinformation.[30,31] Social media has been a major instrument in the dissemination and circulation of misinformation.[32,33] To address this issue, trained health professionals and scientists must take active roles in science communication to combat the spread of misinformation. Given the COVID-19 pandemic, there have been considerable efforts to develop science communication projects that promote accurate information and debunk misinformation. This commentary provides an overview of several science communication projects led by health professionals and scientists to promote accurate information about COVID-19. The objective is to demonstrate the accessibility and feasibility of using science communication as a tool against misinformation.

Manitoba COVID-19 report

The Manitoba COVID-19 Report was an initiative led by staff and students at the Max Rady College of Medicine to address clinically relevant questions about COVID-19.[34] Once per week, questions from the medical community were summarized and assigned to one of six research teams based on their area of focus: clinical description and epidemiology, diagnostics and surveillance, therapeutics, infection prevention and control, public health interventions, and pediatrics. These teams composed of librarians, clinicians, fellows, medical students, and graduate students met several times each week to review the latest evidence pertaining to their assigned questions.[35,36] After extensive peer review, the findings were summarized into newsletters for dissemination. The Manitoba COVID-19 Report published a total of eight reports and saw international impact. Prior to discontinuation, over 9000 health practitioners across Canada, United States, South America, Caribbean/West Indies, and Europe subscribed to the report with an open rate of 33–47%.[34]

COVID alerts

COVID-Alerts, founded by the first author (TL), is a science communication project that uses platforms such as Short Message Service and WhatsApp to disseminate weekly texts about COVID-19 to populations in Kenya. These texts include information about the latest news on COVID-19, tips and guidance on protective measures, and describes how inaccurate misinformation is. The project relies on a peer engagement model where select community members from Kenya are designated peer leaders and made responsible to advocate for the needs of their community. This model has been used for over 40 years in Nairobi, Kenya as part of a public health program to promote accurate health information about sexually transmitted infections.[37] In addition to peer leaders, COVID-Alerts also relies on the support and collaboration between graduate students, researchers, and local clinicians from the University of Manitoba and University of Nairobi.

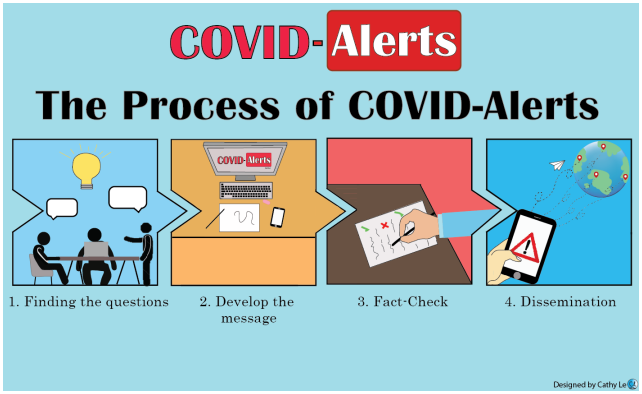

Figure 6. The workflow of 'COVID-Alerts'.

A strength of COVID-Alerts is that it engages all key stakeholders in the process of creating text updates about COVID-19 (Figure 6). The process begins with stakeholders meeting online once per week to discuss community concerns and questions. After a set of key questions are identified, graduate students review and summarize the latest evidence into brief text messages. Visual graphics are also designed to complement these texts for individuals with limited literacy skills. The text messages are then peer-reviewed by all stakeholders and translated into Kiswahili, the national language in Kenya. Finally, the text messages are disseminated through the clinics and peer leaders in Nairobi. As of February 27, 2021, COVID-Alerts has disseminated 5 weekly text messages about COVID-19 to over 15 000 community members in Kenya.

COVID MythBusters

COVID MythBusters (@COVID_mythbusters) is an Instagram account created by second author (JF) and Davina Dobbins from the University of Arizona.[38] The

account provides the public with up-to-date information about SARS-CoV-2 and COVID-19 from peer-reviewed sources and debunks myths surrounding the pandemic. Content is curated in accordance with the common myths listed on the WHO and the Center for Disease Control and Prevention (CDC) websites. Additional information is researched and relayed in an accessible format that is visually appealing to consumers. This is done with the assistance of Hailey Kostusik, a local Winnipeg graphic designer. As the Instagram account gained followers, the use of the "Stories" function of Instagram was used to communicate with followers about their concerns and questions. This feedback loop provides the team with several topics to research and post online. For example, a question was posed to the account regarding how COVID-19 would affect new or expecting parents (Figure 7). There was also a strong desire from followers for a summary of COVID-19 vaccines (Figure 8). The "Stories" function also facilitated interactions such as comments, personal messages, "likes", and re-sharing of the content on followers' personal Instagram pages. To date, the account has 560 followers on Instagram and 53 posts.

Figure 7. Content from @covid_mythbusters Instagram page, posted December 17th, 2020. Slides provide information surrounding COVID-19 and expecting parents, or new parents.

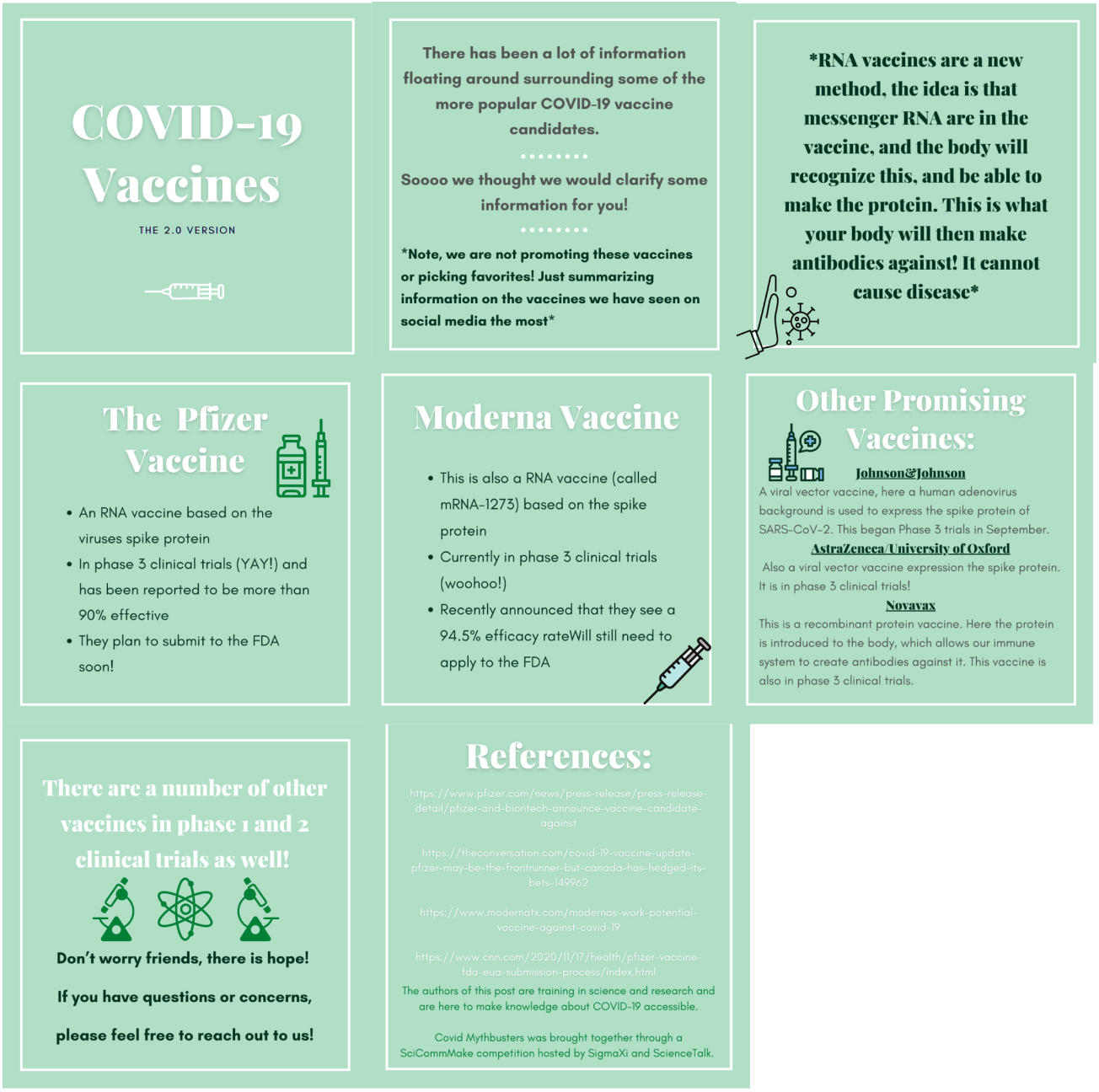

Figure 8. Content from @covid_mythbusters Instagram page, posted November 25th, 2020. Slides describe a summary of COVID-19 vaccine candidates that were being focused on by the media.

An advantage of Instagram is that it enables users to target content at specific demographics and promote content for a low daily fee. This is helpful to target accurate information at communities that are most affected by the pandemic or those who face a spread of misinformation. The COVID-19 MythBusters organizers selected a target age range of 25–45 years old to be the primary audience. The assumption was that these targeted users could help circulate content to a larger secondary audience consisting of both younger (i.e. their children) and older (i.e. their parents, grandparents) populations. This age group was also identified by public health officials in the United States as having the most COVID-19 cases.[39] In order to refine the target geographical locations, the team surveyed where COVID-19 outbreaks in Canada and the United States occurred prior to promotions. The first promotion, Mask Myths, ran for five days with a fee of $20 CAD per day. This was the initiative's largest promotion and resulted in the highest number of impressions (the number of times a promotion appears on an individual's screen) as well as the highest number of promotional clicks (Table 8). Future promotions were set for five days each with a fee of $10 CAD per day to allow for a greater variety of content to be promoted with the remaining funds. From the 53 posts as of submission, COVID-19 MythBusters has reached approximately 45 000 accounts through Instagram.

Table 8. Demographics if Instagram posts by @covid_mythbusters.

Post Promotions	Location of Targeted Audience	Number of Impressions [A]	Number of Promotional Clicks [B]	Age (Years) Demographics	Sex Demographics
Mask Myths: Promoting how masks can stop the spread of the virus	Ontario, Quebec, Georgia, Arizona	17 210	278	18–24yrs: 56% 25–34yrs: 35% 35–44yrs: 9%	Female: 74% Male: 26%
Transmission Myths: Debunking popular myths surrounding the spread of SARS-CoV-2	Arizona, South Dakota, North Dakota	5 591	21	18–24yrs: 41% 25–34yrs: 43% 35–44yrs: 15%	Female: 67% Male: 33%
Treatment Myths: Debunking dangerous myths surrounding how to treat COVID-19	Arizona, South Dakota, North Dakota	4 061	49	18–24yrs: 41% 25–34yrs: 48% 35–44yrs: 11%	Female: 52% Male: 48%
Halloween Safety: Promoting safe practices for those celebrating Halloween	Ontario, Manitoba, Arizona, Montana, South Dakota	4 165	85	18–24yrs: 33% 25–34yrs: 52% 35–44yrs: 16%	Female: 82% Male: 18%

[A] Impressions: The number of times the promotion appeared on an individual screen.
[B] Promotional clicks: The number of times an individual clicked on our promotion.

COVID-19 MythBusters required baseline funding and a substantial time commitment from the developers. The use of a graphic designer was critical to create an aesthetically appealing page that conveyed information without being overwhelming to viewers. The ability to promote posts also allowed the number of people it could reach to increase substantially. While resources were required for this initiative, it also allowed for important information to reach a wide range of people quickly. This could be a beneficial method to use in future public health endeavors when combating misinformation.

Independent initiatives

Scientists and healthcare workers have also started using their personal social media platforms to provide accurate information regarding the SARS-CoV-2 pandemic. Using platforms such as Facebook, Instagram, TikTok and YouTube, these individuals can address questions from their followers. For example, Dr. Samantha Yammine (@science.sam) is a neuroscientist who uses Instagram with the objective of making science accessible to the public.[40] Dr. Yammine keeps her followers up-to-date with research on COVID-19 and answers questions posed by her followers. Another example is Dr. John Campbell, a retired nurse from England who uses YouTube as his science communication platform. In weekly videos, Dr. Campbell critiques new data and explains findings in simple terms that are accessible to the public. His videos incorporate easy-to-follow linear reasoning and require minimal editing.[41] Overall, as social media grows in popularity it has become a tool for public health education. It allows for those working in the public health field to target large populations quickly with few resources required. When used correctly, it results in the accurate and efficient transmission of health information.[42]

Independent initiatives can also leverage existing resources from international organizations to promote accurate information on their social media platforms. The WHO has an audio and video series called "Science in 5" where experts explain scientific concepts in five minutes or less.[43] Both the WHO and CDC have also redesigned their websites to include resources that aim to clarify common misconceptions and knowledge gaps surrounding the pandemic.[44,45] Despite the many available resources, independent initiatives are crucial intermediaries for reaching target and remote audiences that would otherwise not see the information. This further emphasizes the accessibility and feasibility of social media as a tool for independent initiatives to address misinformation.

Conclusion

Misinformation is a contagious and ubiquitous threat that damages public health efforts to combat COVID-19. Preventing and addressing misinformation can help encourage the public to adopt and adhere to safety measures more effectively. The science communication projects described in this commentary illustrate different methods to address misinformation that require varying commitment of time and resources. Some projects may require substantial commitments if they recruit teams of people and/or large investments of time and funding. Other projects may require smaller commitments if they can be accomplished independently

or with limited resources. Ultimately, there are many accessible and feasible methods to address misinformation. This commentary is a call to action for researchers and healthcare professionals to seek opportunities within their reach to educate their peers about misinformation. As misinformation continues to spread and contribute to increasing morbidity and mortality around the world, it is important that researchers and health professionals explore creative ways to counter this infodemic.

Acknowledgements

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References

[1] Understanding the infodemic and misinformation in the fight against COVID-19. Pan-American Health Organization; 2020. [Cited 2021 Jan 4]. Available from: https://iris.paho.org/handle/10665.2/52052.

[2] World Health Organization, United Nations, UNICEF, UNDP, UNESCO, UNAIDS, et al.. Managing the COVID-19 infodemic: Promoting healthy behaviours and mitigating the harm from misinformation and disinformation. World Heal Organ; 2020. [Cited 2021 Jan 4]. Available from: https://www.who.int/news/item/23-09-2020-managing-the-covid-19-infodemic-promoting-healthy-behaviours-and-mitigating-the-harm-from-misinformation-and-disinformation.

[3] Sylvia Chou WY, Gaysynsky A, Cappella JN. Where We Go From Here: Health Misinformation on Social Media. American Journal of Public Health. 2020;110:S273–275.

[4] Brennen JS, Simon FM, Howard PN, Nielsen RK. Types, Sources, and Claims of COVID-19 Misinformation Key findings; 2020.

[5] Iran: Over 700 dead after drinking alcohol to cure coronavirus. Aljazeera; 2020. [Cited 2021 Jan 4]. Available from: https://www.aljazeera.com/news/2020/4/27/iran-over-700-dead-after-drinking-alcohol-to-cure-coronavirus.

[6] Delirrad M, Mohammadi AB. New Methanol Poisoning Outbreaks in Iran following COVID-19 Pandemic. Alcohol and Alcoholism. 2020;55:347–348. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7239215/.

[7] Hassanian-Moghaddam H, Zamani N, Kolahi AA, McDonald R, Hovda KE. Double trouble: Methanol outbreak in the wake of the COVID-19 pandemic in Iran – A cross-sectional assessment. Critical Care. 2020;24:402.

[8] Dozens die of alcohol poisoning in Mexico amid COVID-19 lockdown. Euronews; 2020. [Cited 2021 Jan 4]. Available from: https://www.euronews.com/2020/05/14/dozens-die-of-alcohol-poisoning-in-mexico-amid-covid-19-lockdown.

[9] Yip L, Bixler D, Brooks DE, Clarke KR, Datta SD, Dudley S, et al. Serious Adverse Health Events, Including Death, Associated with Ingesting Alcohol-Based Hand Sanitizers Containing Methanol – Arizona and New Mexico, May–June 2020. MMWR Morb Mortal Wkly Rep. 2020;69:1070–1073. Available from: https://www.sciencedirect.com/science/article/pii/S0022202X1546837X.

[10] Semple K. Health Workers Under Attack During Coronavirus Pandemic. The New York Times; 2020. [Cited 2021 Jan 4]. Available from: https://www.nytimes.com/2020/04/27/world/americas/coronavirus-health-workers-attacked.html.

[11] Health workers become unexpected targets during COVID-19. Econ; 2020. [Cited 2021 Jan 4]. Available from: https://www.economist.com/international/2020/05/11/health-workers-become-unexpected-targets-during-covid-19.

[12] Withnall A. Coronoavirus: Why India has had to pass new law against attacks on healthcare workers. The Independent; 2020. [Cited 2021 Jan 4]. Available from: https://www.independent.co.uk/news/world/asia/coronavirus-india-doctor-nurse-attack-law-modi-health-care-workers-a9480801.html.

[13] Taylor L. Covid-19 misinformation sparks threats and violence against doctors in Latin America. BMJ. 2020;370.

[14] Loomba S, de Figueiredo A, Piatek SJ, de Graaf K, Larson HJ. Measuring the impact of COVID-19 vaccine misinformation on vaccination intent in the UK and USA. Nat Hum Behav. 2021;5:337–348.

[15] Lee BY. Bill Gates Is Now A Target Of COVID-19 Coronavirus Conspiracy Theories. Forbes; 2020. [Cited 2021 Jan 4]. Available from: https://www.forbes.com/sites/brucelee/2020/04/19/bill-gates-is-now-a-target-of-covid-19-coronavirus-conspiracy-theories/?sh=46ec5bf86227.

[16] Wakabayashi D, Davey A, Tracy M. Bill Gates, at Odds with Trump on Virus, Becomes a Right-Wing Target. The New York Times; 2020. [Cited 2021 Jan 4]. Available from: https:

//www.nytimes.com/2020/04/17/technology/bill-gates-virus-conspiracy-theories.html.

[17] Fact check: Bill Gates is not responsible for COVID-19. Reuters; 2020. [Cited 2021 Jan 4]. Available from: https://www.reuters.com/article/uk-factcheck-gates-idUSKBN2613CK.

[18] Satariano A, Alba D. How a 5G Coronavirus Conspiracy Theory Fueled Arson and Harassment in Britain. The New York Times; 2020. [Cited 2021 Jan 4]. Available from: https://www.nytimes.com/2020/04/10/technology/coronavirus-5g-uk.html.

[19] Ahmed W, Vidal-Alaball J, Downing J, Seguí FL. COVID-19 and the 5G conspiracy theory: Social network analysis of Twitter data. J Med Internet Res. 2020;22:e19458. Available from: https://www.jmir.org/2020/5/e19458/.

[20] Mast fire probe amid 5G coronavirus claims. BBC News;. [Cited 2021 Jan 4]. Available from: https://www.bbc.com/news/uk-england-52164358.

[21] Brewis H. Nightingale hospital phone mast attacked as 5G conspiracy theory rages on. The Evening Standard; 2020. [Cited 2021 Jan 4]. Available from: https://www.standard.co.uk/news/uk/nhs-nightingale-phone-mast-arson-attack-5g-conspiracy-a4414351.html.

[22] A HI. 77 phone masts attacked in UK due to coronavirus 5G conspiracy theory. Business Insider; 2020. [Cited 2021 Jan 4]. Available from: https://www.businessinsider.com/77-phone-masts-fire-coronavirus-5g-conspiracy-theory-2020-5.

[23] Jolley D, Paterson JL. Pylons ablaze: Examining the role of 5G COVID-19 conspiracy beliefs and support for violence. Br J Soc Psychol. 2020;59:628–640.

[24] Kuehn BM. Spike in Poison Control Calls Related to Disinfectant Exposures. J Am Med Assoc. 2020;323:2240. Available from: https://jamanetwork.com/journals/jama/fullarticle/2766883.

[25] Chiu A K Shepherd, Shammas B, Itkowitz C. Trump claims comment about injecting disinfectants to kill coronavirus was 'sarcastic'. The Washington Post; 2020. [Cited 2021 Jan 4]. Available from: https://www.washingtonpost.com/nation/2020/04/24/disinfectant-injection-coronavirus-trump/.

[26] Riechmann D, Freking K. Don't inject disinfectant: Blunt pushback on Trump musings over COVID-19. CTV News; 2020. [Cited 2021 Jan 4]. Available from: https://www.ctvnews.ca/world/don-t-inject-disinfectant-blunt-pushback-on-trump-musings-over-covid-19-1.4911201.

[27] Schraer R. Coronavirus: Outcry after Trump suggests injecting disinfectant as treatment. BBC; 2020. [Cited 2021 Jan 4]. Available from: https://www.bbc.com/news/world-us-canada-52407177.

[28] Kluger J. Accidental Poisonings Rise After Trump Disinfectant Comments. Time; 2020. [Cited 2021 Jan 4]. Available from: https://time.com/5835244/accidental-poisonings-trump/.

[29] Perez M. Accidental Poisonings From Bleach And Disinfectants Continued To Rise In April. Forbes; 2020. [Cited 2021 Jan 4]. Available from: https://www.forbes.com/sites/mattperez/2020/05/12/accidental-poisonings-from-bleach-and-disinfectants-continued-to-rise-in-april/?sh=2da5b1bb7b25.

[30] van der Meer TGLA, Jin Y. Seeking Formula for Misinformation Treatment in Public Health Crises: The Effects of Corrective Information Type and Source. Health Commun. 2020;35:560–575.

[31] Walter N, Murphy ST. How to unring the bell: A meta-analytic approach to correction of misinformation. Common Monogr. 2018;85:423–441.

[32] Vosoughi S, Roy D, Aral S. The spread of true and false news online. Science. 2018;359:1146–1151.

[33] Lazer DMJ, Baum MA, Benkler Y, Berinsky AJ, Greenhill KM, Menczer F, et al. The science of fake news. Science. 2018;359:1094–1096. Available from: https://pubmed.ncbi.nlm.nih.gov/29590025/.

[34] Manitoba COVID-19 Report; 2020. [Cited 2021 Jan 4]. Available from: https://www.mbcovid19report.com.

[35] Mackenzie A. Isolated medical students provide weekly COVID-19 updates. UM Today News; 2020. [Cited 2021 Jan 4]. Available from: https://news.umanitoba.ca/isolated-medical-students-provide-weekly-covid-19-updates/.

[36] Informing COVID-19 response: A UM success story. UM Today News; 2020. [Cited 2021 Jan 4]. Available from: https://news.umanitoba.ca/informing-covid-19-response-a-um-success-story/.

[37] Ngugi EN, Wilson D, Sebstad J, Plummer FA, Moses S. Focused peer-mediated educational programs among female sex workers to reduce

sexually transmitted disease and human immunodeficiency virus transmission in Kenya and Zimbabwe. J Infect Dis. 1996;174:8240–8247. Available from: https://academic.oup.com/jid/article/174/Supplement_2/S240/885044.

[38] Frost J, Dobbins D. Covid Mythbusters (@covid_mythbusters) on Instagram;. [Cited 2021 Feb 16]. Available from: https://www.instagram.com/covid_mythbusters/.

[39] Centers for Disease Control and Prevention. COVID-19 Case Surveillance Public Use Data. CDC;. [Cited 2021 Feb 27]. Available from: https://data.cdc.gov/Case-Surveillance/COVID-19-Case-Surveillance-Public-Use-Data/vbim-akqf.

[40] Yammine S. samantha yammine phd — she/her (@science.sam). Instagram;. [Cited 2021 Feb 16]. Available from: https://www.instagram.com/science.sam/.

[41] Campbell J. Post infection immunity, good news. YouTube; 2021. [Cited 2021 Feb 16]. Available from: https://www.youtube.com/watch?v=M3kQoyCCLmY.

[42] Crispin B, Jonathan B. The World's Best Public Health Social Media Campaigns. bangthetable; 2020. [Cited 2021 Jan 4]. Available from: https://www.bangthetable.com/blog/public-health-social-media-campaigns/.

[43] World Health Organization. COVID-19: Science in 5. World Heal Organ; 2021. [Cited 2021 Apr 14]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/media-resources/science-in-5.

[44] Centers for Disease Control and Prevention. Myths and Facts about COVID-19 Vaccines. CDC; 2021. [Cited 2021 Apr 14]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/facts.html.

[45] World Health Organization. Coronavirus disease (COVID-19) advice for the public: Mythbusters. World Heal Organ; 2021. [Cited 2021 Apr 14]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public/myth-busters.

The Hollenberg Clinic: An important contribution to Canadian integrative healthcare

Daniel Hollenberg PhD[†]

Abstract

The Hollenberg Clinic was an important and significant contributor to healthcare models during the 1950s in Canada. Based in Winnipeg, Manitoba, the Clinic was a family-run enterprise, and was in operation from approximately 1949-1958. Based on in-depth interviews with family members and expert sources, as well as analysis of archival documents, a detailed historical description of the Clinic is made. It describes aspects such as Clinic personnel and training, layout and services, and areas of specialty expertise. The involvement of the Clinic physicians in the former University of Manitoba Faculty of Medicine, and research activities as clinician researchers, are highlighted. The argument is made that the Clinic closely modeled the integrative care model of the Mayo Clinic, and was the first in Winnipeg to link integrated care services with clinical investigative medicine.

Keywords: Hollenberg Medical Family; integrative care models; Canadian medical history

Conflict of Interest Statement: None to declare.

Introduction

The Hollenberg Clinic was an important and significant contribution to healthcare models during the 1950s in Canada. Based in Winnipeg, Manitoba, the Clinic was a family-run enterprise, and was in operation from approximately 1949-1958. As the grandson of two of the founding members (Drs. Jake and Esther Hollenberg) and having recently moved to Winnipeg, I became fascinated with the Clinic's story. It is one that has yet to be told in-depth. To fully understand the Clinic's impact and significance, I conducted in-depth interviews with family members and expert sources who could recall details about the Clinic. I also delved into the medical archives held at the University of Manitoba.

Setting the stage: 1950s healthcare in Canada

The Hollenberg Clinic arose in the context of a rapidly changing Canadian healthcare landscape. The post-World War II Canadian population was expanding with associated healthcare needs, and Winnipeg was no exception. Canadian physicians, who had trained in the 1920s and 1930s and who were at the height of their careers, some of whom who had recently returned from the War, recognized the need for comprehensive healthcare. These physicians were looking for new ways to assist Canadians and to apply their medical skills more broadly. National publicly funded healthcare would not be developed for another 20 years, yet many physicians were committed to providing care to Canadians regardless of cost.

In response to Canadians' healthcare needs, numerous clinics in Canada, including those in Winnipeg, were created by groups of physicians based on the concept of "group practice": multiple healthcare professions providing care and services "under one roof." These early forms of group practice were precursors to more fully developed integrative care models that would proliferate in later decades.[1] In the 1950s, this "one-stop shopping" approach to healthcare, pioneered by the Mayo Clinic, was espoused by several physician groups in Winnipeg. According to expert sources, there were at least seven group practice clinics in operation in Winnipeg at this time: "This was a time when these clinics were being developed as a model for how to practice medicine" (Dr. Barbara Kaufman, daughter of Dr. Abe Hollenberg). A few clinics pre-dated the 1950s trend but continued to develop alongside the newer clinics. A number of clinics were family-based, as was the Hollenberg Clinic.

*Correspondence to: d.hollenberg@yahoo.com
[†]OmDza Integrative Health Coaching, Integrative Medicine Consultant

The Hollenberg Clinic: A unique contribution to research and practice

The Hollenberg Clinic consisted of at least 12 personnel: seven physicians (all graduates of the former Manitoba Medical College), one pharmacist, one optometrist/optician, one physiotherapist, and two administrative assistants. Of the seven physicians, five were brothers (Drs. Michael, Abe, Charles, Joseph and Jake Hollenberg), and two were wives of two of the brothers (Dr. Dorothy Hollenberg, née Osovsky, and Dr. Esther Hollenberg, née Gorsey). Of note, the two female physicians were amongst the first small group of female Jewish physicians in Canada. The two administrative assistants were also both sisters of the five medical brothers (Minnie Markel, née Hollenberg, and Bessie Hollenberg). Bessie Hollenberg became the Clinic manager, and Minnie Markel became the manager of the pharmacy (and was also married to the pharmacist).

Construction on the Hollenberg Clinic began in 1947. Designed by architect Frank Ruttan, the Clinic was constructed by the Commonwealth Construction Company of Winnipeg for a cost of $180 000 at 394 Graham Avenue. Although there is no formal record, interviews suggest the Clinic likely opened in late 1948-early 1949. The Clinic was designed to be a large, rectangular two-story building made of Tyndall stone (a quarried stone in Manitoba known for its intricate fossil patterns) and brick, with a foundation enabling the possibility of adding two additional stories.

According to interviews with those familiar with the Hollenberg Clinic, the layout of the Clinic provided for at least ten patient rooms and five medical offices. For ease of access, the reception, pharmacy, and optician/optometrist were located on the main floor. The second floor contained a research library, while the basement housed the diagnostic services of lab and X-ray (assisted by an in-house radiology technician). It appears that the Hollenberg Clinic, as a group practice under one roof, offered at that time (1950) the largest breadth of clinic services in Winnipeg (when combining the two in-house diagnostic services along with the three noted allied health professions on site: pharmacy, optometry and physiotherapy). Originally founding their group practice in 1927 in an office building containing other businesses (the Boyd Building), in the late 1940s the five Hollenberg brothers moved their practice to the free-standing Hollenberg Clinic site. The remaining two physicians and extra services were added when the new Clinic site opened.

The seven physicians were a formidable team supported by the additional in-house clinic and diagnostic services. All seven were generalists in that, as a reflection of their medical training in the 1920s and 1930s, all Clinic physicians could perform most aspects of medicine at that time (including all diagnostics and surgeries). While specialties in Canada began to emerge in the early 1940s, specialty medicine in 1950s Canada was arguably still in its infancy. The physician that "could do everything" was commonplace. Most physicians at this time drew on their extensive training prior to World War II as generalists: "In those days specialties almost didn't exist. Most doctors were physicians *and* surgeons... Every doctor did everything. There was nothing they wouldn't try. There was no such thing as a 'non-surgical doctor.' There was no such thing as a 'referring surgeon'" (Dr. Murray Hollenberg, son of Dr. Michael Hollenberg).

The Hollenberg Clinic physicians each had areas of medical focus and strength such as: anatomy, diagnostics, diabetes, infectious diseases, obstetrics, gynecology, orthopedics, pediatrics, and otolaryngology. According to interviews, the five brothers all held appointments at the University of Manitoba Faculty of Medicine, taught and lectured medical students, and participated in grading examinations. Two of the brothers (Abe and Joseph) were most involved in classroom teaching activities with medical students and onward activities with resident trainees. In addition to being general physicians, Michael and Abe Hollenberg received certification as specialists in internal medicine from the Royal College of Physicians and Surgeons of Canada (RCPSC) in 1944. In 1947, Charles Hollenberg received specialist status in England as Fellow of the Royal College of Surgery in orthopedic surgery. Jake Hollenberg, the youngest of the brothers, also received recognition from the RCPSC in general surgery in 1948. Thus, four Hollenberg brothers ultimately became specialists in their fields. Of the two female physicians in the Clinic, Dorothy Hollenberg focused on pediatrics and lectured on women's reproductive health, while Esther Hollenberg focused mainly on women's reproductive health as a general practitioner. The Hollenberg Clinic was also a satellite teaching site for the University of Manitoba Faculty of Medicine for anatomy and physiology, including dissection. At that time, the Clinic may have been the only free-standing satellite site for students associated with the medical school.

The Hollenberg Clinic founded its practice on the integrative care model of the well-known Mayo Clinic, a pioneer in integrative care. Its services and research are still in operation and continue to lead integrative care models today. Located close to Winnipeg in Rochester, Minnesota, the Hollenberg Clinic physicians would refer patients there to confirm diagnoses made in Winnipeg. The brothers also visited the Mayo Clinic to evaluate its operations. Based on their commitment to integrative care, the Hollenberg Clinic physicians strongly believed that patients should receive the highest quality and most comprehensive care. They maintained that patients should not have to wait great lengths of time or travel far to be treated: "Their focus was to have a building where they could practice, and where their patients didn't have to go out of the building... Where they could get an X-ray, could get their prescriptions filled, could get their eyes examined" (Dr. Barbara Kaufman).

Illustrating their commitment to integrative practice, archival documents show that at least two of the Clinic brothers (Michael and Abe) were also devoted

to clinical research. This was quite rare for medicine in the 1950s, in that physicians were often clinicians or researchers, not both. At the time, the discipline of "clinical research" was not yet fully established. Prior to opening the Clinic, these two brothers received post-graduate research training in the 1930s, both as National Research Fellows at the Johns Hopkins University School of Medicine in Baltimore. Their combined research focused on areas such as internal medicine, neurology, and hematology. This work resulted in a number of manuscripts examining adrenal and thyroid function, kidney function, jaundice, surgical sutures, eyesight, hernia, and pioneering treatment techniques for diabetes mellitus that were applied directly at the bedside.[2–12] Of note, one publication[12] by Dr. Michael Hollenberg on hernia was in the American journal, Surgery, with the title page caption, "From The Hollenberg Clinic," implying that the Hollenberg Clinic was known internationally as a site for clinical research.

What singled out the Hollenberg Clinic from other group practices in Winnipeg was their emphasis not only on comprehensive care under a single roof, but also their direct link to clinical investigative medicine as well as its role in physician education. While other clinics focused mainly on grouping new specialties together, the Hollenberg Clinic physicians focused on the practice of medicine as a whole. Not many practices at the time could boast of a reference library, housed in one of the larger rooms in the Clinic, with concurrent gastric motility studies ongoing in the basement. The Hollenberg Clinic was an early Canadian innovator in integrative care models and clinical investigation. The number of physicians with wide-ranging clinical and specialty expertise, along with the addition of readily available in-house allied health and diagnostic services, combined with the focus on innovative and relevant research followed clearly in the footsteps of the Mayo Clinic. When the Hollenberg Clinic closed its group practice officially in 1958, the building became known as "The Doctor's Building," where Michael and Joseph Hollenberg still kept their practice while the rest of the building housed other medical practices. The building still stands today in downtown Winnipeg where it is now home to non-medical businesses.

Overall, the Hollenberg Clinic made historic contributions to Canadian healthcare and helped set the stage for the emerging field of clinical research. While other group practice clinics in Winnipeg operated in the 1950s, with a few even succeeding and expanding to the present day, the Hollenberg Clinic clearly made its mark: "Their healthcare delivery was first-rate. When you went there, they could do bloodwork, chemistry, X-ray. The main concept was, you didn't just do the physical examination, you [the Hollenberg physicians] also ordered a bunch of tests, and you had the people [lab; X-ray] right there in the building, to do the tests" (Dr. Marty Hollenberg, son of Abe Hollenberg).

Conclusion

It is meaningful to conclude this summary of the Hollenberg Clinic with an excerpt from one of the Clinic physicians, Dr. Abe Hollenberg, who gave the welcome address to the incoming class of medical students in 1956 at the University of Manitoba (published in the 1956 University of Manitoba Medical Journal).[13] Commenting on the role of medicine, he states that it encompasses:

> ...the obligation to regard every human being of whatever station in life, of whatever race or color, as a sacred trust when he presents himself to you for help. This obligation is all the more compelling as the total knowledge of the science and art of Medicine is the property of all humanity; because the contributions for its advancement have come from scientists of all races and of all lands. Medicine transcends all political and racial boundaries - it is universal and is meant for all (Dr. Abe Hollenberg, Honorary President of the Manitoba Medical Students Association, 1956-1957).

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References

[1] Hollenberg D. Uncharted ground: Patterns of professional interaction among complementary/alternative and biomedical practitioners in integrative health care settings. Social Science & Medicine. 2006;62(3):731–744.

[2] Hollenberg MS, Vincent S. Changes in the adrenal bodies and thyroid resulting from inanition. Journal of Physiology. 1920;54:li–lixxi.

[3] Hollenberg MS, Vincent S. The effects of inanition upon the adrenal bodies. Endocrinology. 1920;4:406–10.

[4] Hollenberg MS, Cameron AT. The nature of chlorine combination in the urine. Journal of Biological Chemistry. 1920;49:239–41.

[5] Hollenberg MS, Cameron AT. The relative toxicity of the halides and certain other anions. Journal of General Physiology. 1920;4:411–22.

[6] Hollenberg A. Visual sensory reflexes and color blindness. Journal of the Optical Society of America. 1924;9(4).

[7] Hollenberg MS. On the verification of the principle of reflex visual sensations. Journal of the Optical Society of America. 1924;8:713–30.

[8] Hollenberg A. The theory and treatment of Diabetes Mellitus. University of Manitoba Medical Journal. 1929 Dec;1:25–33.

[9] Hollenberg A. A deep ligature tier. Canadian Medical Association Journal. 1936;35:74.

[10] Hollenberg A. Treatment of Diabetes Mellitus. Manitoba Medical Review. 1937 Feb;p. 19–20.

[11] Hollenberg A. Protamine zinc insulin and its use in Diabetes Mellitus. Manitoba Medical Review. 1940 Apr;p. 69–70.

[12] Hollenberg A. Radiographic diagnosis of hernia into the lesser peritoneal sac through the Foramen of Winslow. Surgery. 1945;18(4):498–502.

[13] Hollenberg A. Address welcoming the new class in medicine of 1956. University of Manitoba Medical Journal. 1956;28(1):3–5.

When Breath Becomes Air – A book review and discussion

Karim Sidhom BSc[†]

Abstract

This review examines *When Breath Becomes Air* by Paul Kalanithi. The book is a memoir that recounts Kalanithi's compelling story of a neurosurgeon-turned-patient after a terminal lung cancer diagnosis in his mid-thirties. Herein is an analysis of the messages Kalanithi attempts to articulate. He explores concepts brought up amidst fatal contemplations and reflections, and also calls into question the underlying assumptions that gave rise to those thoughts. The review summarizes Kalanithi's life events, his choices, and uncovers why those choices may have come about. It also analyzes why the author elected to tell his story using styles drawing from fiction and poetry as opposed to academic writing. Finally, the review offers an interpretation of the final message Kalanithi and his wife, Lucy, hoped to convey to their readers.

Keywords: memoir; Paul Kalanithi; When Breath Becomes Air

Conflict of Interest Statement: None to declare.

Introduction

There exists a certain point at which a breath simply becomes a semantic component of air. However, this is far from the point of the late neurosurgeon Paul Kalanithi's memoir, *When Breath Becomes Air*. Rather, he uses this phrase to echo Baron Brooke's poetry as an analogy of life becoming death. What makes Kalanithi's memories so striking is not just the poetic and somewhat dividing prose in which they are written, but also their depth. He does not simply recall his past, but also dissects the pieces out of it for the reader to appreciate. A penetrating quality characterizes the story of a man, so used to crawling along a reciprocal relationship with the death of his patients, now facing his own mortality. All his training did not prepare him for the role inversion he faced. Kalanithi found himself in his own upside-down world confronted with the mortality he dedicated his life to defy. Nevertheless, the reader is acquainted with Kalanithi before and after his cancer diagnosis. He welcomes readers with open arms into his childhood, family life, marriage, and workplace. In many ways, Kalanithi's life exemplifies a great deal of what a legacy of love and pain may inspire.

Summary & analysis

Throughout his book, Kalanithi guides us through his memories and contemplations with a rhythm that fellow author and physician, Abraham Verghese, describes in the foreword as "unforgettable" (p. 9).[1] Verghese foreshadows the memoir, saying, "see what courage sounds like" (p. 11),[1] which braces the reader for a rare glimpse of fragile valor. The reader observes much of Kalanithi's personality from the confidence he exudes from paragraph to paragraph. Kalanithi writes with an unadulterated fervor and passion for the subject matter. Yet, he also exposes a quiet, although ever-present, self-criticism. The grandeur of his personage in this setting begs the question: are his words reflective of his true nature or were they an enamored and edited account of a glorified diary? As with much good writing, hyperbole and metaphor are to be used to tug and pull at the tendinous cords of a reader's heart. The memoir of a passionate doctor and husband should not be held in contempt for the use of a poet's toolbox. Kalanithi's writing carries us from his days of certainty that he would never be a doctor to his medical rite of passage in the cadaver lab and beyond. The poetic flow he uses is anything but typical of the academic writing one would expect from the archetypical surgeon. Kalanithi elects to use the same style of writing he fell in love with as a child growing up in Arizona. This decision is likely more than simple reminiscence. In part, it demonstrates the fight against his diagnosis. Kalanithi loved literature and always wanted to write - not as a scientist, but as an author. Although he felt the calling of medicine, Kalanithi always looked forward to a time when he could write his own book. Given that he had so little time in medicine, it would be easy to say that he missed his chance. However, such reasoning is incongruent with Kalanithi's mindset. In this way, even

*Correspondence to: sidhomk@myumanitoba.ca
[†]Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada

the act of writing this memoir, in addition to its style, is a testament to Kalanithi's struggle with his cancer diagnosis.

Kalanithi hauls the reader back and forth through his own medical dichotomy. He describes the amazing feats of a neurosurgeon as well as the debilitating and humbling back spasms he experienced as a patient. His bravery in writing reflects his way of life. One cannot help but wonder about the nature of his zeal: directed first towards literature, followed by neurosurgery, and, finally, his family. It is reasonable to inquire whether this trinity was demonstrative of priority or instead demonstrated simple subsequence. The question remains whether he was truly a "family man". Did life events reveal a dedication to his family that existed all along or was his commitment to family a decision of born of capacity rather than choice? If not for his diagnosis, would Kalanithi truly be as family-oriented as he depicted himself? These are questions the reader must answer for themselves.

Verghese's thoughts from the forward must be echoed when he confesses, "after reading the book... I felt inadequate". He perhaps admires the integrity with which Kalanithi writes. Dr. Kalanithi, the amazing neurosurgeon, family man, scientist, author, and scholar is awe-inspiring. This is because his memoir is real, Kalanithi himself becomes relatable to the reader, and the reader vicariously experiences his accomplished and bountiful life. He offers an intimidating truth to the reader: ***Dr. Paul Kalanithi*** is possible for anyone. The fact that he exists implies that any person can be a neurosurgeon, a "family man", a scientist, an author, and a scholar. It means that one cannot defer to the archetype of a surgeon that is too busy to write, conduct research, or be there for their child's soccer game. Kalanithi is awe-inspiring because this memoir proves that such an existence is possible. However, for that reason, this author takes the biased and perhaps self-preserving perspective that Kalanithi's memoir may not be entirely authentic.

> Maybe, Kalanithi was just an archetypal surgeon. When confronted with death, he may very well have been forced to revisit his life choices. Perhaps he was simply fortunate to be married to a wife that was willing to overlook his former blinding passion for neurosurgery.
>
> Maybe, one cannot be at once a surgeon, "family man", scientist, author, scholar, and cancer survivor.
>
> Maybe, it is enough to just try to be an amazing surgeon, family man, scientist, author, and scholar.
>
> Maybe, Kalanithi was not actually amazing at all those things, but just tried to be.
>
> Surely, that is enough.

There is a tragic irony that a man so dedicated to protecting the lives of others suddenly lost his own. He believed himself to be David facing off against his personal cancerous Goliath. Kalanithi's deep convictions and unrelenting hope are what allowed him to fight with such vigor. It was not the fight itself that proved valuable though, but rather the awakening and awareness that it gave him. The memoir describes it much like an epiphany that one could see slowly blossoming. However, the flower that emerged seemed to have been the product of his growth through dying. Kalanithi longed not for "the sensationalism of dying, and not exhortations to gather rosebuds, but: Here's what lies up ahead on the road." (p. 215).[1] This phrase alone sums up a fatally avoidant approach that our culture takes to the nonexistent conversations regarding our mortality. Such ephemeral thoughts rarely reach the mouth. When they do, they only slip out to be once again slipped underneath another barely separate pile of tedium and small talk. It was thus by writing a memoir that Kalanithi was able to state his position on death and dying with his own mortality as testament. The choice to write a memoir gives a reflective instead of reportorial narrative to the story that allows for a deeper understanding of the human condition.

The vulnerability of Kalanithi's story includes the accounts of not only his friend's foreword, but also his wife Lucy's epilogue. Verghese does not claim to know Paul deeply, despite how strongly he may wish he did. Yet, Verghese does validate the strength of Paul's character. To speak so well of another man with so much as a single meeting and a couple of essays only substantiates the biography of Lucy's "paladin" recounted (p. 212-213).[1] This is to say that his soul was not one you had to spend time getting to know. Rather, he is presented as the type of person who you can have a conversation with and leave feeling like you have known them your whole life. Kalanithi wore his heart on his sleeve through the pages of his memoir, and Lucy Kalanithi gladly continued his legacy. Her account of Kalanithi's journey is reassuring in a way. By choosing to continue living within the glass walls of her husband's journal she affords the reader a sense of intimacy. She lets us so much further into his life than otherwise imaginable. It allows for a conversation of sorts with someone we have heard so much about, but until now have never had the pleasure to meet. In this estranged but now reconciled manner, Lucy's words were the richest of all. She ends the story recounting more than the beautiful meaning of a breath made with love. Lucy speaks to the sorrow and pain she felt as well as her ongoing love for Kalanithi. These are feeling that all float in the air of his death and in the breath of his daughter, Cady.

Conclusion

In essence, *When Breath Becomes Air* narrates the heartfelt chronicle of a doctor, friend, patient, husband, and father who dedicated himself to fight against the death of others and, eventually, his own. Kalanithi's words float across the pages of his memoir thanks to his familial love for literature and his own life experi-

ences from such a young age. This eventually fostered a curiosity that drove him towards medicine in search of the life-and-death experiences he felt were needed to substantiate his own morals. Only when he neared the end of his medical training was his curiosity fully rewarded by an all too personal encounter with that vital dichotomy. However, his words do not stand alone in this account. Rather, they are surrounded by the love of his peers and family that he valued so dearly. Being forced to realize your own mortality for Kalanithi "in a sense, had changed nothing and everything" (p. 131).[1] The hope is that readers can appreciate this change without the lived experience that Kalanithi needed to realize it.

In dissecting the fibers that connect the pages of Paul Kalanithi's memoir, I believe I have described the underlying reasons that compelled him to share his experiences. As medical students, we are forevermore driven towards our studies, our future careers, our goals, and soon-to-be patients. As passionate as we may be to that end, we cannot allow that passion to blind us to how we may be acting outside of our role as soon-to-be physicians. There is always another patient, there is always more research, there is always a conference to attend. However, there is not always time. Kalanithi's story is indeed tragic, but he was far from a tragedy. In Lucy's words "he was in the final hours of his life but who he had always been. For much of his life, Paul wondered about death - and whether he could face it with integrity. In the end, the answer was yes" (p. 225).[1]

References

[1] Kalanithi P. When Breath Becomes Air. New York: Random House; 2016.