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GLOBAL HEALTH

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EDITORIAL

Editors' welcome

Uma L. S. Sreedhar, Joyce Guo

Introduction

Tēnā koutou katoa and welcome to Issue 34 of Te Hautaka o ngā Akongā Rongoā, the New Zealand Medical Student Journal (NZMSJ). The theme of this issue is "Global Health," which is an important topic for medical students and health professionals. It is our privilege to share with our readers a wide range of insightful and high-quality articles by health care professional students, clinicians, and academics from Aotearoa and abroad.

Global health has been thrust into the spotlight by the ongoing coronavirus disease 2019 (COVID-19) pandemic, but it has long been a focus of international collaboration. The United Nations published its sustainable development goals (SDGs) in 2012 and included its third goal: to "ensure healthy lives and promote wellbeing for all at all ages."[1] The wording of this SDG reflects the changing perspective of global health as an entity. Inequity is now recognised as the fundamental obstacle that must be overcome in pursuing health and wellbeing for all. Inequity takes many different forms, including a lack of access to health care and the continuing disparities in representing certain groups in research and decision-making.[2,3] In this complex health landscape, at the crossroads of geopolitical, socioeconomic, and biophysical influences, it can be challenging to know where we fit in as medical students and clinicians with a passion for global health. The scale of the task at hand can also be overwhelming, especially for those just beginning their journey.

We believe current and future health care professionals in Aotearoa have a vital role in our collective global health. Through education and sustainable changes, the ambitious goals that we see can become achievable. We hope that this issue of the NZMSJ will highlight the stories of people who have found diverse opportunities in global health and inspire a new generation of health professionals to contribute to this critical work.

A brief overview of articles within this issue

This issue showcases fantastic editorials from two experienced clinician-researchers in New Zealand who share their journeys and delve into different facets of global health. Professor Philip Hill, the McAuley Professor of International Health at the University of Otago and the founding Director of the Centre for International Health, advocates for global health teaching in the medical curriculum and proposes opportunities to create a better starting point for this in Aotearoa. Professor Hill also explores the need for collaborative global health research to share learning and empower those most affected by health problems to create change. In our second editorial, we hear from Dr Avinash Sharma, a general surgeon and former Global Cancer Disparities and Surgical Oncology Fellow at Memorial Sloan Kettering Cancer Center in New York. Dr Sharma recounts his experiences working as a surgeon to provide necessary surgical care to communities in sub-Saharan Africa. Dr Sharma also discusses the inequity of access to health care around the world and the need for change at a grassroots level to sustainably address upstream determinants of health. These editorials provide essential learnings for medical students to look at global health from different angles, taking both clinical- and public health-level approaches to its challenges and opportunities. We are very grateful to Professor Hill and Dr Sharma for their inspiring contributions.

This issue includes many excellent academic articles covering a broad spectrum of thought-provoking topics. Alexander Wellington presents a review article about chronic myeloid leukaemia and highlights the genetics and recent advancements in treating this disease. Dr Roy Spires reviews the current literature on managing mid-shaft clavicle fractures and the outcomes of both surgical and nonsurgical management. In an intriguing case report, Dr Avroneel Ghosh discusses the pathogenesis of drug-induced aseptic meningitis and predisposing factors. Anneke Tomkins *et al.* look at the association between the mRNA COVID-19 vaccination and myocarditis. We are pleased to share a selection of the 2021 Bachelor of Medical Sciences with Honours abstracts from both the University of Auckland and the University of Otago. We also welcome academic essays from the two winners of the 2021 Wilson-Allison Memorial Prize in Dermatology, Neakiry Kivi from the University of Otago and Thomas Swinburn from the University of Auckland, who both propose novel and compelling solutions to the problem of scabies in New Zealand and the Pacific area.

We are delighted to be continuing our three highly engaging article series in this issue. The "Clinical Pearl" series returns with another fascinating case. Dr Chelsea Heaven, Dr Teresa Holm, Dr Jamie-Lee Rahiri, and Mr Mark Sanders present a case of amoxicillin clavulanate induced liver injury. They discuss the need for awareness of the adverse effects that may result from such a commonly prescribed medication. The "Māori Health Review" in this issue, authored by Quintin Smith and Dr Tyler Stevens, focuses on the Well Child Tamariki Ora review of Oranga Tamariki and the recommendations to redesign the programme to create a more whānau-centred approach. The authors discuss the implications of this review to reduce inequities and its relevance to all current and future clinicians. Finally, our "Statistics Primer" feature, written by Andrew Gray, Dr Claire Cameron, Dr Ari Samaranayaka, and Associate Professor Robin Turner from the University of Otago, tackles the very relevant topic of which statistics software is best to use. We are excited to share these articles with our readers.

Acknowledgements and concluding remarks

The Editorial Board is incredibly grateful to the Universities of Auckland and Otago for their ongoing academic and financial support of the NZMSJ. We would like to further extend our gratitude to the Medical Assurance Society, the Royal Australian and New Zealand College of Psychiatrists, Specialty Trainees of New Zealand, and

DermNet for their generous funding of the NZMSJ. Our sincere thanks to Catherine's Creations and Medisave for sponsoring the prizes for our monthly Researcher Spotlight initiative, and the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) for their continuing sponsorship of our annual RANZCOG Blog Post Award for the best student-authored blog post published on our NZMSJ Blog each year. We would also like to thank Professor Frank Frizelle for his generous financial support of the Verrall Award, which will be awarded to the best academic article published in the NZMSJ this year. Our 2021 Verrall Award winner was Natasha Mitchell, who published original research in Issue 33 on the use of smartphone applications for the monitoring of inflammatory bowel disease symptoms. As always, we would like to acknowledge our New Zealand Medical Students' Association colleagues for their ongoing support and our Advisory Board members who continue to support the NZMSJ and share their immense wisdom and experience. Finally, the authors would like to thank the Editorial and Commercial boards, the expert reviewers, and the student peer reviewers for their tireless commitment to getting this issue to publication.

We hope NZMSJ readers will enjoy the array of thought-provoking articles included in Issue 34. We would like to congratulate all the authors who have contributed to this issue and encourage our readers to submit their work to the NZMSJ in the future.

"The essence of global health equity is the idea that something so precious as health might be viewed as a right." – Dr Paul Farmer.

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INVITED EDITORIAL

The career and realisations of a global surgeon

Avinash Sharma

36-year-old Miriam told me she first noticed a change in her right breast two years ago. There was a firmness in the upper outer portion of her breast. She thought nothing of it, since it was not stopping her from going about her daily work. Faced with the demands of caring for five children, in addition to the daily two-hour commute from her village to sell cassava roots in the nearby township of Ijebu-Jesa in Osun State, Nigeria, taking time out to have her breast examined was not an option. While there was a women's health clinic at the local community centre, the resident doctor had recently left for the United Kingdom (UK), and Miriam was not sure if they would see her for this problem. Visiting a private doctor would cost her two months' worth of income. Almost no one she knew had health insurance; in fact, most had not heard it existed.[1]

In the last year, however, things had become progressively worse. Her right breast was now larger, with a tender, hard lump occupying most of the normal breast tissue, about to break through the skin. The skin itself had changed, resembling more of an orange peel, and her right arm was swollen down to her fingers. In conjunction with these changes, she was now increasingly tired, which meant that the two-hour commute from her village took more than three hours, and tending her crops was more difficult. She saw her local healer, who prescribed her some herbal leaves to apply to the affected breast. This temporarily helped to ease some of her pain. As I sat opposite her in our stiflingly warm outpatient clinic room (the electricity was down due to local government restrictions), she told me, "The hospital is the place you go to die. All of my family members who came here did not leave, but now I have no other option. The pain is too much and I cannot work."

I began to counsel her on our next course of action. We discussed the reason for the swelling in her arm was because the cancer had now spread out of the breast. We would need to operate to remove the breast and lymph glands under her arm to help her pain. I gave her a list of materials she would need to collect prior to her operation, including bandages, dressings, suture material, intravenous lines, and bags of saline solution, amongst other supplies. These items were all the patient's responsibility to source from the local market and pay for out of pocket. Invariably, they were imported from India via Lagos, with local production of such items being almost non-existent. If an item was not available, she would have to travel to the nearest largest town, Ibadan (an additional two to three hours by road), at an even greater cost.

That evening, I reflected on Miriam's condition, and recalled a conversation with my mentor surgeon, T. Peter Kingham. It was September 2017, and we sat in a plush Upper East Side office in Manhattan, New York at Memorial Sloan Kettering Cancer Center. I had just begun my time as the inaugural Global Cancer Disparities Fellow after qualifying as a general surgeon in New Zealand. He told me, "Global surgery research can only be done in the field; you have to go out there and experience it first hand. You're going to love West Africa. There has been an outbreak of Ebola in North Nigeria, but we don't think it will travel. Just remember to take your malaria prophylaxis, and make sure your medical evacuation insurance is up to date."

I also reflected on how starkly different things would have been for Miriam in New Zealand. She would, at least, have access to a staging computed tomography (CT) scan to rule out distant metastases (not just spinal and chest X-rays), as well as a tissue biopsy of the breast to allow molecular profiling with hormone receptor status. These investigations would have enabled the commencement of neoadjuvant therapy to help downstage her disease and potentially offer a cure. Unfortunately, the CT scanner in the university hospital closest to Miriam's home was defunct because of technical issues, and no technician was available for more than six months. Prior to her symptoms becoming unbearable, Miriam would have been able to see a primary health care physician without devastating financial costs. As far as surgery was concerned, her team would be able to get as many supplies as needed "off the shelf." I contemplated her statement that the "hospital is the place that you go to die," and how, in many respects, from my experience of sub-Saharan Africa, she was probably correct. Regrettably, patients with cancer often delay seeking help until they are very symptomatic and cannot work. As a result, their disease process is so advanced that management goals shift from curative to palliative, and many, as Miriam pointed out, do not leave the hospital.

Miriam's case highlights some of the many challenges and inequities faced by patients with surgical problems in low and middle-income countries (LMICs) compared to patients living in high income countries (HICs). For most people, the surgical operation is the easiest part of the equation, even allowing for the risks associated with delayed presentation and advanced stage. However, it is only one factor in the total solution. In these settings, there are multiple issues that contribute to adverse, inequitable health outcomes, such as: a lack of universal health care, or insurance, leading to catastrophic financial costs; poor access to primary health care services with screening for early stage disease; shortages of health care workers, with a "brain drain" to more affluent areas of the world; a dearth of ancillary services such as pathology and radiology; and challenges associated with health literacy and a distrust of service providers.[1–5] Providing surgical care in these settings clearly requires a holistic, horizontal approach that strengthens the health system as a whole, working with local providers and ministries rather than targeting a particular disease process. The advantage of this approach is that it has the potential to provide benefits for a broad spectrum of health problems and lead to more sustainable change. Whilst, in the last two decades, the global surgical field has been focused in many ways on defining the extent of the burden of surgical disease, there is now movement to improve global surgical outcomes through collaborative research, defining guidelines, and measuring outcomes. GlobalSurg (initially set up by UK medical students) and the National Institute for Health and Care Research

(NIHCR) Global Health Research Unit on Global Surgery are examples of this type of collaborative network, with over 5000 clinicians in over 100 countries.[6]

It would appear that the situation faced by Miriam is likely to become more common, with a steady shift in the burden of disease in LMICs from communicable to non-communicable disease (NCD), in particular, cancer.[7,8] According to recent International Agency for Research on Cancer Global Cancer (GLOBOCAN) estimates, by 2030, 75% of new cancer cases will be within low and middle-income countries.[9] In sub-Saharan Africa, despite the fact that cancer burden is predicted to double by 2030, the entire region accounts for <1% of worldwide medical cancer expenditures.[10] NCDs threaten to overwhelm fragile health systems in these settings and lead to dramatic rises in health and social care costs in the near term.[11,12] In the region, out-of-pocket health expenditures are a major contributor to poverty, and a lack of adequate social protection (such as health insurance) has the potential to drive families and individuals further into poverty. The severe drain on services, health budgets, and resources as a result of the global coronavirus disease 2019 (COVID-19) pandemic has further compounded the problem and disproportionately affected these fragile systems.[13]

The world has recently been shocked by the untimely death of a colossus and major global health pioneer, Paul Farmer. Farmer was the co-founder of Partners In Health, a non-profit organization that provides free medical care in low-income countries including Haiti, Peru, and Rwanda. He has immeasurably changed the health outcomes for millions of patients around the world through a systems-based approach focused on addressing inequities. Farmer's life work, captured in the Netflix documentary film *Bending the Arc*, began as a medical student in Haiti. Farmer and his family spent his teenage years travelling in a mobile home, mostly in Florida, where he worked picking oranges alongside Haitian migrant communities. As a student at Duke and Harvard, where he studied anthropology and medicine, he volunteered at a hospital in Cange, in central rural Haiti. During this time, he noted the harsh realities for the underprivileged when accessing health care. During the acquired immunodeficiency syndrome (AIDS) epidemic in Haiti, he went door to door delivering anti-retrovirals to underprivileged families. Over the years, he raised millions of dollars for an expanding network of health facilities.[14] He also inspired generations of medical students and health care professionals throughout the world, particularly through global health programmes established at Harvard Medical School and more recently, at the University of Global Health Equity in Butaro, Rwanda. There is no doubt that Paul Farmer's extraordinary life journey and career, starting as a medical student and motivated by a passion to help society's most vulnerable, exemplifies the sheer scope within which one can effect change on a global level.

Reflecting on my own journey into global health, I feel this was in part shaped by experiences during my childhood. Being born and raised in New Zealand, my parents always made me aware of the fact that I was very blessed to have seemingly limitless opportunities to succeed in life compared with others elsewhere in the world. This was brought home to me forcibly during trips that I made to India at an early age. There, I witnessed first hand how those in circumstances less fortunate than mine had to work much harder just to survive. The images and experiences of extreme poverty left a deep impression on me and a sense of social awareness. Inspired by the work of my grandparents in Fiji caring for the underprivileged, illiterate, and elderly, I chose to pursue a career within medicine. I hoped this would equip me with some skills to address these wider determinants of health. After completing my medical degree at the University of Auckland, I was fortunate to work with Professor Ian Bissett, Professor John Windsor, and Professor Papaarangi Reid. Together, we investigated the socially stigmatized condition of faecal incontinence, and we demonstrated up to 12% of New Zealanders are affected, and Māori disproportionately so.[15] My mentors encouraged me to pursue further postgraduate studies in public health, and during my surgical registrar years, I volunteered in the South Pacific. Through Memorial Sloan Kettering Cancer Center and the collective visions of New Zealander Sir Murray Brennan, T. Peter Kingham, and Professor Isaac Alatise, I catapulted from New Zealand to New York and West Africa to help their efforts in establishing a Global Cancer Disparities programme. I divided my time in Nigeria between operating with local surgeons; teaching medical students, residents and surgeons; and conducting research into novel risk factors for the development of breast and bowel cancer in the region. During my time, it was immensely satisfying to see a transition over a period of six months where patients like Miriam diagnosed with breast cancer were able to get routine molecular analysis for receptor status on biopsies.[16] This would then allow treatment with endocrine or chemotherapy and ensure better clinical outcomes. Now, with a view to a future at the University of Auckland Surgical and Translational Research Centre (STaR) with Professor Ian Bissett and Professor John Windsor, we are looking to expand the Indigenous and Global Surgery Group. We welcome interest from medical students and junior doctors keen on pursuing a career in Global Surgery.

As I think back to my own time as a medical student, I wonder whether the gaps between HICs and the LMICs are narrowing compared to where things stood nearly two decades ago. It is with optimism that we look to the next generation of health care professionals, the medical students of today, to take up the challenge and continue to aspire to achieve equitable outcomes for patients across the globe. As the burden of surgical disease increases across LMICs, patients like Miriam will continue to require motivated health care professionals who focus on these wider determinants of health outcomes and are driven to address inequities.

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INVITED EDITORIAL

From an elective in Nepal to research collaborations in Africa, Asia, and the Pacific – my journey in global health

Philip Hill

I undertook my medical school training in Auckland, graduating in 1992. I was certainly not one of the top students. My only A+ was in physiology, a subject which I really enjoyed. I found the hospital culture of my clinical years challenging because of the hierarchical nature of the environment and all the egos. In my sixth year, I went to a combined government and mission hospital surgical service in Pokhara, Nepal, for my medical elective. It was an amazing experience, especially because my host suggested I could go into the valleys to the west and see what they were doing on their public health projects. I think he could see that I wasn't happy assisting in the operating room and all that went with it.

It was in the hills of Nepal that I found the type of work that I could really get enthusiastic about, and the public health interventions in the villages sparked my interest. From that point on, with some advice from others, I attempted to map out a career path that involved specialty training as a physician in infectious diseases, overlapping with specialist public health training. I even managed to get some cross-crediting from each training programme. I wanted to focus on the public health aspects of infectious diseases and to have a strong, deep foundation. From there, I wanted to learn how to develop and evaluate interventions, and I wrote to the heads of major tropical disease research units around the world to seek advice and look for openings. I was shortlisted for a Nuffield scholarship, which I planned to use towards a PhD on malaria in Thailand, with the Oxford Tropical Unit there. However, I pulled out of the interview when I was offered a post as a clinical epidemiologist at the British Medical Research Council unit in The Gambia, West Africa.

In The Gambia, I led a large, multi-disciplinary study of tuberculosis cases and their household contacts. I found that I was good at research, and was given significant leadership opportunities through various circumstances that arose. I also managed to be involved in building pneumococcal research projects, including a large evaluation of the implementation of the pneumococcal conjugate vaccine. I ran projects that utilised all the major epidemiological study designs, and learnt about all the challenges of doing research in a low-resource setting. There, I also developed a desire to help those who worked on my team undertake necessary training to achieve their goals. In 2008, I returned to New Zealand, having won the opportunity to be the first holder of the newly endowed McAuley Chair in International Health, and Founding Director of the research Centre for International Health.

International health as a term has been usurped by "global health," which has been defined as collaborative trans-national research and action for promoting health for all.[1] The intent is for a worldwide perspective that leads to equitably improved health.[2] It is both an evolution and a rejection of the colonial approach of the early days of tropical medicine, and of the development aid approach of international health.[3]

There are several agreed key features of a global health perspective:

1. It is oblivious to territorial boundaries between different countries. As such, by its very nature, it requires collaboration between countries on behalf of all.
2. There is a high level of global interconnectedness in the 21st century that requires a truly global approach to health.
3. Humans across the world have many vulnerabilities in common.
4. There is a multiplicity of underlying social, economic, environmental, and political determinants of health globally.
5. There is extreme global inequity and a real need for equitable outcomes across the world.
6. A wide range of professionals have a role to play in making necessary breakthroughs, with expertise in health specialties, business and economics, law, agriculture, veterinary medicine, environmental science, and the basic sciences, as examples.
7. Global health leaders need to be able to address the health priorities of all countries, no matter where they themselves are placed.
8. Research is crucial to provide the evidence base for global health interventions.
9. Global health is action-focused, dissatisfied with the status quo, and impatient for change.

Medical training has generally been a long way behind in incorporating global health into the curriculum. Doctors need to be equipped with the knowledge and skills to practise appropriately in an increasingly globalised world. Johnson et al[4] wrote a very timely editorial in the Lancet in 2012 proposing the key learning outcomes in global health for medical students, arising from a collaborative initiative by a United Kingdom global health learning outcomes working group. These outcomes were described under six key areas: global burden of disease, socioeconomic and environmental determinants of health, health systems, global health governance, human rights and ethics, and cultural diversity and health.

Johnson et al[4] proposed that there should be a mix of compulsory teaching, optional teaching for those with a special interest in global health, and pre-elective training. Global health learning outcomes should be integrated across the curriculum, rather than implemented as a standalone course, as many are natural extensions of current teaching topics. However, there is little evidence that New Zealand medical schools have adjusted their curricula in any substantial way to produce global health "literate" doctors. Furthermore, recent reports of medical elective "shams" have exposed serious institutional and student failings with respect to meaningful engagement in low resource settings.

Unfortunately, perhaps linked to their evolution from a colonial past, global health initiatives have been largely initiated and dominated by high resource countries. Only a few programs have emerged in academic institutions in low resource countries. It is crucial that

academic institutions reach across geographic, cultural, economic, gender, and linguistic boundaries. The understanding and the scope of global health needs to be built from the voices and perspectives of those who suffer the most. Collaborative education and research programmes should in no way aim to primarily build the resources and reputation of institutions in high resource countries through their activities in low resource countries.

Indeed, many feel that global health, as it has evolved, is irretrievable and needs to be deconstructed completely. There are calls for a decolonised and decentralised approach to global health initiatives; one that moves beyond tokenism into real and accountable commitments to transformative change for the benefit of all the citizens of the world.[5] This is certainly the hope for New Zealand global health initiatives. A major focus should be learning about, and respecting, the true value of people and things that are already present in low resource settings.[6] Global health respects human rights and ownership. There is room for negotiation and dialogue, and for deeper understanding. In global health, everyone should be the winner. Global health seeks engagement for the long term, to enable freedom and an improved lifestyle on an ongoing basis.

The Centre for International Health at the University of Otago is the first major global health research centre in New Zealand. It is focused on training students from all over the world in research at Masters and PhD levels. At its core are two professorial groups, both focused on different aspects of infectious diseases; and more recently, a new group has been developed for non-communicable disease research. While based within the Health Sciences Division, there was an intention for the Centre to have University-wide engagement; hence, the Otago Global Health Institute (OGHI) was established. This institute has a leadership group of senior researchers across all four divisions of the University (including the professors of the Centre for International Health), and across all three major campuses. The membership of OGHI has risen to around 150 researchers from inside and outside the University. As OGHI has evolved, it has increasingly recognised global imbalances and built a strategy that is an outworking of a basic vision of "a world where health problems are resolved by those who are most affected by them."

It is important for New Zealand medical students to become "global health literate" in an increasingly interconnected world. A key question is whether there is a possibility for them to utilise their training for the benefit of those in low resource settings; or is this idea too inherently "colonialist"? Certainly, a desire to help people in low resource settings plus a basic medical degree are an increasingly unlikely combination to be sufficient for engagement. It is true that in many countries, there is a lack of medically trained people willing to spend their careers in rural settings or dangerous places. However, for the long term, it would seem best if well-resourced local solutions are found that deal with the incentives and disincentives. While a basic medical training is no longer "enough," there are lots of opportunities for engagement. As New Zealand medical students and young doctors who are interested in global health, you should want to bring to the table the very best that you can offer. To do this, you will want to maximise your training and skillsets. Find the thing in health that really excites you and that you want to put your time and effort into training towards. It might be some obscure super-specialty, or something very general. It may be that you have special ability to combine business acumen with health provision, and you dream about helping others replicate such a model to multiply the availability of health services around the world. Or, like me, maybe you will find that you have the ability to build research activities at an internationally competitive level and can help those from low resource settings to successfully negotiate their way along that path. This includes enabling them to set up something that has a realistic chance of success when they go back to their home country. When they are successful, they may choose to continue to collaborate with you and others globally to solve their country's most pressing health needs.

In my personal experience, I have found engaging with people from different cultures incredibly rewarding. I am terrible at learning languages, which is made worse by the fact that I now collaborate simultaneously with people from multiple different countries. However, I have come to realise that people know at a deep level if you actually care about them and respect who they are, even if you struggle to learn their language and need some reminding about cultural differences. One thing that stands out to me is the richness in process and outcomes that comes to all things, including high-level scientific research, if everyone involved is able to bring to the discussion what they have. At a global level, there is a huge hole where the Pacific voice is largely missing in health and health research. Pacific people have something unique to offer, and this includes weaving all that they have learned from thousands of years of history into scientific endeavour. A large part of making this happen is to support Pacific people and communities to combat both the institutional and internalised racism that creates barriers to their further involvement in global health.

In Aotearoa, we are developing an understanding of the health inequities that Māori face and the need for decolonising at all levels, including health. While we have a long way to go, we perhaps have a better understanding of partnership than many other well-resourced countries. Relationships characterised by equal partnership and reciprocity are crucial in global health. This means both parties bringing what they have to the table, and moving forward together for mutual benefit. We also have a reasonable understanding in Aotearoa about inequities in access to these forums and are learning to actively address these. Therefore, it is crucial that access to the decision-making process is a priority in global health initiatives.

We have a long way to go in Aotearoa New Zealand in the area of global health. There is a lack of training for medical students in their curriculum; there is only one major global health initiative in a university; there is very little funding for global health research from within our country, and training pathways for medical graduates are not established. The future holds the potential for exciting work alongside, and in partnership with, our brothers and sisters across the Asia-Pacific region in particular.

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INVITED ARTICLE: CLINICAL PEARL

A case of amoxicillin clavulanate drug induced liver injury

Chelsea Heaven, Teresa M Holm, Jamie-Lee Rahiri, Mark Sanders

Introduction

Amoxicillin clavulanate (Augmentin) is one of the most commonly used antibiotics in New Zealand (NZ).[1] There are a number of known adverse effects of this drug, affecting the cutaneous, gastrointestinal, hepatic, and haematologic systems.[2] Hepatic adverse effects, although rare (17 cases per 100,000 patients treated with amoxicillin clavulanate), include drug induced liver injury (DILI).[3,4] This case of DILI secondary to amoxicillin clavulanate after admission with choledocholithiasis highlights the importance of recognising and treating rare but severe medication adverse effects.

Case

A 26-year-old female non-smoker presented to hospital with six days of upper back, shoulder, and right upper quadrant (RUQ) abdominal pain and a two-day history of pruritis. There was no relevant past medical history, family history, drug allergies, or regular medications. No recent antibiotic use was reported. A distant medication history showed previous dispensing of multiple antibiotics, including amoxicillin, flucloxacillin, and amoxicillin clavulanate. On examination, her abdomen was soft, with mild RUQ tenderness, negative Murphy's sign, and no guarding or peritonism. Important investigative results are presented in Table 1.

Table 1: Key investigations and results

Day	Investigation	Findings and Treatment
1 Admission	Biliary USS MRCP Blood tests	Cholelithiasis + biliary sludge CBD to 8 mm GGT peaks at 353 U/L
4		Start amoxicillin clavulanate
9	ERCP	Biliary sphincterotomy + CBD balloon clearance with removal of numerous stones
11	MRCP	No extrahepatic biliary tree dilatation or intraductal stone, CBD 4 mm
12		Stop amoxicillin clavulanate
15 Discharge		
17 Readmission	Blood tests	CMV, EBV, HIV, hepatitis B, hepatitis C negative. TFTs, IgM, IgG, IgA, liver antibodies, ANCA, parietal cell antibodies within normal limits
18	MRCP	No cholelithiasis or choledocholithiasis CBD 5 mm
19	Blood tests	Bilirubin peaks at 344 µmol/L
23	Blood tests Hepatology review	PR peaks at 1.6 (reversed with vitamin K) Diagnosed with DILI secondary to amoxicillin clavulanate
25	Blood tests	ALP peaks at 268 U/L
29 Discharge		
78	Blood tests	Bilirubin normalises to 16 µmol/L

Legend: red: important admission or discharge events, blue: important blood test results

Key: ultrasound (USS), magnetic retrograde cholangiopancreatography (MRCP), common bile duct (CBD), gamma-glutamyl transferase (GGT), endoscopic retrograde cholangiopancreatography (ERCP), cytomegalovirus (CMV), Epstein Barr virus (EBV), human immunodeficiency virus (HIV), thyroid function tests (TFTs), immunoglobulin (Ig), antineutrophil cytoplasmic antibodies (ANCA), prothrombin ratio (PR), drug induced liver injury (DILI), alkaline phosphatase (ALP)

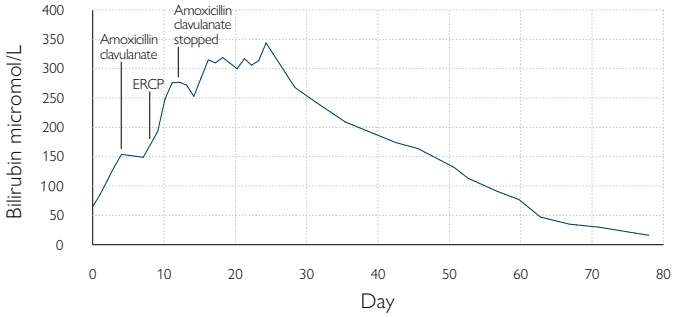
Progress

Clinically, the patient became jaundiced with worsening pruritis prior to antibiotic commencement. Biochemical and radiological investigations raised the concern of choledocholithiasis. The patient showed early signs of a developing infection; therefore, oral amoxicillin clavulanate was commenced on day four and endoscopic retrograde cholangiopancreatography (ERCP) was organised. On day nine, intravenous amoxicillin clavulanate was given and ductal stones were extracted via ERCP. Oral amoxicillin clavulanate continued post-procedure until day 12. The patient was discharged on day 15 but was readmitted on day 17 with ongoing pruritis and worsening cholestatic liver function tests (LFTs). The usual pathogenesis of choledocholithiasis would see LFT derangements improving in the days following ERCP; however, this case showed an increase in bilirubin to 344 µmol/L, peaking 16 days post-ERCP and 13 days post-cessation of the antibiotics, prompting investigations for a secondary pathology. Magnetic resonance cholangiopancreatography (MRCP) was undertaken, and did not find retained ductal stones. Viral and autoimmune hepatitis panels also returned negative results. Inpatient bile salt binders were commenced, and remaining treatment was supportive. A consulting hepatologist diagnosed the patient with amoxicillin clavulanate-induced DILI. At day 29, the patient was discharged with follow-up blood tests and ongoing bile salt binders. Continued monitoring showed normalisation of bilirubin and other LFTs on day 78 as shown in Figure 1.

Discussion

This case highlights the importance of recognising amoxicillin clavulanate as a cause of DILI. This patient presented with choledocholithiasis and obstructive jaundice which was treated with ERCP. Despite this, she developed prolonged jaundice and hepatitis. Repeat MRCP

Figure 1: Bilirubin blood test results



Key: endoscopic retrograde cholangiopancreatography (ERCP)

showed no further intraductal stones, and viral and autoimmune investigations were negative. In this case, treatment was symptomatic with bile salt binders and supportive care.

This case is a timely reminder of how a commonly prescribed antibiotic in NZ can have serious adverse effects with the potential to cause significant morbidity and mortality. In 2018, 11% of people who visited their general practitioner were prescribed amoxicillin clavulanate at least once.[1] While amoxicillin clavulanate-induced DILI is usually self-limiting with a good prognosis, there are rare reports of fulminant hepatitis resulting in death, even in the young and otherwise healthy patient.[2–5] Risk factors predisposing to acute liver failure have not been well identified.[3]

While the pathophysiology of amoxicillin clavulanate-induced DILI is unclear, it is known to be independent of the dose, duration, or route of administration.[6] The estimated risk of hepatic adverse effects is 17 per 100,000 prescriptions for amoxicillin clavulanate.[3,4] DILIs can be cholestatic, hepatocellular, or mixed. Cholestatic DILI often results in an obstructive LFT picture with an elevated bilirubin.[2,4,5] Conversely, hepatocellular DILI will result in an ALT three times normal and an ALT/ALP ratio five times normal.[2,4,7] However, patients can also demonstrate a mixed DILI with ALT three times and ALP twice that of the upper limit of normal.[2,7] Amoxicillin clavulanate-induced DILI is usually cholestatic, but can also be hepatocellular or mixed.

Current research postulates that amoxicillin clavulanate-induced DILI is an immune hypersensitivity reaction, where there is an inappropriately exaggerated immune response against an antigen.[2,4,5,6,8] Neoantigens are thought to be produced by the reactions of beta-lactam structures within the antibiotic and host proteins.[5,8] The neoantigen is presented to receptors on undifferentiated immune cells. This results in activation of the immune system, including the production of cytotoxic CD8+ T cells. Cytotoxic CD8+ T cells act in a number of ways to kill their target cell. In keeping with this, CD8+ cytotoxic T cell invasion has been observed in the portal triad of the liver, mediating damage to liver cells.[5,8]

DILI can be caused by multiple drugs, some of which include diclofenac, azathioprine, nitrofurantoin, co-trimoxazole, anti-tuberculosis treatments, antineoplastic agents, and tricyclic antidepressants.[7] Even with successful identification and withdrawal of a causative drug, approximately 4% of idiosyncratic DILI progresses to acute liver failure.[7] A prospective American DILI network (DILIN) study in 2014 included 660 patients between September 2004 to July 2011 with definite, highly likely, or probable DILI. It found that 9.4% (n=62) of patients with DILIs required a liver transplant or died within six months.[9] They found that patients with adverse outcomes were treated with the offending agent for a longer period of time (67 days) compared to those with self-limiting DILIs (31 days).[9] If DILI is not considered in the differential diagnosis, the causative agent may not be withdrawn, and the severe consequences of this could include the need for a liver transplant or even death.

Amoxicillin clavulanate is one of the most commonly prescribed antibiotics in New Zealand; however, DILI is an under-recognised and important adverse drug reaction that should not be forgotten. Early recognition is vital, as morbidity and mortality for patients can be high, especially if left untreated. Although rare, it is important for clinicians to consider DILI in the context of rising bilirubin in a patient with negative hepatobiliary imaging (MRCP) who has recently taken or is currently taking amoxicillin clavulanate.

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ACADEMIC

The genetics of chronic myeloid leukaemia and recent advancements in therapy

Alexander Wellington

Abstract

Each year, approximately 750 people (commonly >65 years) are diagnosed with leukaemia in the United Kingdom (UK). Of every 100 cases of leukaemia, 15 are diagnosed with Chronic Myeloid Leukaemia (CML), also referred to as chronic myelogenous leukaemia. CML is a form of cancer affecting immature white blood cells (i.e. leukocytes). Individuals with CML present with a raised white blood cell count. CML is characterised by the unregulated growth of myeloid cells arising from a transformed haematopoietic stem cell (HSC). Leukocytes serve vital roles in the innate immune system. For example, neutrophils (a type of granulocyte) are highly mobile and first responders in inflammation. Neutrophils are activated for phagocytosis or the release of cytokines, and recent studies have shown their role in neutrophil extracellular traps. This article outlines the pathophysiological mechanisms and genetic basis underlying the development of CML. It also highlights recent advancements in targeted therapies to combat disease severity and progression.

Genetics of Chronic Myeloid Leukaemia

Chronic Myeloid Leukaemia (CML) is part of a group of myeloproliferative disorders (MPDs) characterised by the uncontrolled proliferation of myeloid cells in the bone marrow. CML is caused by a chromosomal translocation between the long arms (q-arms) of chromosomes 9 and 22, resulting in the fusion of the 5' part of the Breakpoint Cluster Region (BCR) gene located on chromosome 22 (22q11) to the 3' part of the Abelson Murine Leukaemia (ABL1) gene located on chromosome 9 (9q34). This leads to the formation of the BCR-ABL1 fusion gene on the derivative chromosome 22, also known as the Philadelphia (Ph) chromosome. As a result of this reciprocal t(9;22) (q34;q11) translocation, the derivative chromosome 9 is longer, whilst the derivative chromosome 22 (the Ph chromosome) appears distinctly shorter than its normal counterparts, as represented in the diagram below (Figure 1)[1].

The resulting BCR-ABL1 fusion gene encodes for the BCR-ABL1 fusion protein, which has a constitutively active ABL1 protein tyrosine kinase. Protein tyrosine kinases (PTK) are the enzymes responsible for catalysing the transfer of a phosphate group from adenosine triphosphate (ATP) to the tyrosine residues of the substrate proteins. The ABL1 PTK is involved in the regulation of various cellular processes, including cell differentiation and proliferation, by switching other enzymes in the cells on and off. ABL1 is a cytosolic PTK, also referred to as a non-receptor tyrosine kinase (nRTK). Furthermore, non-receptor tyrosine kinases (nRTKs), a subgroup of the tyrosine kinase family, are vital mediators in signal transduction pathways.[2] For example the Janus kinase (an nRTK), when associating with a cytokine receptor, is responsible for transducing signals via the JAK/STAT pathway (composed of Janus kinases (JAKs) and signal transducer and activator of transcription proteins (STATs)), the principal signalling pathway for the regulation of cell growth and apoptosis.[3] In the bone marrow, excess ABL1 tyrosine kinase signalling results in the proliferation of immature myeloid cells which are resistant to apoptosis,[4] a characteristic of CML.

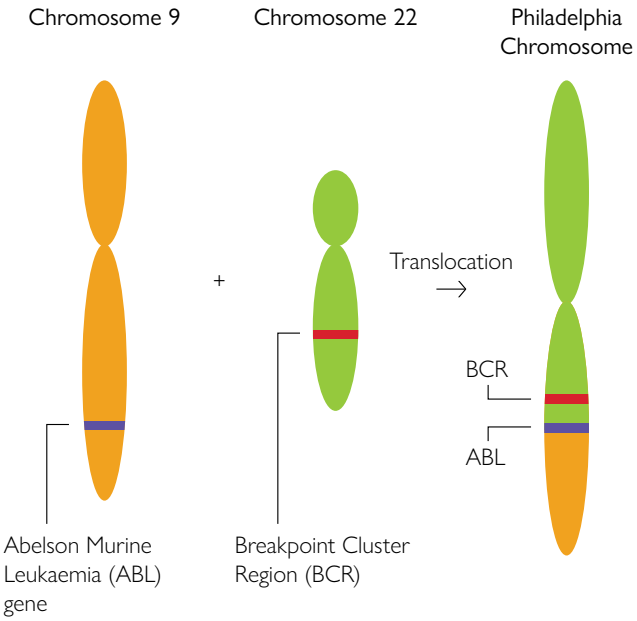

Figure 1. Graphic representation of the translocation of chromosomes 9 and 22 into the Philadelphia chromosome. Prior to translocation (left), chromosome 9 is elongated, with the Abelson Murine Leukaemia (ABL) gene illustrated by a blue band, whereas chromosome 22 is truncated, with the Breakpoint Cluster Region (BCR) identified as a red band. Post-translocation (right) the Philadelphia chromosome and the site of the newly formed BCR-ABL1 oncogene (fusion of BCR and ABL genes), following reciprocal translation, as identified by arrowed red and blue bands respectively. (Figure 1 adapted from Granatowicz et al. (2014)).[1]

Clinical Features

CML presents with different clinical manifestations according to the WHO classification and severity of the disease. These inform treatment choice. The phases of CML include the chronic phase (CP), affecting 90–95% of patients with CML; the accelerated phase (AP); and the blast phase (BP).[5] Individuals with CML-CP may experience symptoms of anaemia and splenomegaly (40–50% of patients), which include lethargy, malaise, anorexia, early satiety, referred splenic pain, and left upper quadrant fullness.[6] Rarer clinical features include thrombocytopaenia, prolonged coagulation times, thrombocytosis, leucocytosis, crystal arthropathies, priapism in males, upper gastro-

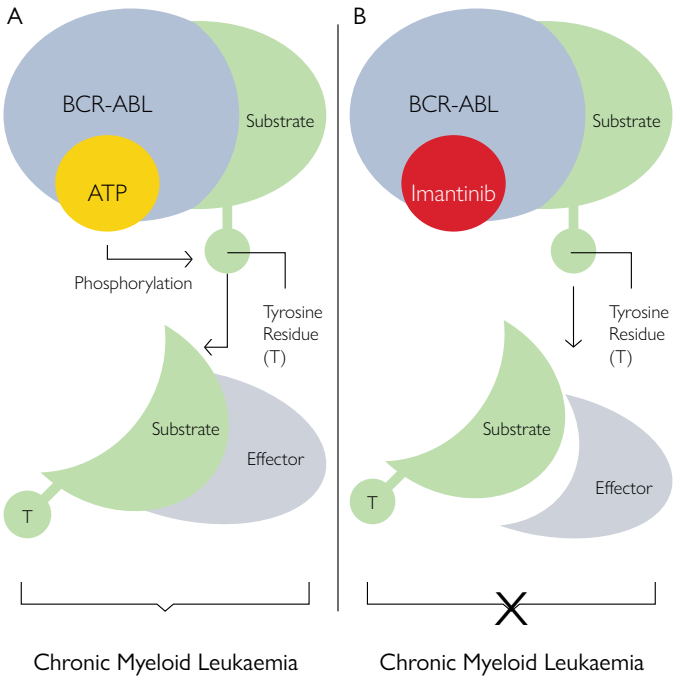

Figure 2. Graphic representation of the mechanism of inhibition of the Breakpoint Cluster Region (BCR)-Abelson Murine Leukaemia (ABL) gene by imatinib (Tyrosine Kinase Inhibitor (TKI)) in chronic myeloid leukaemia (CML). A (left) illustrates the substrate-bonded BCR-ABL oncoprotein with adenosine triphosphate (ATP) in its kinase pocket. The activation of the substrate is identified by the phosphorylation of a tyrosine residue which causes the downstream phosphorylation of effectors, contributing to increased cell proliferation and decreased apoptosis. B (right) demonstrates the occupation of the kinase pocket and ATP inhibition by imatinib, preventing the activation of its substrate and potential downstream effectors (Figure 2 adapted from Savage & Antman (2002)).[9]

intestinal bleeding and ulceration, basophilia, and retinal haemorrhages.[6,7] Despite white blood cell (WBC) counts frequently exceeding 100 x 10^9/L, leukostatic symptoms (i.e. dyspnoea, sedation, ataxia, confusion) are uncommon, alongside hepatomegaly (<10% affected), global lymphadenopathy, and mucocutaneous disease infiltration.[8]

Targeted Therapy

ABL-1 specific tyrosine kinase inhibitors (TKIs), like imatinib, are the treatment of choice for CML patients. TKIs block tyrosine kinase activity by competitive inhibition of adenosine triphosphate (ATP) at the catalytic site of ABL1.[10] This assists in the prevention of proliferation and promotes apoptosis of CML cells. Imatinib is recommended for individuals with Philadelphia chromosome-positive CML presenting in the chronic phase (or blast phase, depending on whether the individual has not received imatinib previously).[11] However, some patients do not respond to first and second-generation TKIs (including imatinib, dasatinib, bosutinib, and nilotinib). This can be due to single point mutations, such as the T315I mutation, resulting in a single amino acid substitution from threonine (T) to isoleucine (I) at the amino acid residue 315 on the BCR-ABL1 fusion gene.[12] This has no effect on the structure of the BCR-ABL1 protein; however, due to the absence of a hydroxyl group on isoleucine, TKIs are unable to create hydrogen bonds with the mutated BCR-ABL1 protein. Isoleucine is larger than threonine and extends over the hydrophobic pocket (or "gatekeeper") at residue 315, which blocks the entry of TKIs into the active site.[13]

Ponatinib is a dual kinase inhibitor[14] that was designed to selectively inhibit the non-receptor tyrosine kinase, proto-oncogene c-Src and Abl family tyrosine kinases, as well as the BCR-ABL1 tyrosine kinase with the T315I mutation. Ponatinib differs from first- and second-generation TKIs due to a triple bond ethynyl linker. This allows Ponatinib to span the isoleucine molecule to prevent it blocking the enzyme's active site.

All structures are optimised by the addition of trifluoromethyl and 4-methylpiperazine for the inhibition of the BCR-ABL protein. Additionally, hydrogen bonds are made available by the binding of an amide linkage to multiple residues, such as the carbonyl group of the amide linkage, with residue D381. Due to these optimisations, Ponatinib is highly versatile and effective in potently inhibiting native and mutant forms of BCL-ABL1 and has a stronger potency to inhibit tumour growth. Caution is advised, as Ponatinib may increase an individual's risk of infection and bruising in the extremities due to a reduced white blood cell and platelet count. Possible side effects of TKIs include fatigue, weakness, appetite loss, and swelling and discolouration of the skin.[15]

Furthermore, omacetaxine mepesuccinate, a recently approved chemotherapy drug, is prescribed to individuals with accelerated phase CML and to individuals resistant to multiple CML targeted- and immune-therapies.[16] The drug is designed to inhibit ribosomal protein translation by interacting with the free ribosome and then embedding into the A-site of the large ribosomal subunit. This prevents complementary base pairing that is necessary between mRNA and tRNA molecules, ultimately inhibiting the initial phase of translation.[17] However, the side effects of this agent are severe and include nausea, fatigue, diarrhoea, anaemia, and potential skin irritation or infection.[8] Interferon (IFN) therapy has been recently re-introduced alongside chemotherapy as a treatment option. Unlike TKIs, IFNs specifically target leukemic stem cells and CML progenitors.[18,19] Although IFNs are known primarily for their ability to protect cells from an infection caused by a virus, they can directly inhibit cell proliferation and promote cell apoptosis. For example, IFN-alpha, which is produced in a white blood cell infected with a virus, can express over 300 genes encoding apoptotic proteins (i.e. anti-viral proteins).[18] Furthermore, IFNs are able to target regulators in the cell cycle, and to an extent, block specific phases in the cell cycle, causing cells to undergo apoptosis. Likewise, IFNs have also proven vital when incorporated with transfer therapy (i.e. TKIs), as two recently published case reports[20,21] identified a complete eradication in cases with resistance to TKIs via the T3151 mutation.

Conclusion

In summary, there are many emerging therapies for the management and hopeful cure of CML; however, the impact and significance of TKIs as the main treatment option cannot be understated. TKIs have transformed CML from an invariably fatal disease, unless a bone marrow transplant was performed, into a relatively manageable condition consisting of a pill taken once or twice daily, with fewer side effects than chemotherapy.[22] Since the introduction of TKIs, 80–90% of individuals diagnosed with chronic phase CML no longer appear with detectable levels of cells with the BCR-ABL gene, and the five year survival rate for CML has tripled from 22% in 1970 to 72% in 2000.[23] Newer studies have indicated that TKI therapy can be stopped following successful molecular remission, and roughly half of patients remain disease-free for many years thereafter.[24,25] Furthermore, the effective advancement of CML therapy, deeming it the "poster child" of precision medicine, would be unattainable without an in-depth understanding of the genetics underpinning the causes of CML: a chromosomal translocation of chromosomes 9 and 22 resulting in the formation of the Philadelphia chromosome.

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ACADEMIC

Association between mRNA COVID-19 vaccination and myocarditis

Anneke M Tomkins, Martin K Stiles

Abstract

In early December 2019, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan City, China, causing the first cases of coronavirus disease (COVID-19). It rapidly spread globally, and by 11 March 2020, a pandemic was declared by the World Health Organisation (WHO). The unprecedented global disruption to the spheres of society, the economy, and personal health placed increasing pressure on the development of safe and efficacious vaccines against COVID-19. Of those developed, the Pfizer (BioNTech/Comirnaty BNT162b2) and Moderna (mRNA-1273) vaccines both utilise messenger RNA (mRNA) technology to provide immunisation against COVID-19. Clinical trials have demonstrated high efficacy of these mRNA vaccines in providing protection against COVID-19.[1] However, reports from the Centres for Disease Control and Prevention (CDC) have described an association between the mRNA COVID-19 vaccines and the development of myocarditis. International literature has identified myocarditis developing in young males following mRNA COVID-19 vaccination. Preliminary results reported by the Centre for Adverse Reactions Monitoring (CARM) suggest that this adverse effect has also occurred in the New Zealand (NZ) population. The true incidence of post-vaccination myocarditis remains uncertain, as recorded cases rely on passive reporting systems; hence, there may be under-reporting of cases. Therefore, continued evaluation of case reports, retrospective studies, and ultimately an active reporting system, will be required to determine the rate of myocarditis following COVID-19 mRNA vaccination. In the interim, it has been determined that the benefits of the COVID-19 vaccination in reducing the risk of developing COVID-19 outweigh the potential adverse effects of the vaccine.

Discussion

DEVELOPMENT OF MRNA COVID-19 VACCINES

mRNA vaccines have been rapidly developed for the prevention of COVID-19. In December 2020, the United States (US) Food and Drug Administration (FDA) granted emergency authorisation to two mRNA vaccines: the Pfizer vaccine and the Moderna vaccine.[1] Both of these vaccines are recommended as an initial two-dose schedule to ensure an adequate immune response.[1]

Multinational, placebo-controlled, observer-blinded trials have been conducted to assess the efficacy of the mRNA COVID-19 vaccines. It was concluded that the Pfizer vaccine was 95.0% effective (95% CI, 90.3–97.6) in preventing infection with COVID-19, and the Moderna vaccine, 94.1% (95% CI, 89.3–96.8) effective.[2,3] In regard to local reactogenicity, pain at the injection site was the most common adverse vaccine reaction reported by trial recipients who received either the Pfizer or Moderna vaccine.[2,3] In the Pfizer clinical trial, pain was reported more frequently among the younger participants (83% after first dose; 78% after the second dose) compared to participants older than 55 years (71% after the first dose; 66% after the second dose).[2] After the first and second doses of the Moderna vaccine, 84.2% and 88.6% of participants in the younger and older age groups, respectively, reported pain at the injection site.[3] This local reactogenicity resolved within one to two days and was graded as mild-to-moderate in severity.[2,3] The most frequent systemic adverse drug reactions reported by participants receiving either of the vaccines included fatigue, headache, fever, myalgia, arthralgia, nausea, vomiting, and chills, and were more common among the younger participants.[2,3] These minor adverse reactions following both vaccines were transient and self-limiting, resolving within a few days post-vaccination.[2,3] In these clinical trials, myocarditis was not listed as an adverse drug reaction.

ASSOCIATION BETWEEN MRNA COVID-19 VACCINATION AND MYOCARDITIS

Myocarditis is an inflammatory disease of the heart muscle, which may manifest following infection from a wide spectrum of pathogens, including viruses (the most common cause), bacteria, and fungi.[5] Myocarditis may also be induced by cardiotoxins and hypersensitivity reactions.[5] Epidemiological studies show that myocarditis occurs more commonly in men than women, with a median age of 33 years.[6] Male patients with myocarditis are, on average, significantly younger than females, with prevalence highest in the 16–20-year-old age group.[6] Clinical manifestations of myocarditis include chest pain, dyspnoea, palpitations, and fever, with subsequent diagnostic investigations revealing elevated troponin levels and/or abnormal findings on electrocardiogram, echocardiogram, or cardiac MRI.[7] Globally, the background rate of myocarditis is estimated to be 22 cases per 100,000 person-years.[7]

INTERNATIONAL DATA

Vaccine-associated myocarditis is a rare adverse reaction that has previously been associated with the smallpox vaccine, with less frequent informal reports following other vaccines.[9] Myocarditis was not reported as a potential adverse event in clinical trials of COVID-19 vaccines, and adverse cardiac events of any kind occurred in <0.1% of trial participants, with rates comparable in recipients of the vaccine and recipients of the placebo.[8]

Initial reports of myocarditis following COVID-19 mRNA vaccination emerged from Israel at the end of April 2021. After distributing 5 million vaccinations, the Israeli Ministry of Health reported 62 cases of myocarditis developing in vaccinated people.[10,11] Of these, the majority of cases followed the second vaccination. There was a strong male predominance, and a particularly high incidence in men under 30 years of age (1 in 20,000 men).[10,11] There were two reported deaths in 62 cases of post-vaccination myocarditis.[10,11] Following these initial reports, on 9 July 2021, the WHO Global Advisory Committee on Vaccine Safety issued an official statement regarding the risks of myocarditis following mRNA COVID-19 vaccination.[14]

The Vaccine Adverse Event Reporting System (VAERS) is the US reporting system for vaccine safety. This is a passive reporting system which relies on individuals to report their adverse treatment reactions to the CDC and FDA. At the time of the CDC COVID-19 Vaccine Safety Update delivered in 23 June 2021, approximately 296 million doses of COVID-19 vaccinations had been administered across the US, 52 million of which had been administered to people 12–29 years of age.[7] Of these, 30 million were first and 22 million were second mRNA vaccine doses.[7] The CDC reported that as of 11 June 2021 there had been a total of 1226 reports of myocarditis to VAERS following mRNA COVID-19 vaccination, combining cases from both the Pfizer and Moderna vaccines.[12]

Of the VAERS-reported myocarditis cases, the majority followed the second mRNA vaccine dose of either the Pfizer or the Moderna vaccine.[12] Of the two mRNA vaccines, the Pfizer vaccine was associated with the majority of myocarditis cases.[12] VAERS data shows that those developing myocarditis following vaccination had an average age of 30 years for the first vaccination dose and 24 years for the second vaccination dose. The average time of symptom onset was four days following the first vaccination dose and three days following the second vaccination dose. The data from VAERS shows that the majority of people who experienced myocarditis as an adverse reaction from either dose were male: first dose 66%, second dose 79%.[12] The group with the highest incidence of reported myocarditis following COVID-19 vaccination for both doses was males in the 12–39 year age bracket. As of 28 June 2021, 780 of the 1226 reports of myocarditis to VAERS were regarding those under the age of 30 years.[13] VAERS data showed that after 4,337,287 second doses administered to men aged 18–24 years, there were 233 reports of myocarditis in a 21-day window following administration of the vaccine, when 2–25 would have been expected based on background rates and prediction models.[12] After 5,237,262 doses administered to women in this age group, 27 cases were seen in a 21-day window following administration of vaccine, against a prediction of 2–18.[12] The overall data from VAERS as of 11 June 2021 found in the 12–29 year age group who received an mRNA COVID vaccine there were approximately 40.6 cases of myocarditis per million second doses among males, and 4.2 cases per million second doses among females. For persons over 30 years of age, the reported rates were 2.4 and 1.0 per million second doses for males and females, respectively.[14]

Given the apparent skewed prevalence of myocarditis developing in the younger population following COVID-19 vaccination, the CDC prioritised a review of myocarditis in those under 30 years. Of the 323 cases identified in this age group, the median age was 19 years. 291 were male, and 32 were female.[7] 92% of these patients experienced onset of symptoms within seven days of vaccination, the median interval being two days between vaccine administration and symptom onset.[7] Patients tended to present with chest pain, associated with ST or T-wave changes on electrocardiogram (ECG) and elevated cardiac markers, with fewer reports of abnormal cardiac imaging.[7] Supportive therapy was the mainstay of treatment, with targeted cardiac medications and interventions adopted when appropriate.[7] Although treatment data reported to VAERS is largely preliminary and incomplete, many patients have experienced resolution of symptoms with conservative treatment such as non-steroidal anti-inflammatory medications.[7] 309 of the 323 patients were hospitalised, but the acute clinical course was generally mild.[7] Of these hospitalised patients, 295 were discharged, and 79% of these patients had fully recovered and returned to their normal daily activities by the time of review.[12] There were no reported deaths in this data set.[7,12] Follow-up of these patient outcomes will be essential in order to ascertain the long-term outcomes after myocarditis occurring after COVID-19 vaccination.

The Medicines and Healthcare products Regulatory Agency (MHRA) in the United Kingdom (UK) has implemented the Yellow Card scheme, a passive reporting system to flag potential side effects and adverse reactions to the COVID-19 vaccine. As of 7 July 2021, an estimated 19.7 million first doses of the Pfizer vaccine and 1.1 million doses of the Moderna vaccine have been administrated in the UK. Within this, 87,789 Yellow Cards had been reported for the Pfizer vaccine and 8,953 for the Moderna vaccine.[4] Of these Yellow Cards, there were 81 reports of myocarditis following the administration of the Pfizer vaccine and 9 reports of myocarditis following the Moderna vaccine.[4] These reports corroborate international findings that there is a consistent pattern of cases occurring more frequently in males, more commonly after the second vaccine dose, and that cases are usually associated with mild and self-limiting symptoms.[12]

NEW ZEALAND DATA

As of January 2022 in New Zealand, everyone aged five years and over is eligible for COVID-19 vaccination. CARM is a Dunedin-based national monitoring centre for adverse reactions to treatments. This is a passive reporting system which relies on health professionals to report suspected adverse reactions to CARM. CARM collaborates with other international monitoring centres, including the database of WHO's International Drug Monitoring Programme.

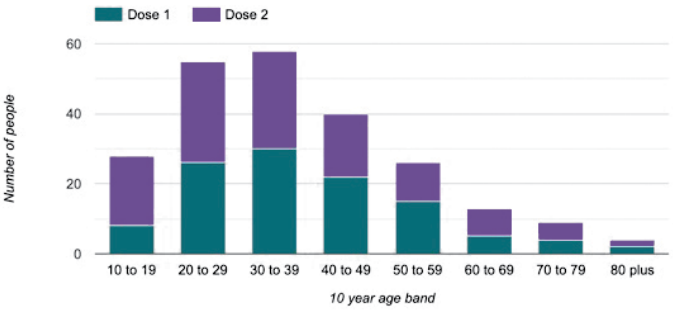

Figure 1 - Graph depicting the cases of post coronavirus disease (COVID-19) vaccine myocarditis in New Zealand reported to the Centre for Adverse Reactions Monitoring (CARM) (data up to December 1 2021).[18]

An initial communication from CARM on 21 June 2021 officially reported that Medsafe has concluded that myocarditis is a rare side effect of immunisation with the Pfizer vaccine.[15] This was further corroborated with an alert issued by CARM on 20 December 2021 containing updated statistics since the inclusion of reports for children aged 12–16 years.[18] CARM's most recent report concurs with the international findings that myocarditis typically occurs in younger men, shortly after the second dose of the vaccine, and cases are typically mild with a short recovery period.[15,18] The latest issue reports that CARM has received 233 reports of spontaneous myocarditis, 58% of which were males, and 52% of cases occurred after the second dose.[18] CARM emphasises that the reports of myocarditis do not necessarily have a causal relationship with the administration of the vaccine and may represent coincidental events.[18] As the rate of myocarditis following COVID-19 infection is a higher rate than after vaccination, CARM concludes that the benefits of the Pfizer vaccination outweigh the risk of adverse events, including myocarditis, for people of all age groups.[15,18]

LIMITATIONS

One of the most significant limitations of the data on the association between myocarditis and mRNA COVID-19 vaccination is the voluntary reporting systems upon which this data relies.[16] Passive surveillance is a reporting system which relies on patients seeking healthcare and then healthcare professionals recognising the connection as a vaccine-associated adverse event. Active surveillance is when officials actively search for information by contacting healthcare providers.

The US VAERS, UK Yellow Card Scheme, and NZ CARM are all passive reporting systems, collating data which is voluntarily supplied from healthcare professionals and members of the public. These passive monitoring systems are a suboptimal method of surveillance with potential for under-reporting and incomplete data. Due to the nature of passive reporting, adverse events, including myocarditis, may have

a coincidental relationship to the timing of vaccine administration and not necessarily be confirmed side effects from the vaccine.

Active surveillance monitoring has the capacity to provide more accurate and complete data; however, it is more resource- and expense-intensive. Databases involved in active monitoring contain millions of enrolled patients; thus, have high potential to identify rare adverse events. The Global Vaccine Data Network (GVDN) is a multinational research network involving six continents, 17 countries, and 21 population sites, representing over 290 million people. The GVND is an example of an active monitoring system which has the capacity to investigate vaccine safety and effectiveness. The University of Auckland group UniServices has been awarded nearly NZ$8 million by the CDC to coordinate a COVID-19 vaccine monitoring study with the GVDN database.[17] Until the publication of the data from this study, adverse vaccine reactions will continue to be collated through passive monitoring systems.

RISK-BENEFIT ANALYSIS

Although cases of myocarditis following COVID-19 vaccination are rare, given the large number of doses administered, it is an important safety consideration, particularly in the young male cohort where cases of myocarditis are more prevalent.

Rapidly emerging international data has demonstrated a plausible correlation between the development of myocarditis and the mRNA COVID-19 vaccination. Given the strong correlation of myocarditis following COVID-19 vaccination in the young male cohort, there is particular concern for the risks of the vaccine in this population group. The Advisory Committee on Immunisation Practices (ACIP) in the US has assessed the benefit-risk balance of mRNA vaccines in adolescents and young adults, comparing the benefits (prevention of COVID-19 disease and associated hospitalisation, ICU admission, and death) to the risk of myocarditis following vaccination.[7] It was concluded that the benefit outweighed the risk in all populations. However, the balance of the benefits against the risks varied by age and sex due to the higher prevalence of myocarditis in young males and the higher risk of poor outcomes related to COVID-19 related illness with increasing age.[7] Per 1 million second-dose mRNA COVID-19 vaccinations in males aged 12–29, there are estimated to be 39–47 cases of myocarditis after COVID-19 vaccination versus 11,000 cases of COVID-19 and subsequently 560 hospitalisations, 138 intensive care unit admissions, and 6 deaths.[7] Per 1 million second-dose COVID vaccinations for persons ≥30 years, there are estimated to be three to four myocarditis cases after COVID-19 vaccination versus 15,300 COVID-19 cases, 4,598 hospitalizations, 1,242 ICU admissions, and 700 deaths.[7] Therefore, at the CDC ACIP meeting, it was concluded that, based on international data, the benefits of the COVID-19 vaccination to the individual and population outweighed the potential adverse event of myocarditis.

A population health lens must also be applied when weighing up the benefits and risks of the COVID-19 vaccination. The ACIP has predicted that in the foreseeable future there will be no alternatives to mRNA vaccines that provide the same level of protection against infection, hospitalisation, and death from COVID-19 for the adolescent age group, who have a higher prevalence of myocarditis adverse vaccine reactions.[7] Additionally, the benefit of protection against COVID-19 illness that the vaccine offers is important in this cohort in ensuring continued education and social activities. Ethnic considerations are also essential. Stemming from colonisation, systemic racism and structural inequities embedded in the healthcare system mean that Māori face a much greater health burden from COVID-19. It is estimated that COVID-19 hospitalisation and fatality rates are 2.5 times greater for Māori than non-Māori.[19] Achieving equitable vaccination rates for Māori is thus crucial in reducing their healthcare burden. However, analysis of vaccine uptake per rate ratio of Māori compared with non-Māori reveals that in the majority of age groups, the rate is <1.0, meaning Māori are vaccinated at lower rates than non-Maori.[20] The Māori population is younger overall than the non-Māori population in New Zealand; thus, any changes in vaccine policy for the young male cohort have the potential to disproportionately affect young Māori who already have lower vaccination rates.[7,21] This has the potential to exacerbate poorer health outcomes from COVID-19 related illness in an already vulnerable community.[7,19]

Conclusion

Current national and international data has demonstrated an association between myocarditis and mRNA COVID-19 vaccination. Passive international reporting systems demonstrate a higher incidence of post-vaccination myocarditis in young males, although this has not been replicated yet in New Zealand. Continued surveillance is required to determine the causal relationship between the development of myocarditis and COVID-19 mRNA vaccination, ideally with future analysis through an active reporting system. COVID-19 vaccine administration continues to be recommended for everyone aged 12 years and older, given the risk-to-benefit ratio. Serious complications related to COVID-19 pose greater risk than the potential adverse events following vaccination, including the risk of myocarditis post-vaccination in the young male cohort.

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ACADEMIC

Pathogenesis and predisposing factors in drug-induced aseptic meningitis: A case study

Avroneel Ghosh

Case Presentation

A 61-year-old European man was admitted with two days of progressive high-grade fevers, neck stiffness, and headache. He started taking ibuprofen 400 mg three times a day for an ankle sprain 24 hours prior to his symptoms. He was screened for genitourinary, gastro-intestinal, and cardiorespiratory causes for his symptoms, which were negative.

Collateral history revealed previous admissions with meningitis but suggested his current presentation was more severe than the previous admissions in 2012 and 2016, neither of which yielded identifiable pathogens on lumbar puncture, despite showing neutrophilic pleocytosis. He had also taken non-steroidal anti-inflammatories (NSAIDs) prior to those admissions.

The patient had no other significant medical history and took no regular medications. He was a non-drinker, an ex-smoker (5 pack-years), and normally independent in his activities of daily living.

On examination, the patient was tremulous and flushed. His temperature was 38.2°C. Kernig's and Brudzinski's signs were positive, and he complained of moderate photophobia in a well-lit room. No focal neurological signs were noted, and apart from his ankle, all systems examinations were unremarkable.

Blood tests revealed mildly elevated inflammatory changes (C-reactive protein 8 mg/L and white cell count (WCC) 15.1×10^3/μL). Liver, thyroid, and renal function tests were normal, as were electrolytes, B12, folate, creatine kinase, and lipase. Blood cultures, human immunodeficiency virus (HIV), and Treponemal serology were negative. Head imaging with computed tomography (CT) and magnetic resonance imaging (MRI) was normal, and a lumbar puncture showed a neutrophilic pleocytosis (WCC 67×10^6/L; 54% neutrophils) with raised protein (820 mg/L) and normal glucose (2.8 mmol/L). Cerebrospinal fluid (CSF) cultures were sterile, and a polymerase chain reaction (PCR) panel was negative for herpes simplex virus 1 and 2, varicella zoster virus, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and enterovirus. There were no other sources of infection found through either a CT chest or echocardiogram.

PROBLEM LIST

1. Recurrent Aseptic Meningitis
   a. Neutrophilic Pleocytosis
   b. PCR-negative
   c. Temporal association with NSAIDs

2. Right Ankle sprain

The patient was commenced empirically on ceftriaxone, benzylpenicillin, acyclovir, and dexamethasone for meningitis. Based on his unexplained neutrophilic pleocytosis and the temporal relationship of his recurrent admissions with NSAIDs, a provisional diagnosis of drug-induced aseptic meningitis (DIAM) was made — likely NSAID-induced. Ibuprofen was discontinued, and antibiotics were ceased within three days. His symptoms improved markedly over the course of his admission.

The patient was discharged after five days. He was followed up in clinic two weeks later with fully resolved symptoms and no further complaints. He was advised to avoid NSAIDs and prescribed alternative pain relief for his ankle.

Discussion

Aseptic meningitis is the inflammation of the meningeal membranes in the absence of an identifiable pathogen. While viruses are the most common culprit, bacteria, fungi, rheumatological conditions, and neoplastic processes are also known causes.[1] It is also an uncommon, yet increasingly reported, adverse effect of certain drugs. Due to its recurrent nature, association with a specific medication, and resolution upon drug withdrawal, DIAM is an important diagnosis of exclusion in prevention and management.

DIAGNOSIS

Most often presenting clinically with the classical signs of meningitis or meningoencephalitis — fever, headache, meningism, and sometimes rash — DIAM is difficult to distinguish from infectious meningitis.[2] Recent research comparing the clinical and biological characteristics of DIAM and viral encephalitis suggests DIAM CSF generally shows neutrophilic pleocytosis, normal-to-low glucose, and increased protein,[3] as was the case with this patient. While neutrophilic pleocytosis is indicative of DIAM, partially treated bacterial meningitis and fungal meningitis must be excluded. Neuroimaging is typically normal, although cases of diffuse cerebral oedema or contrast enhancement have been reported. If, alongside these findings, symptoms arise and resolve within days of commencing and ceasing the causative agent, DIAM should be considered. While only a drug re-challenge would be confirmatory, it would be unethical, given the risk of a recurrence of unknown severity.

RISK FACTORS

An updated literature review of 192 case studies identified four drug groups consistently associated with DIAM.[4] NSAIDs, especially ibuprofen, were the commonest, followed by antibiotics, anti-epileptics, and immunosuppressive-immunomodulatory therapies. Prior exposure to the causative agent was present in 26–35% of cases, and time to onset post-administration ranged from minutes to months. There was no evidence suggesting developing DIAM was dose-dependent for any drug class.

Specific drugs implicated in DIAM include:[4,5]

- NSAIDs
  Ibuprofen, naproxen, diclofenac, celecoxib
- Antibiotics
  Trimethoprim-sulfamethoxazole, trimethoprim, amoxicillin, sulfamethoxazole, ciprofloxacin, valacyclovir, isoniazid, penicillin, metronidazole, cephalosporins, pyrazinamide
- Immunosuppressive-immunomodulatory therapies
  Intravenous immunoglobulin (IVIG), cetuximab, infliximab, methotrexate, sulfasalazine, leflunomide, etanercept, adalimumab
- Anti-epileptics
  Lamotrigine, carbamazepine

Recurrence in DIAM is not uncommon, especially in the presence of underlying conditions.[3,4] Systemic Lupus Erythematosus (SLE) is the most frequently reported underlying association with DIAM, with up to 59% of recurrent DIAM cases having SLE, even if subclinical. Other auto-inflammatory conditions are also associated with DIAM.[4] Female sex is a risk factor, although this may be confounded by the female predominance of SLE. Although reported in previously healthy individuals too, screening and follow-up for auto-inflammatory conditions in these patients may be indicated, as case reviews indicate subsequent development of these conditions can occur months after DIAM episodes.[6]

PATHOGENESIS

The pathogenesis of DIAM is not yet fully understood. However, evidence suggests mechanisms may differ between drug groups.[7] Immune hypersensitivity reactions are postulated in systemic NSAID, antibiotic, and IVIG-related cases. However, local cytokine-mediated release through direct meningeal irritation from intrathecal drug administration has also been reported.

Numerous theories have been posited in the development of NSAID-induced aseptic meningitis. Although the majority are ibuprofen-induced, most patients have tolerated different NSAIDs before and after developing meningitis, suggesting no link to inhibition of the cyclooxygenase pathway.[7] A delayed hypersensitivity reaction theory is supported by data through the common temporal association with intake and symptoms, resolution upon withdrawal of the offending agent, and allergic symptoms (rash in 22%, facial oedema and conjunctivitis in 22%). Specifically, T-cell mediated hypersensitivity has been observed in confirmed DIAM through a positive lymphocyte transformation test (LTT).[8] Thus, *in vitro* blood or CSF testing through LTT or enzyme-linked immunospot (ELISpot) assays may be useful in distinguishing DIAM from infective causes based on cytokine release and drug-specific cell activation and hypersensitivity. Confirmation of this theory may establish safer diagnostic methods for excluding infective processes than a drug re-challenge. However, latency is not always shorter upon re-exposure, and symptoms are not always more severe.

Alternatively, it has been suggested that causative drugs may interact with hapten-like CSF or meningeal proteins, stimulating an antibody-mediated inflammatory response.[9] However, given the lack of drug dose-dependence of DIAM and the limited CSF uptake of ibuprofen, this theory is not fully explanatory.

Trials demonstrated that patients with SLE have increased sensitivity to ibuprofen through specific cell-mediated immunity, despite some never being exposed to it previously.[10] This possibly occurs through a cross-reactivity process between ibuprofen and naturally occurring antibodies or immune complexes and would explain individual sensitivities and the predisposition of DIAM for those with or without auto-inflammatory conditions.[7] However, aseptic meningitis is a known neurological manifestation of many of these conditions. This may be due to abnormal inflammasome activity shifting the balance of the innate immune system to a proinflammatory state.[11] This results in greater cytokine production and plays an important role in chronic inflammatory processes, although the role of inflammasomes in DIAM has not yet been investigated. The pathogenesis of this case of DIAM is unclear, although the increased severity of his current symptoms, temporal association with intake, and resolution upon withdrawal of ibuprofen may fit a hypersensitivity picture.

CLINICAL RELEVANCE

DIAM presents a clinical challenge for diagnosticians, as symptoms and CSF findings are often insufficient to differentiate it from infectious meningitis. Furthermore, DIAM risk with certain antibiotics introduces the differentials of DIAM versus inadequately treated bacterial or fungal meningitis. However, third-generation cephalosporins like ceftriaxone, which this patient was started on, very rarely cause DIAM.[12]

While DIAM is more common in patients with underlying systemic conditions, it is important to differentiate true DIAM from complications of the other condition(s). Immunosuppressive conditions and drugs may cause susceptibility to atypical infections, while SLE is a cause of lupus aseptic meningitis, although it produces a more typically lymphocytic pleocytosis.[7]

This patient's symptoms had resolved fully at follow-up two weeks following his discharge. He was advised to avoid NSAIDs and keep careful track of the medications he takes, including over-the-counter ones. With no literature reviews or trials demonstrating the likelihood or time course of previously healthy individuals developing an autoimmune condition following DIAM, this patient should have antibody screening for conditions like SLE now and in subsequent months. Given his rapid resolution, avoidance of ibuprofen alone will likely prevent further recurrence, although care should be taken with NSAIDs in general. DIAM research consists primarily of case reports and literature reviews, primarily focusing on patients with underlying disorders. Future research may involve investigating the potential role of *in vitro* investigations as diagnostic testing for DIAM.

CONCLUSION

Overall, DIAM is a rare, yet important, cause of aseptic meningitis. A comprehensive medication history is important, with emphasis on non-prescription drugs, given the increasing accessibility of over-the-counter medications. While it presents similarly to bacterial meningitis, DIAM is an important diagnosis of exclusion when evidence of recurrent meningitis or underlying rheumatological disorders is present.

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ACADEMIC

Midshaft clavicle fractures: A review of current literature

Roy Spires

Abstract
Clavicle fractures are the most common fracture in the human body, accounting for 5–10% of all fractures presenting to the Emergency Department. The treatment of clavicle fractures historically has been more on the conservative side, but there has been recent evidence that operative management could reduce the incidence of adverse outcomes post-fracture. This review focuses on analysing the previous and present scientific literature on post-operative and post-conservative clavicle complications. This review concludes that the evidence for surgical management of clavicle fractures with certain indications is controversial and further studies are required.

Introduction

The clavicle is a bilateral long, slender, S-shaped bone, articulating medially with the clavicular notch of the manubrium, and laterally with the acromion of the scapula. It serves as a rigid support to allow the scapula to move freely, leading to maximal range of motion of the humerus. It also protects the neurological and vascular structures of the upper limb, and transmits compression forces from the hand to the axial skeleton, reducing the risks of appendicular injury.[1]

Clavicle fractures usually occur from trauma to the shoulder, such as landing on one's shoulder, or a fall on an outstretched hand. Incidence peaks within the first decade of life, comprising of 80% of all clavicular fractures, with a stepwise decrease in incidence in each subsequent decade, but with an increased chance of malunion.[2] Clavicle fractures can be categorised into thirds: proximal, middle, and distal clavicle fractures, with distal clavicle fractures being further subdivided according to the Neer Classification: Types I–IV, with further subtypes.[3] There are other classification systems that exist for clavicle fractures, such as Robinson's and Craig's, but we will focus on the Neer classification system as it is the oldest and most widely used.

Middle third clavicle fractures are the most common, at 80%,[4] due to strong muscular and ligamentous attachments at the medial and distal ends of the clavicle. Lateral third clavicle fractures occur next most commonly, at 20–30%, and proximal third clavicle fractures are the rarest, at 1–2%, and are usually due to serious injury, such as vehicular injury.[5]

Review

There are widely-accepted absolute indications for surgical management of acute clavicular fractures, including open fractures, damage to neurological and vascular structures, and a so-called "floating shoulder."[6] Surgical techniques either fall into open (with plating) or closed reduction (with intramedullary nailing). Indications for conservative management include minimal displacement of the fractured clavicle with no neurovascular compromise.[6] Conservative management includes using a sling and a figure-of-eight bandage with adequate analgesia.[7] There are many relative and controversial indications for surgical versus non-surgical management for clavicle fractures, including mild displacement.[8] Patient preference and co-morbidity are strong factors in determining management for these patients. Other factors which are relative indications for clavicular fixation include a higher energy injury, as these have a higher risk of nonunion, high degree of displacement, and specific fracture patterns.[9] The only New Zealand-specific guideline the author of this paper could find anywhere was the Starship guideline for paediatric clavicle fractures, in which a displaced middle/lateral third clavicle fractures was not an immediate indication for operation, but would have to be discussed with the on-call orthopaedic registrar on a case-by-case basis.[10] It is important to note, however, that these are simply guidelines and are not peer-reviewed literature.

Historically, clavicle fractures, most notably middle third fractures, were managed non-operatively, with internationally renowned orthopaedic surgeons Carter Rowe and Charles Neer (father of the modern shoulder arthroplasty) publishing studies in the 1960s. Rowe and Neer published retrospective cohort studies with 566 and 2235 patients with clavicular fractures in each study, with a nonunion rate of 0.8% and 0.1% respectively.[3,11] Both Rowe and Neer, alongside other surgeons during the 1960s–1990s, stated that nonunions and malunions were of radiological interest only, without any long-term clinical sequelae for the patient, and sang praise for conservative-based management due to the comparative downsides of potential surgical complications.[12] Surgical complication rates were higher in decades past, and with penicillin only being mass-produced in 1945,[13] the antibiotic arsenal was more limited than it is now. With a large number of patients in each of the exposure and comparison groups, and due to these papers being the first to systematically review operative and non-operative management, these studies were widely accepted. These studies have been criticised in recent times, on two main points: the inclusion of paediatric patients in their studies, and the omission of symptomatic and functional sequelae of nonunion and malunion.

One of the first studies criticising the widely-held belief of lack of significance of malunion and nonunion was by Hill et al in 1997, studying 52 non-surgically managed clavicle fractures, where in the group of eight patients with non-union fractures, seven (87%) had pain at rest, compared to the group of 44 unionised fractures, only six (14%) of patients with unionised clavicle fractures having pain at rest.[14] All other measures showed decreased function, including decreased shoulder range of motion.[14] One issue with the accuracy of this paper is that even though 242 patients had clavicular fractures, only 52 responded to the questionnaires from the researching team, leading to a small sample size of eight nonunions. The method of measurement is also not as robust as more recent studies, as questionnaires were the main method of reporting function, and actual quantitative scores such as the Disabilities of the Arm, Shoulder, and Hand (DASH) Questionnaire or Constant-Murley Shoulder Outcome Score (Constant Score)

were not used, with the former only having been introduced to the medical literature the year prior.[15] However, similar studies conducted later purported the same findings. In more recent years, some meta-analyses of surgical and nonsurgical methods of treatment such as Wang et al's 2019 meta-analysis of 13 randomised controlled trials (RCTs) showed surgical management to have a decreased risk ratio of 0.57 for complications, with a statistically significant increase of function in Constant scores by 4.7 points, but a decrease in DASH score of 6.34.[16] This study had a large sample size, was adequately powered, and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were adhered to. The drastic difference between functional scores could be because out of the 13 RCTs, only six of them had functional Constant score data, and five of them had functional DASH data, which could mean that all 13 RCTs were not evaluated equally in terms of functional outcome. However, the authors of this meta-analysis concluded that there was significant functional improvement with surgical management.

The inclusion of paediatric patients in Rowe and Neer's studies casts further doubt on the true rate of nonunion in the adult population, as the rates of malunion with the paediatric population are lower.[3,11] Children exist in an osteogenic environment, meaning that the healing processes are already ongoing at the time of fracture, decreasing the risk for nonunion.[17] Until recently, paediatric clavicle malunions were only found in case reports, due to their exceeding rarity.[18] A study by Pennock et al in 2018 showed a remarkably high malunion rate, as in a group of 545 adolescents with midshaft clavicle fractures, only 25 (4%) did not show any paediatric (<10 years old) malunions.[18] This study tripled the number of reported cases in the literature at the time, but there were limitations to its accuracy. Limitations to this study include that out of 25 patients with clavicle fractures, eight (32%) of the patients had had prior fractures to the clavicle, decreasing the union rate compared to an "unfractured" paediatric population, and confounding the actual risk of clavicular fracture.

In contrast to the paucity of reported paediatric clavicle malunion rates, adult malunion rates have been documented since the 1960s; some papers portrayed no change in function between surgery and conservative management. A meta-analysis by Axelrod et al[9] in 2020 analysed 22 RCTs regarding the risk of nonunions post midshaft clavicular fracture, finding that out of 585 non-operative patients, 65 patients (11%) developed malunion, compared to out of 1554 operative patients, with only 51 (3.3%) developing malunion. Supplementary measures of function one year post-operatively (utilising the DASH and Constant scores) showed an average of 3.8 and 4.5 point increases in functional scores in the operative group compared to the non-operative group; however, the 95% confidence interval (CI) was not statistically significant.[9] Axelrod et al[9] purport that even though malunion and nonunion rates are better in operative groups radiographically, this does not necessarily correlate with function, echoing sentiments of Rowe and Neer (however with a much higher non-operative nonunion/malunion rate).[3,11] The meta-analysis itself is robust, with a large sample size, and only included studies with a low risk of bias according to the Cochrane Collaboration's tool for assessing the risk of bias in RCTs.[19] A further, robust meta-analysis by Amer et al[20] in 2020 analysed 954 midshaft displaced clavicular fractures and showed similar results, with out of 457 non-operative patients, 64 patients (14%) developed nonunion, in contrast with out of 497 operatively managed patients, only seven (1.4%) developed nonunion. This study also could not find any statistically significant difference between functional scores for operative and non-operative management.

What does this all mean? We have multiple meta-analyses which show that operative management for adult midshaft clavicular fractures reduces the risk of nonunion and malunion, but there is a bifurcation of opinion regarding the increase of function and quality of life of patients in the long term. Some of these discrepancies may be explained by the fact that there is no gold standard for functional improvement after upper limb injury.[21] Even DASH and Constant, the most common scores, still have their flaws, such as bias in self-reporting and a lack of certain measures of function, such as shoulder stability.[22] There are also differences in patient demographics, whose differences in culture can explain differences in self-reported questionnaire-based function.[22] However, these explanations do not fully explain this difference in function post-fracture. There are clear indications for surgery, such as a floating shoulder or neurovascular compromise, but there are many relative and controversial indications for conservative and surgical management. An argument could be made for favouring nonsurgical management for relative indications for clavicle fractures, due to the complications that can come with surgery, as well as the cost to the District Health Board, but there is a clear decrease in nonunion/malunion with surgery, whose relevance is not fully clear and explained. As always, with simple questions come complicated answers; further research is required, such as a New Zealand-specific cohort study on conservative and surgical management of relatively-indicated midshaft clavicular fractures, analysing functional and radiological short- and long-term outcomes.

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ACADEMIC

Turning the tide on the "seven-year itch" in seven months

Thomas Swinburn

"Imagine you are a wealthy philanthropist with unlimited funds. Discuss the problem of scabies in the New Zealand-Australia-Pacific area. How will you use your wealth to correct the problem?"

Introduction

Scabies, or mate māngeongeo riha, is a dermatological condition of significant public health concern in the Oceania region. It causes extreme itching, which can be unbearable, and can lead to debilitating sequelae, including rheumatic heart disease (RHD). In this essay, I will firstly consider scabies from a clinical perspective, before exploring the challenges this disease poses in the Pacific, Australia, and Aotearoa New Zealand. Finally, I will outline my imaginative, ambitious vision into which I would invest philanthropic funds. I believe my proposal could feasibly make substantial in-roads into control of the "seven-year itch" in seven months by harnessing synergies with coronavirus disease 2019 (COVID-19) management.

Clinical Overview

Scabies is a skin infection caused by the parasitic mite *Sarcoptes scabiei var. hominis*.[1] This common condition can affect anyone, and particularly those at the extremes of age. Risk factors include poverty, overcrowding, institutional living, and immunodeficiency. Transmission occurs via skin-skin, sexual, and indirect contact.[1] The mites induce type I and/or type IV hypersensitivity reactions, manifesting as an intensely itchy rash which has highly heterogenous clinical presentations.[2] Broadly speaking, scabies can be conceptualised as having asymptomatic, typical, nodular, complicated, or crusted appearances.[3]

Diagnostic work-up includes microscopy, skin biopsy, and dermatoscopy.[1] Consensus criteria published by the International Alliance for Control of Scabies (IACS) in 2020 guide the ultimately *clinical* diagnosis.[4] Scabies can be treated effectively with scabicides. These may include topical permethrin or oral ivermectin; the latter is typically used for mass treatment. Other measures include laundering and sanitation measures.[1]

With effective treatment, scabies generally improves within a few days, and resolves within a month. Complications include secondary impetigo, cellulitis, sepsis, post-streptococcal glomerulonephritis, and, crucially for the Aotearoa New Zealand landscape, RHD.[5,6] Crusted scabies is a particularly contagious variant with distinct risk factors, classically presenting as a scaly rash with minimal to no itch.[7] Institutional scabies is another subset with specific management from a public health standpoint.[3]

Scabies in the Pacific, Australia, and Aotearoa New Zealand

Let us now apply a population health lens to the problem of scabies in the Pacific, Australia, and Aotearoa New Zealand. Consecutive Global Burden of Disease studies have estimated the worldwide prevalence of scabies between 2010 and 2017 to vary from 100 to 200 million.[8,9] In 2015, scabies accounted for 0.21% of disability-adjusted life-years (DALYs) from all conditions.[10] Within this global context, scabies presents a significant public health challenge in Oceania.

Despite being a common, problematic condition with frequent complications and significant impact on morbidity, quality of life, and health systems, responses to scabies in the Pacific have never been prioritised.[9] Indeed, scabies was only added to the World Health Organisation List of Tropical Neglected Diseases in 2017.[11] The Pacific has the third highest age-standardised DALY burden of 21 regions globally, at 120.34 DALYs per 100,000 people.[10] The Pacific nations Papua New Guinea and Fiji are among those with the highest estimated prevalence of scabies worldwide.[10]

Some of the largest studies of scabies have occurred in Pacific nations such as Fiji and the Solomon Islands, which provide case studies of this condition in developing Pacific nations.[9] A landmark, world-first national survey of scabies and impetigo prevalence in Fiji involving 10,887 participants across 75 urban and rural communities estimated a national prevalence of 18.5% in 2015.[12] Alarmingly, prevalence was double in Indigenous iTaukei Fijians compared with non-Indigenous Indo-Fijians, and 43.7% in children aged five to nine.[12] A subsequent prospective study over 48 weeks identified 788 hospital admissions for skin and soft tissue infections (SSTIs), of which 72% were attributable to sequelae of scabies.[13] These presentations occupied 10% of hospital bed capacity over this time, reflecting a significant health system impact. Similarly, Indigenous Fijians and those aged below five or above 55 were more likely to present with SSTI.[13]

As a further example, the picture in the Solomon Islands is similar. A recent study involved 20 villages in the Western Provinces, with nurses conducting clinical assessments on 5239 participants against 2020 IACS diagnostic criteria. Overall prevalence was estimated at 15%, with individual villages having prevalences varying between 3.3% and 42.6%.[14] These findings concord with earlier estimates.[15] Beyond purely medical impacts, scabies impacts quality of life, with flow-on effects for education and employment prospects.[16] Research into the wider social and economic impacts of scabies is needed.[8]

Less is known about scabies in Australia and Aotearoa New Zealand, which, unacceptably, may reflect the characterisation of scabies as a condition affecting marginalised communities within developed countries.[17] Australian research has tended to focus on crusted scabies in Aboriginal communities in northern Australia, who are believed to have among the highest rates of crusted scabies worldwide; approximately one in three may be infected in some communities.[9] A two-year prospective study in the Northern Territory highlighted the difficulty in effectively managing this disease in endemic settings, building the case for public health leadership.[18] A total of 80 patients experienced 92 episodes of crusted scabies, of whom 95% were Indigenous and 71% were from remote Indigenous communities. Despite successful treatment, the majority of the 33 episodes of recur-

rence were attributed to re-infection within the community. Patients required isolation precautions for a median duration of two weeks, impacting individuals, their families, and the health system. Undiagnosed community cases presented a risk for institutional outbreaks, undermining individual treatment strategies.[18]

In Aotearoa New Zealand, scabies is a particularly concerning public health problem because of its association with RHD, a serious, preventable, and highly inequitable disease which has been described by leading epidemiologist Professor Michael Baker as a "disease we shouldn't have."[19] A recent cohort study following 213,957 children in Auckland revealed that those diagnosed with scabies were almost nine times more likely to develop acute rheumatic fever (ARF) or chronic RHD over five years after adjusting for confounders, providing epidemiological evidence that these diseases are linked.[20] Risk factors for both scabies and ARF include Māori and Pacific ethnicity, male sex, low socio-economic status, and dental caries. A subsequent study concluded scabies control could be important in reducing rates of ARF.[21]

A Vision for Scabies Disease Control

Turning now to consider how to address the challenge of scabies in Oceania, it is empowering that the framing of this essay question invites blue-sky thinking. This style of problem-solving is valuable and perhaps underemphasised in medical training. However, in what follows, I make the case that solutions need not be unattainable fantasies. Rather, the current COVID-19 environment provides a unique opportunity for philanthropic investment to make a meaningful difference to scabies control by harnessing the public health synergies between COVID-19 and scabies management.

In devising a solution, I thought pragmatically about the "here and now." My observations as a frontline COVID-19 vaccinator inspired my thinking. I recognised that mass COVID-19 vaccination presents a unique proposition; collectively, we are wanting almost everyone to have a meaningful interaction with a trusted healthcare professional. Whilst the unequivocal message surrounding COVID-19 has rightfully been to vaccinate, vaccinate, vaccinate, what if we vaccinate, vaccinate, vaccinate — and *innovate* by combining a scabies control programme with the existing measures for COVID-19?

In essence, I am proposing that a community dermatology approach to scabies is integrated alongside the current COVID-19 response. At the broadest level, a scabies control programme would need to comprise mapping disease burden, enacting control strategies, monitoring and evaluation, and managing other major issues.[22] Concretely, this would require three pillars: surveys to estimate disease prevalence, population treatment with mass drug administration (MDA) where scabies prevalence exceeds 10%, and active case management.[17,22] Community education and addressing upstream factors would also be important.[23] Unequivocally, community partnership and Indigenous self-determination must be embedded within any response.[6,24]

Disease prevalence surveys could be carried out seamlessly and simultaneously with a COVID-19 vaccination appointment. Simple clinical algorithms probing key features of history and examination have been shown to identify scabies with high sensitivity and specificity by non-expert clinicians in constrained conditions.[6] These could therefore be appropriately administered by healthcare workers in vaccination clinics. An intrusive, time-consuming, full-body skin examination that has traditionally comprised the diagnostic workup would clearly not be practical in this setting. However, an abbreviated inspection of the exposed aspects of the upper and lower limbs has been shown to detect scabies with 90% sensitivity regardless of disease severity, or the presence or absence of impetigo.[25] Whilst this requires more training to administer, it could be conducted alongside a COVID-19 vaccination.

Population treatments for scabies, such as MDA, have demonstrated proof of concept in communities where the disease is endemic: five communities in the Solomon Islands participated in an intensive treatment programme between 1997 and 2000, comprising a single 200 mc/kg oral dose of ivermectin (or a permethrin regime where ivermectin was contraindicated), followed by active case-finding tri-annually.[26] No further interventions occurred after 2000. 15-year follow-up indicates scabies has been virtually eliminated from these communities; of 388 individuals followed up, only one person was diagnosed with scabies, and 12 people reported a household contact had been diagnosed with scabies in the previous year.[26]

For this proposal, once communities with high prevalence of scabies are identified, a single oral treatment could be offered alongside an eventual COVID-19 booster shot.[27] Admittedly, part of the success of the Solomon Islands study may be attributable to the relative isolation of the participating communities.[26] Whilst this characteristic would not be replicable in pre-COVID times, the regional lockdowns across Aotearoa New Zealand and further afield in the region that seem inevitable for the foreseeable future may go some way to providing the isolation required for MDA to be effective long-term.

Finally, the COVID-19 pandemic has necessitated resourcing significant contact tracing capacity and expertise, which could be applied to active case management of patients with scabies and their contacts. A scabies programme run in partnership between the Northern Territory government and Aboriginal communities using an active case-finding strategy demonstrated a statistically significant 44% reduction in recurrence in patients with crusted scabies, and a 75% reduction in presentations of any type of scabies in contacts.[24] Scabies is not currently a notifiable disease in Aotearoa New Zealand[28]; making scabies notifiable, as the Northern Territory did in 2016, would be a valuable first step.[18] Similarly to COVID-19, whilst lockdowns may lead to overcrowding and scabies transmission, this risk can be mitigated with timely identification and intervention.

Competing health priorities in resource-limited settings have often been cited as barriers hampering better scabies control[6,9,17]; I would argue that scabies and COVID-19 ought to be thought of as *complementing* priorities. Nonetheless, this intervention would need to consider health workforce capacity to take on new initiatives, whilst also taking care not to oversaturate health consumers with information. Acceptability of MDA would need to be assessed, although qualitative research indicates attitudes may be favourable where scabies is endemic.[29]

Whilst targeting two health conditions simultaneously may seem fanciful at best and delusional at worst, it would not be without precedent; in the Solomon Islands, scabies mapping and treatment occurs alongside programmes for trachoma and yaws.[8] Just as sexual health physicians have embraced current pandemic settings as a "once-in-a-lifetime opportunity" to break chains of sexually transmitted infections,[30] ambitious, win-win thinking will allow us to maximise this window to control scabies. As with COVID-19, scabies vaccination may join the future toolkit.[31]

Conclusion

In conclusion, scabies is a parasitic infection that presents a significant, pressing, and ongoing challenge in Oceania. The parallels between scabies and COVID-19 are striking; both diseases may benefit from aggressive case-finding, population treatments, and reduced movements. Given large parts of the population are now engaged with public health discourse and measures, the COVID-19 pandemic presents a unique opportunity for a scabies control programme grounded in public health and community dermatology principles.

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ACADEMIC

Solving a mighty mite problem

Neakiry Kivi

"Imagine you are a wealthy philanthropist with unlimited funds. Discuss the problem of scabies in the New Zealand-Australia-Pacific area. How will you use your wealth to correct the problem?"

Introduction

Scabies is an extremely itchy skin disease caused by infestation of the mite, *Sarcoptes scabiei var. hominis*.[1,2] Incidence of scabies was estimated globally at 455 million per year, causing 3.8 million years lived with disability, and our Pacific region is one of the most affected areas in the world.[3,4] Scabies is primarily transmitted via skin-to-skin contact, where the female mite burrows into the skin, causing a hypersensitivity reaction on the trunk and limbs.[5] Scabies is often labelled as a disease of poverty and overcrowding.[1,6,7] Spread requires close personal contact, resulting from crowded housing conditions and institutional settings such as prisons, schools, hospitals, and care homes.[1,5] Stepping into the shoes of a wealthy philanthropist with unlimited funds, there is great opportunity to correct this problem of scabies in the New Zealand-Australia-Pacific area. In order to reach as close to elimination as possible, a five-pronged approach is proposed, as there is no one simple solution.

Burden of Scabies

Mite burrows can lead to skin breaches and have direct downregulating effects on host immunity. Secondary infection from the bacteria *Streptococcus pyogenes* and *Staphylococcus aureus* can cause impetigo, cellulitis, and abscesses. Further progression may result in post-streptococcal glomerulonephritis and acute rheumatic fever.[1,6] Afflicted individuals can experience unbearable itching, causing bleeding and sensitive wounds. Consequences of these visible and painful lesions range from mental distress, lack of sleep, and social stigmatization, to uncertainty of cure and burden of downstream disease.[6,8] Due to the nature of spread, outbreaks can easily affect families and wider communities.

Understanding Determinants of Scabies

The social determinants that contribute to scabies operate from an individual to a national, and even global level. As depicted in Figure 1, there are a range of factors that reinforce inequitable scabies outcomes in our New Zealand-Australia-Pacific region. Identifying the various pathways that lead to scabies will guide the approach to correcting the problem. New Zealand, Australia, and the Pacific Islands have marked differences in population size, ethnic diversity, land mass, governmental structures, economic worth, and historical contexts, to name a few. Thus, the determinants of scabies in each region will differ. Correcting the problem of scabies in such varied environments will require multiple strategies and interventions at a range of upstream and downstream levels.

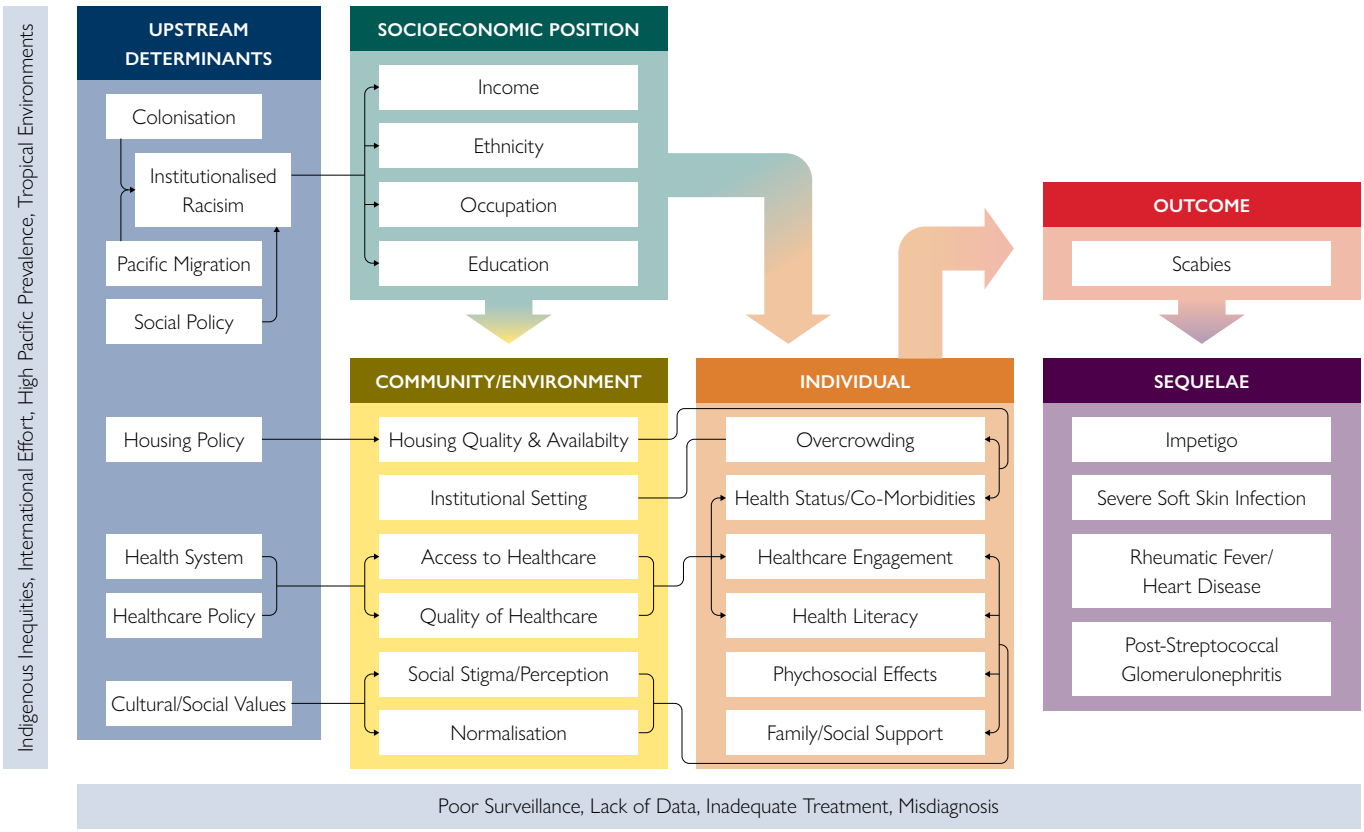
1. IDENTIFYING PREVALENCE

It is vital to accurately quantify the burden of scabies in the New Zealand-Australia-Pacific region before any intervention. A 2015 systematic review aimed to identify the prevalence of scabies worldwide, yet concluded the overall quality of studies was poor.[10] However, islands of the Pacific were noted to be the most affected, with the highest prevalence in the general population found to be in Papua New Guinea at 71%.[10] Indigenous communities of Northern Australia were also recognised to have high scabies prevalence.[10] Prevalence data dating back to the 1970s showed that scabies disproportionately burdened Māori and Pacific populations.[11,12] Thus, there is a need for updated data to re-quantify the effect of scabies in these vulnerable groups. Providing funding for high-quality national studies to measure disease occurrence in New Zealand, Australia, and the Pacific Islands allows for identification of areas or population groups that are most affected. This information is crucial for targeting where scabies control strategies should be implemented. Continued measurements over time can also illustrate the potential successes of attempts at scabies reduction.

2. STREAMLINING DIAGNOSIS

Early and accurate detection of a scabies case is critical for initiating treatment and to prevent further spread. However, the practice of clinically diagnosing scabies can be challenging, as there are limited signs specific to an infestation.[5] The International Alliance for the Control of Scabies developed a criteria for scabies diagnosis which factors in patient history, physical examination findings, and direct visualisation of mites.[13] Although this provides great opportunity for consistency and standardisation, there is still need for additional practices, tools, and tests that offer accurate diagnosis, especially in low-resource or remote areas.[1] Current strategies such as light microscopy, videodermatoscopy, and histopathological diagnosis can be limited by high cost and lengthy turnaround time.[14] To date, no point-of-care or simple laboratory test has been established and refined for routine use. Continued research into genomic sequencing, serological assay, and molecular-based techniques would benefit from increased funding to expand investigations of new diagnostic tools and methods. For instance, several polymerase chain reaction methods show potential for rapid and accurate diagnosis; however, their validity is limited by lack of testing in humans.[15] Creating and utilising low-cost equipment can allow for delivery of high-quality care to more rural and remote areas of Northern Australia and the Pacific Islands. For example, initial trials into the use of affordable video microscopes as tools for scabies diagnosis found they were just as effective as costly video dermatoscopes.[16] In addition, expansion of convolutional neural networks, a type of artificial intelligence, to recognise the appearance of scabies lesions in combination with imaging could be another accurate, quick, and low-cost diagnostic tool.[17] Various strands of investigation have been discussed, all advantageous in differing ways. Therefore, provid-

Figure 1 — Social Determinants of Scabies in the New Zealand-Australia-Pacific Area[9]



ing funding into these diverse research fields allows a broad toolkit to be available to clinicians making a scabies diagnosis.

3. EFFECTIVE TREATMENTS

Many treatments for scabies are available; however, there are still several gaps in knowledge and accessibility that exist. Permethrin cream is widely used; however, there is often poor compliance among index cases and contacts due to skin irritation, inadequate application, and inconvenience.[18] In New Zealand, 5% permethrin cream is fully funded by the government; however, the more practical and effective oral ivermectin requires special authority so is less accessible.[19] Regarding ivermectin, further study is needed into its safety in young children and pregnant women, as well as optimising dosage.[20] Within the same family as ivermectin, moxidectin may be a promising alternative.[21] Moxidectin has a longer half-life, which covers the entire scabies mite life cycle, so may be suitable as a single oral dose. *In vitro* studies have found moxidectin is superior to ivermectin for scabies treatment.[22] Further exploration may result in development of treatments which are more effective, safe, and tolerable than what is currently available. This is another area of research that should be provided funding to advance investigations.

In terms of a program or strategy for treating scabies, mass drug administration (MDA) is a method of delivering treatment to whole communities regardless of whether individuals have a positive diagnosis of scabies. The aim is to aggressively interrupt transmission of the mites, thereby reducing and preventing cases.[23] A global systematic review of 12 scabies MDA programmes using ivermectin demonstrated on average a 22% absolute and 73% relative reduction of scabies prevalence.[24] The Skin Health Intervention Fiji Trial (SHIFT) trial involving three Fijian islands resulted in a 94% relative reduction of scabies after 12 months and maintained an 89% relative reduction after 24 months, demonstrating the prolonged protection and effect of MDA.[25] The World Scabies Program is an organisation that has implemented successful MDA interventions in Fiji and the Solomon Islands.[26] Philanthropic partnership could allow for the extension of MDA programs into other Pacific Islands. Despite the success of MDA in some settings, the political and social nuances of mass treatment may be less acceptable in higher-income urban settings of New Zealand and Australia. This illustrates why a multi-faceted approach is essential for correcting the problem of scabies.

4. IMPROVING UPSTREAM FACTORS

Disparities in scabies burden between indigenous and non-indigenous populations are prevalent in New Zealand and Australia.[10,12] There are a range of scabies risk factors — such as overcrowded housing, health status, health literacy, and lack of engagement with primary care — which are all associated with low socioeconomic status. Māori and Pasifika in New Zealand, and Aboriginal communities in Australia, are more likely to be negatively impacted by all these determinants, and hence, experience worse health outcomes.[27,28] Poor housing and living conditions, associated with low economic status, are recognised drivers of scabies transmission.[7,27] In New Zealand, there is a housing and overcrowding crisis that disproportionately affects Māori and Pasifika.[29] Only 4% of NZ Europeans live in crowded housing conditions, compared with 38% of Pasifika and 20% of Māori.[30] In Australia, 24% of state-owned and managed Indigenous housing is classed as overcrowded.[31] Charitable organisations across New Zealand and Australia such as the Housing Foundation, Habitat for Humanity, and the Foundation for Indigenous Sustainable Health all build and repair homes for sustainable living.[32–34] Partnership and financial contribution to these groups could allow more people to live in healthy homes. Countries such as Singapore have seen a positive impact on the burden of skin infections, including scabies, and their complications, such as post-streptococcal glomerulonephritis, with government-led improvements in housing.[35] Therefore, improving housing quality in communities with a high burden of scabies can contribute to a reduction in prevalence by cutting off key transmission methods of the mites. Scabies is so tightly interwoven with communities of high deprivation, ethnic inequities, and risk of comorbid and downstream disease, that its spread will continue to be perpetuated unless upstream determinants of health are addressed.

5. ACKNOWLEDGING CULTURAL VALUES

Māori, Pasifika and Aboriginal cultural beliefs which wrestle with colonial European structures may negatively impact their engagement with healthcare, personal perceptions, social interactions, and health literacy, which can all contribute to a greater burden of scabies disease. An example is the Māori concept of "*whakamā*" which approximates to feelings of shame, inferiority, inadequacy, and self-doubt.[36] Social exclusion, stigmatisation, and embarrassment are commonly experienced by those with scabies.[8] Manifestations of *whakamā* can result in isolation from social supports and reduced health-seeking behaviour.[1,27] Among Aboriginal and some Pacific cultures, scabies may be "normalised" and perceived as harmless or minor due to its common occurrence.[31] Skin infections can be believed to clear up on their own, and hence, some are less likely to report infestation, seek help, and participate in education.[28,37] A skin health program operating in remote Aboriginal communities of East Arnhem, Australia implemented routine scabies screening, treatment in clinics and homes, and distribution of permethrin cream. Despite their efforts, prevalence remained unchanged after five years, as they were unable to achieve adequate levels of community involvement.[38] There is a need for collaborative, empowering, and mana-enhancing approaches which encourage people to engage with treatment. This is an area where funding further research and qualitative studies would be valuable to understand the perspectives of communities most burdened by scabies. Aboriginal people generally seek traditional bush medicine over Western medicine as they feel more in control of their health.[39] Tea tree oil aligns with Indigenous healing culture and demonstrates scabicidal properties.[40] Incorporating this traditional ingredient into treatment programmes may result in greater cultural acceptance. Pacific people's individual health is reflected in the wellbeing of their family and communities — a more holistic view.[41] Acknowledging Māori cultural beliefs during patient interactions can improve health literacy and health outcomes.[39] These are all important perspectives that could be reflected in social campaigns. Integrating cultural beliefs and maintaining community engagement will underpin the success of any scabies intervention.

Conclusion

Current health systems and structures in place do little to protect vulnerable populations from poor scabies outcomes. Diagnosis is difficult, even by experienced clinicians, and current treatments are not always effective. Delay in initial diagnosis often means close contacts are already infected, and the cycle of spread continues. With the unlimited resources of a wealthy philanthropist, five areas to receive generous funding have been identified with the goal of correcting the problem of scabies in the New Zealand-Australia-Pacific region:

1. Data collection and prevalence studies
2. Development of accurate, rapid, low-cost diagnostic tools
3. Enhancing current treatment and expanding treatment programs
4. Looking upstream to improve housing quality
5. Understanding cultural beliefs to strengthen engagement

There is no simple solution for eliminating scabies. Without accurate diagnostic methods, data from prevalence studies may not be reliable. A miracle cure will provide little benefit if not socially acceptable and culturally safe. Aggressive treatment campaigns are not a substitute for improving quality of housing, access to healthcare, and socioeconomic status. The factors that contribute to poor scabies outcomes all work in tandem, so attending to only some will not be enough. With unlimited funds comes limitless opportunity; thus, all five areas described must be addressed to effectively combat scabies.

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About the author

› Neakiry is a fifth-year medical student with a keen interest in dermatology. This essay was the University of Otago winner of the 2021 Wilson-Allison Memorial Prize in Dermatology.

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ACADEMIC: ABSTRACTS

BMedSc(Hons) abstracts

Various Authors

Freehand 3DUS measurement of the triceps surae muscle volume in premature infants *in vivo*

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Introduction
Premature birth (gestational age <37 weeks) is a leading cause of childhood morbidity and mortality, associated with significant motor sequelae that have profound implications for health, development, and function. The aim of this study was to investigate the volume of the triceps surae muscle in premature infants at three and six months old, adjusted for prematurity.

Methods
Using freehand 3D ultrasound, the bilateral volumes of the medial gastrocnemius (MG), lateral gastrocnemius (LG) and soleus (SOL) were assessed at three and six months corrected ages in seven infants. Scanning was performed by a single researcher, while two researchers independently digitised the images for volume calculation.

Results
The mean volumes of the MG, LG and SOL were 1.74 mL (1.34–2.23), 0.94 mL (0.82–1.06) and 4.15 mL (3.16–4.88) and 2.58 mL (2.14–3.12), 1.36 mL (1.23–1.64) and 5.14 mL (4.45–6.03) at three and six months respectively.

Conclusions
Muscle volume (MV) determines muscle strength and indicates muscle growth. Reduced growth of the triceps surae during infancy is associated with muscle weakness, motor delays and impairments. As the first study to measure MV in premature infants during their first six months of life, these results provide insight into the effects of prematurity on muscle growth and may assist in establishing a structural basis for milestone attainment, determining the aetiology of motor impairments, and facilitating detection of abnormal development.

Effects of maternal position on placental blood flow and restriction — an MRI study.

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Introduction
Supine sleep position is an independent, modifiable risk factor for late stillbirth, with a disproportionately larger impact on pregnancies with fetal growth restriction (FGR). Magnetic resonance imaging (MRI) has revealed that maternal supine position reduces oxygen transfer across the placenta in healthy pregnancies, but the impact in FGR is unknown.

Materials and Methods
12 women with FGR and 27 women with healthy pregnancies at 34–38 gestational weeks underwent MRI in both left lateral decubitus (LLD) and supine positions. Blood flow in the maternal internal iliac arteries and umbilical vein was assessed using phase-contrast MRI. A combined diffusion-relaxation imaging protocol (DECIDE) was used to measure placental perfusion and oxygenation.

Results
In FGR pregnancies, supine position caused a 20% reduction in total internal iliac arterial flow (p=0.01) and no significant change in umbilical venous flow (5%, p=0.55). During the LLD position, growth-restricted fetuses experienced a 14% lower oxygen saturation, 21% lower placental oxygen transfer, and 32% lower oxygen delivery to the fetus than in healthy pregnancies (p=0.004, p=0.001, and p=0.002, respectively). Supine position caused fetoplacental oxygen saturation to reduce from 65.6% to 61.3% (p=0.004) in healthy pregnancies, while in FGR, oxygen saturation was 56.7% in supine position and 54.5% in LLD (p=0.31).

Conclusion
This is the first study to non-invasively quantify the effect of maternal position on maternal and fetoplacental blood flow and oxygenation in FGR pregnancies. Growth-restricted fetuses are tolerating chronic hypoxaemia which may make them more vulnerable to the reduction in placental blood supply caused by supine position.

The impact of COVID-19 lockdown on Chinese care homes in New Zealand

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Introduction
In response to the coronavirus disease 2019 (COVID-19) pandemic, the New Zealand government implemented nationwide lockdowns in 2020 and 2021. Subsequently, visiting restrictions were enforced in care homes across the country. This placed an already vulnerable population at risk of functional and cognitive decline as well as psychological difficulties due to isolation. There is a lack of evidence on the experiences of vulnerable minority groups during the pandemic. The Chinese community is one of the fastest-growing ethnic groups in New Zealand and faces additional challenges, including language barriers, differing cultural beliefs, and COVID-19-related discrimination. This study aims to explore the experiences of Chinese care home residents in New Zealand during the COVID-19 lockdowns.

Materials and Methods
We performed semi-structured interviews with predominantly Chinese individuals (n=18) across two Chinese-run care homes in Auckland from April to June 2021. Participants included residents (n=6), family members (n=6), and facility staff (n=6). Interviews were conducted and transcribed in either English or Mandarin Chinese. We coded the interview transcripts and performed thematic analysis to synthesise overarching themes.

Results
The preliminary analysis suggests that lockdown led to difficulties for families in fulfilling the obligation of filial piety. Relationships between residents, family, and staff were enhanced by the use of technology. However, Chinese residents with dementia may face barriers to technology use.

Conclusions
The lockdown promoted a sense of unity among residential facilities included in the study. The necessary and rapid adoption of technology during lockdown was beneficial and strengthened relationships between residents, family, and staff.

Evaluation of post-operative outcomes with wearable sensors following robotic-assisted and conventional knee arthroplasty

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Introduction
Traditional patient-reported outcome measures (PROMs) have failed to highlight differences in outcome when comparing knee replacement designs and implantation techniques. Wearable sensors, such as inertial measurement units (IMUs), provide a cost-effective and portable solution for evaluation of post-operative outcome in combination with traditional PROMs. The aim of this study was to demonstrate the feasibility and reliability of using ankle-worn IMUs for remote patient monitoring (RPM) in the early post-operative period for patients with conventional total knee arthroplasty (TKA), unicompartmental knee arthroplasty (UKA), and robotic-assisted TKA (RA-TKA).

Materials and Methods
44 patients undergoing primary knee arthroplasty (19 RA-TKA, 17 TKA, and 8 UKA) for osteoarthritis were prospectively enrolled. Community-based RPM was performed pre-operatively, then weekly from post-operative weeks two to six using IMUs and PROMs. IMU-based metrics included: cumulative impact load, bone stimulus, and impact asymmetry. PROMs scores included: Oxford Knee Score (OKS), EuroQol Five-dimension with EuroQol visual analogue scale, and the Forgotten Joint Score.

Results
Preliminary results showed significant improvements in mean impact asymmetry by 67% (P=0.0055), bone stimulus by 41% (P<0.0001), and cumulative impact load by 121% (P=0.0349) between post-operative week two and six. The mean change scores for OKS were 7.5 (RA-TKA), 11.4 (TKA), and 11.2 (UKA) over the early post-operative period (P=0.144). Interestingly, PROMs scores (OKS) did not always reflect the same trend as IMU-derived limb usage between the different implantation techniques.

Conclusions
We present a quantitative, scalable, and low-maintenance RPM system using IMUs that can supplement traditional PROMs to provide a more holistic overview of post-operative recovery following knee arthroplasty. Furthermore, these data suggest a difference in the functional outcome of TKA and UKA patients that might be overlooked by using PROMs alone.

Qualitative and quantitative analysis of bacterial microcolonies in the tonsils of patients with tonsillar hyperplasia

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Introduction
Tonsillar hyperplasia (TH) can cause a spectrum of clinical presentations, ranging from obstructive sleep apnoea to recurrent tonsillitis. Current treatment options are limited to antibiotics and tonsillectomy. Recent studies have identified bacterial microcolonies in tonsillar tissue, but it is unclear whether they provoke an immune response.

Materials and Methods
Tonsils were collected from 25 paediatric and ten adult patients undergoing tonsillectomy for TH. Tissue sections with microcolonies were stained using fluorescent in-situ hybridization (FISH) targeting *Streptococcus* spp., *Haemophilus influenzae*, and *Fusobacterium* spp. Immunohistochemistry (IHC) was used to identify T and B lymphocytes. Microcolonies from adjacent tissue sections were dissected via laser. The bacterial load of these microcolonies will be determined using Droplet Digital PCR.

Results
In a preliminary dataset including 18 children and five adults, 91% of patients had at least one microcolony, with a mean of 4.3 identified per patient. *H. influenzae* was detected in 86% of microcolonies, followed by *Fusobacterium* spp. (43%) then *Streptococcus* spp. (33%). Bac-

teria-lined crypts were detected in 48% of patients, with *Streptococcus* probe-positive cells accounting for the greatest area. Lymphocytes were found co-localized with microcolonies within the crypt lumen in 81% of patients.

Conclusions
We have successfully developed a combined FISH-IHC protocol that allows simultaneous visualization of clinically relevant bacteria and immunocytes within tonsillar tissue. The consistent co-localization of lymphocytes with microcolonies does not match typical lymphocyte behaviour, and we hypothesize this may contribute to TH pathogenesis. Further studies comparing TH to normal tonsil tissue are required to determine the pathogenic effect.

Genetic relationships between alcohol consumption, serum urate and gout.

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Introduction
Alcohol consumption is a risk factor for elevated serum urate and gout. Several single-nucleotide polymorphisms (SNPs) have been associated with both alcohol consumption and serum urate or gout in separate genome-wide association studies (GWASs). The aim of this study was to systematically assess the relationships between these SNPs and alcohol consumption in influencing serum urate levels and gout.

Materials and Methods
Candidate SNPs were identified by comparing serum urate, gout, and alcohol consumption GWASs for overlap. These were tested for association with each phenotype among >450,000 European individuals from the UK Biobank using multivariable-adjusted regression analyses. Interaction terms were used to quantify SNP-alcohol interactions in influencing serum urate and gout. The nature of these relationships was evaluated using genotype-stratified or mediation analyses.

Results
35 SNPs were assessed. Most SNPs were associated with alcohol consumption and serum urate or gout in opposing directions. Only SNP rs11940694 at the *KLB* gene demonstrated consistent directions of association with each phenotype. The direct effect of *KLB* accounted for most of the total observed effect on serum urate and gout, with smaller, indirect effects mediated through alcohol consumption. SNPs at *LOC100507053* (rs11733695), *ADH1B* (rs1229984) and *ADH1C* (rs141973904) showed non-additive interactions with alcohol consumption for serum urate. *ADH1B* (rs1229984) additionally showed a non-additive interaction for gout.

Conclusion
The study findings are strongly indicative of pleiotropic effects at each SNP on serum urate levels and gout that are independent of their effects on alcohol consumption. Novel interactions were identified between *ADH1B* and alcohol intake to influence serum urate and gout.

Neuroinflammatory pathways in the midcingulate cortex in Huntington's disease.

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Introduction
Huntington's disease (HD) is a genetic neurodegenerative disorder that can result in motor, mood, and cognitive symptoms. HD pathophysiology has been linked to the process of neuroinflammation — the presence of inflammatory mediators and reactive glial cells in the brain parenchyma. Many signalling pathways likely interact to propagate neuroinflammation in the brain. Neuroinflammation is thought to cause cell loss, and in the anterior cingulate cortex, cell loss has been correlated with HD mood symptoms. The presence of neuroinflammation and cell loss in the HD midcingulate cortex (MCC) has not been investigated yet.

Materials and methods
This project investigated the presence of neuroinflammatory pathways in 14 HD and nine control post-mortem human MCC samples using next-generation sequencing. HD cases were split into the symptom profiles of motor, mood, and mixed. These data were analysed using Gene Ontology (GO) enrichment analysis. These results were validated with Nanostring nCounter gene assays and western blotting experiments.

Results
We have found 24 upregulated inflammation-related genes including Toll-like receptors, classical complement, AQP4, CHI3L1, P2X7R, S100A9, and SPP1 across HD cases. However, 13 inflammation-related markers, including chemokines, were downregulated. GO enrichment analysis reflected this, with multiple inflammation-related GO terms being upregulated and downregulated in all HD mood and motor groups. In mood HD cases, seven inflammation-related genes were upregulated and none were downregulated.

Conclusion
These results present a complex picture of potential inflammation priming in the HD MCC, rather than overt neuroinflammation.

Sleeve gastrectomy for weight loss impacts the gastric conduction system

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Introduction
While sleeve gastrectomy is an effective treatment for obesity and type 2 diabetes, it can be complicated by gastro-oesophageal reflux, nausea, and food intolerance. The stomach's greater curvature is removed, including the normal gastric pacemaker region. This thesis aimed to evaluate the impact of sleeve gastrectomy for weight loss on gastric electrophysiology using body surface gastric mapping (BSGM).

Method
Patients at least three months post sleeve gastrectomy were recruited (n=21) and compared to healthy controls (n=25). The patient group was recruited from all patients who had a sleeve gastrectomy at Auckland District Health Board in the five years prior to study commencement. The control group was taken from a previous study. Gastric myoelectrical activity was measured using BSGM comprising 64 electrodes on a conformable array and a wearable reader (Alimetry, Auckland). Recordings were a 30 minute fasted baseline and four hours post-meal. Gastrointestinal symptoms were measured and quality of life questionnaires were employed.

Results
Sleeve gastrectomy patients reported low symptom burdens. Gastric slow wave frequencies were consistently lower in patients compared to controls (mean 2.36 vs 2.93 cycles per minute, p<0.001). Gastric myoelectrical amplitude was lower in sleeve gastrectomy patients (19.1 vs 42.2 μV; p<0.001), although this difference may be due to patients having a greater body mass index causing signal attenuation. The power ratio was comparable (1.42 vs 1.71; p=0.85). Analysis of slow wave conduction direction patterns were not significantly different between groups (p=0.64).

Conclusion
This thesis suggests most patients following sleeve gastrectomy develop a stable gastric pacemaker at a lower intrinsic frequency. It did not indicate that the altered electrophysiology correlated with gastrointestinal symptoms. Application of BSGM in other and more symptomatic cohorts may provide new insights into the impact of alteration of normal gastric anatomy on gastric conduction.

Neuromelanin distribution with T1 mapping, histology and OCT

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Introduction
Neuromelanin-sensitive magnetic resonance imaging (MRI) has the potential to provide a means for early detection of neurological degenerative diseases such as Parkinson's disease. This project was aimed at developing a method of quantifying neuromelanin distribution to allow correlation with MRI T1 maps, as a proof of principle toward more generally using T1 MRI maps to determine in-vivo neuromelanin distribution. A good method to quantify neuromelanin is elusive, and this was our challenge.

Materials and Methods
Four neurologically normal ex-vivo human brains were obtained from the University of Auckland Human Anatomy Laboratory. These were extensively imaged using a variety of preparation techniques and MR imaging sequences including T1 mapping. This tissue was then carefully dissected for neuromelanin quantification. Several histological techniques were investigated. Optical coherence tomography (OCT), a technique which uses lasers to measure the attenuation of tissue, was investigated and optimised for neuromelanin quantification.

Results
Ex-vivo brains were successfully scanned with a variety of MRI sequences, providing quantitative maps. Histological quantification of neuromelanin with or without staining is semiquantitative. We have had some success in developing OCT as a method to quantify neuromelanin.

Conclusions
The absolute quantification of neuromelanin is difficult. Several histological methods can provide semiquantitative data. OCT seems to be a promising novel approach.

Optimising perioperative pain management: short-term inpatient use and long-term opioid prescribing following surgical procedures at Counties Manukau Health

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Introduction
Opioid analgesics are commonly prescribed following total knee arthroplasty (TKA) to manage pain and improve recovery. Prolonged opioid use following surgery can lead to short- and long-term adverse effects.

Methods
A series of retrospective cohort studies were completed to review current opioid prescribing practices at Counties Manukau Health following selected orthopaedic and general surgical procedures, including TKA. Various perioperative factors were investigated for associations with postoperative short- and long-term opioid use. These included inpatient consumption of sustained-release (SR) opioids and Quality of Recovery-15 scores (QoR-15) following TKA. Patients were stratified into two groups by inpatient use or avoidance of SR opioids, and three groups by QoR-15 score: low (<25th), medium (25–75th), and high (>75th percentile).

Results
SR opioid use was associated with increased inpatient and outpatient opioid use. Total inpatient opioid consumption between postoperative days zero and three was not significantly different between the SR groups (157.5 mg vs 167.5 mg oral morphine equivalent [OME], p=0.14). Dispensing of oxycodone was significantly greater in the SR opioid group at one and two months following discharge (p=0.01 and 0.03 respectively). Lower QoR-15 was associated with continued outpatient opioid dispensing. In the low QoR-15 group, 87.9% were dispensed either morphine or oxycodone within 30 days following discharge, compared to 56.3% in the high QoR-15 group (p=0.005).

Conclusion
Numerous patient-related and perioperative factors can impact on postoperative opioid use. The avoidance of SR opioids and the identification of patients with low quality of recovery may be important components of opioid-sparing postoperative pain management.

How good is the visually enhanced vestibulo-ocular reflex at identifying combined cerebellar and vestibular dysfunction

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Introduction
The visually enhanced vestibulo-ocular reflex (VVOR) can help iden-

tify combined cerebellar ataxia and bilateral vestibulopathy (CABV). The participant's head is passively rotated while they are instructed to fixate on a stationary target. A reduced eye movement response indicates a positive (abnormal) result. However, there is yet to be a verified method for conducting the VVOR. The sensitivity and specificity of the test for neurological disorders has not been determined either.

Materials and methods
Testing was conducted at five frequencies of rotation while gain (ratio of eye to head movement) was measured using video-oculographic goggles. Four groups of participants were tested: healthy controls, cerebellar ataxia (CA), bilateral vestibulopathy (BV), and CABV. Results from the patient groups were compared with the 95% reference range of healthy controls.

Results
Use of a metronome achieved good control of the head rotation frequency. Control group analysis showed no effect of frequency ($p=0.146$) nor age ($p=0.981$) on VVOR gain. Compared with controls, gains of CABV participants were decreased at all frequencies. In the CA and BV groups, gains were mostly within the normal range. Some BV patients exhibited a decreased gain at frequencies above 0.50 Hz, but never over the lower frequencies.

Conclusion
The metronome is a validated tool for controlling the frequency of manual head rotation. The gain findings are consistent with the theoretical framework that considers VVOR as an additive process between vestibular and cerebellar eye movements. An abnormal VVOR at or below 0.5 Hz appears to be a specific indicator of CABV.

Use of Computational Fluid Dynamics in Assessment of Aortic Valve Disease

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Introduction
Aortic stenosis (AS) is one of the most prevalent types of valvular heart disease, costing more than $30 million annually in New Zealand. AS is an active process whereby the aortic valve becomes calcified, stiffening the leaflets, which impairs its ability to open normally. It is believed that the pathophysiology of AS is triggered by mechanical and adverse haemodynamic shear stress.

This study piloted the use of computational fluid dynamics (CFD) — a branch of applied mathematics that specialises in modelling fluid movement — to simulate these stresses. We aimed to develop an analysis pipeline for clinical use, whereby cardiac magnetic resonance imaging (MRI) images could be used with CFD to generate more patient-specific aortic valve shear stress results.

Methods
The complex equations governing fluid dynamics can be solved using programs called CFD solvers. We used cardiac MRI images to provide the valve geometry and velocity inlet boundary conditions to enable estimation of the aortic valve shear stress.

Results and conclusions
This study compared a general-purpose CFD solver, "ANSYS," and a cardiovascular-specific solver, "CRIMSON." We successfully generated aortic valve shear stress measurements for three patients and succeeded in generating a pipeline by which shear stress measurements can be obtained from cardiac MRI. However, the pipeline was time-consuming, and the results generated from our patients were highly variable. We conclude that the current pipeline is unlikely to be feasible for clinical use for patient-specific aortic valve shear stress estimation. Future research and numerous improvements are required before this pipeline can be clinically applied.

Modelling the Effect of Inflammation on Chitinase 3-like 1 Expression.

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Introduction
Chitinase 3-like 1 (CHI3L1) is a protein believed to play a role in activating immune cells, tissue remodelling, and blocking cell death. CHI3L1 is increased in several inflammatory conditions, such as inflammatory bowel disease (IBD). Accordingly, measurement of CHI3L1 levels shows potential as a novel biomarker, or possible drug target. However, further research is required to determine the role of CHI3L1 in inflammation and the underlying mechanisms involved.

Methods
Caco-2 (epithelial) and THP-1 (macrophage) cell lines were cultured for 48 hours before stimulating with TNF-α, IL-1β and IL-6 at 10 or 100 ng/ml for one, three, six, and 24 hours. Changes in CHI3L1 gene and protein expression were measured by real-time PCR and ELISA, respectively. As a control, the expression of IL-8 (gene and protein) was measured in the same samples. Treated cells were immunostained to visualize whether CHI3L1 expression is cell surface-associated and/or cytoplasmic.

Results
In Caco-2 cells, CHI3L1 gene expression increased after three hours of exposure to IL-1β and TNF-α, but not IL-6, when compared to the control. Surprisingly, this was not followed by a measurable increase in CHI3L1 levels in the same cell culture supernatants or cell lysates. Measurement of IL-8 gene expression and protein levels confirmed cell responsiveness to the stimuli. Preliminary results from THP-1 cells show higher CHI3L1 protein levels compared to the Caco-2 cells. The immunostaining technique used failed to detect CHI3L1 protein in Caco-2 cells, and demonstrated CHI3L1 is predominantly cell surface-associated in THP-1 cells. Further optimization of methods may be required to confirm these findings.

Conclusion
These results suggest that epithelial cells may not be the primary source of the high levels of CHI3L1 reported in individuals with IBD. Instead, it remains a possibility that macrophages responding to proinflammatory cytokines may instead contribute to this response.

Lung Function and Cardiovascular Risk at Age 45 in the Dunedin Multidisciplinary Health and Development Study

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Background
This study aimed to investigate associations between lung function and cardiovascular risk in a general population sample of men and women aged 45.

Methods
The relationship between lung function and cardiovascular risk score was assessed using linear regression among 863 participants of the Dunedin Multidisciplinary Health and Development Study cohort. Lung function was determined by spirometry, body plethysmography, gas diffusion tests, and airway conductance. Log-transformed cardiovascular risk scores determined using two multivariable cardiovascular risk algorithms (Predicting Risk of Death in Cardiac Disease Tool (PREDICT) and Framingham Risk Score (FRS)) were used as the dependent variables. The association was investigated cross-sectionally and longitudinally using changes in lung function between ages 32–45 as the predictor.

Results
Cross-sectionally, low lung volumes were associated with a greater cardiovascular risk score (both log-PREDICT and log-FRS). This association was stronger in women than in men. The association was independent of body mass index (BMI) and smoking history, and was present in never smokers. Associations were not found between cardiovascular risk and measures of airway function (forced expiratory volume over one second/forced vital capacity ratio and specific airway conductance (sGaw)) or gas transfer (diffusing capacity for carbon monoxide/alveolar ventilation). Similar associations were observed in the longitudinal analyses between changes in lung function between ages 32–45 and cardiovascular risk score at age 45.

Conclusion
Low lung volumes at age 45 and accelerated pulmonary function decline between ages 32–45 are associated with a higher estimated cardiovascular risk score. This association is stronger in women, is independent of smoking and BMI, and is present in those who have never smoked.

INVITED FEATURE: STATISTICS PRIMER

What statistical software should I use? And does it actually matter?

Andrew R. Gray, Claire Cameron, Ari Samaranayaka, Robin M. Turner

Introduction

With so many options available, a question that researchers often ask us as biostatisticians is, "what statistical software should I use?" When faced with performing statistical analyses, if you search online, talk to your colleagues or supervisors, or browse your favourite bookstore, you will potentially find many, many options. Wikipedia lists over one hundred![1] This article will focus on general advice and look at software commonly used in the health sciences, specifically (in alphabetical order), GraphPad Prism, IBM SPSS Statistics, Microsoft Excel, R, SAS, and Stata.

An important point to keep in mind is that *using statistical software* is not the same thing as *doing biostatistics*. As Stuart Pocock, a notable medical statistician, said nearly forty years ago:

> *"I would like to refer briefly to the frequent misuse of statistical packages. Since they make each analysis task so easy to perform, there is a real danger that the user requests a whole range of analyses without any clear conception of what [they are] looking for… Thus, my main message here is that use of computers is no substitute for clear thought."*[2]

We should carefully think about our statistical analyses long before we have data in hand, preferably when we're first starting to design our study. These analyses are important when we're preparing funding applications, study registrations, ethics applications, protocol papers, and (most obviously) statistical analysis plans. We should also keep in mind that we will need to adhere to reporting guidelines, such as the Consolidated Standards of Reporting Trials (CONSORT) and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statements.

A decision-making process

We suggest that there are four steps to consider when deciding what statistical software to use. It's useful to keep in mind that on occasion we find that more than one statistical programme will be needed.

1. What do I need to do? A good start is understanding where you want to go in terms of your statistical analyses. This will require a solid understanding of your research question(s), the type(s) of data you anticipate collecting, the analyses you will need to precisely address your research question(s), and how you plan to communicate your findings. Most of the time, it will be useful to involve a biostatistician early in the project to make sure you're not missing something that will cause problems further down the line.
2. What do I already know how to do? If you already have experience with particular statistical software, it could be efficient to keep using that (as long as it will do what you need, of course).
3. What resources do I have (or can I get) access to? If you have identified that you will need to use software you're not already familiar with, or unfamiliar parts of software you have used before, you'll need to consider how you can reach the necessary level of expertise. If you have time, you might be able to find courses that will help you close the gap between what you already know and what you need to know. Some software might incur a cost depending on your institution's software licences. We find it's worth asking the information technology specialists at your institution in case a licence is available that makes commercial software either free, or very cheap. If you're planning to do the analyses yourself, the software used by your colleagues or supervisor(s) might be another consideration.
4. What do I want to be able to do in the future? If the first two points match up, you might be tempted to stop thinking about statistical software. Planning and implementing a research project is time-consuming, and it can be very easy to forget, at least momentarily, that this might not be the only time you need to do your own statistical analyses. It's reassuring to keep in mind that learning to use one programme will help develop your confidence with other programmes[3] in the future. It's also important to remember that whatever software you choose to use now might not exist, in its current form, or at all, for your entire research career! This is another excellent point to discuss with a biostatistician.

But at least I can use whatever software I want and get the same results, right?

While this is broadly true, it's important to note that software packages will sometimes give different results due to different default options. There are several options when we perform even simple analyses such as Chi-squared and Mann-Whitney U tests (such as continuity corrections and exact versus asymptotic tests). Sometimes you can change these options yourself, and other times, the designers of the software have already made these decisions for you. Forgetting this point can lead to frustration when a co-investigator, who might be a biostatistician, using different software, keeps getting slightly different results.

A danger with software that presents multiple versions of statistical tests alongside each other, as SAS and SPSS Statistics sometimes do, is that we might (subconsciously) choose the method or option that will give the most favourable p-value, having not decided in advance which is the most appropriate. Having a sufficiently detailed plan of the statistical analyses before they are performed is essential.

Writing your statistical methods

Once you've used your chosen software to perform your analyses, you will need to provide enough detail in your work (whether this is a journal article, thesis, or something else) so that the reader can understand what you did. A good goal to keep in mind when doing

this is to provide enough information so that a competent (bio)statistician with access to your data, but not your actual computer code or step-by-step instructions for using a point-and-click interface, could reproduce your results without extensive trial and error. This includes citing the software used and any user-written packages you've relied on (including the versions for both). It's crucial to explain when non-default options were used. Similarly, if you have chosen between approaches depending on what you find when you explore your data or statistical models, it's essential that you explain clearly how and why you have done this.

Quick overviews of some software options

This section will provide an overview of some statistical software commonly used in health research (in approximate order of complexity). All of these programmes have recent updates, and we anticipate that new versions of each will be released in the future. There are many other statistics programmes that we do not have space to cover and come across less frequently.

MICROSOFT EXCEL

While Microsoft Excel is very limited in terms of the statistical analyses it can do, it has the advantage of familiarity for many researchers. It can be used for activities such as data entry, data cleaning, "mechanical" calculations (where the same formula is repeatedly applied to data, such as with standardisation), descriptive statistics, and constructing tables and figures. There are inbuilt functions and extensions adding more statistical methods, but the authors wouldn't recommend using these over dedicated statistical software. We sometimes see researchers who started using Microsoft Excel because it seemed easier, but who then found that they couldn't do what they needed, or what reviewers or examiners asked them to do.

GRAPHPAD PRISM

GraphPad Prism has less functionality compared to the other options below, reflecting the statistical tests, models, and graphs that its designers think their users will want. It encourages a point-and-click approach, and while this can be very appealing for beginners, we find that this approach makes it much harder for researchers to update or expand the statistical analyses they've performed. Since reviewers and examiners will often request further or different analyses, we strongly prefer software that allows the use of code, as the four packages described below do.

IBM SPSS STATISTICS

While not used by the authors, SPSS Statistics is very popular among researchers and provides a point-and-click interface alongside a code-based approach. Part of the reason for the authors not using it is that we find SPSS Statistics syntax to be less straightforward than other software, making it harder for researchers to learn, write, read, and understand and make changes to their analyses in the future. If you're using SPSS Statistics, we strongly recommend that you save the code generated by the dialogue boxes so that you can reproduce your analyses on updated data or with modifications to the analyses themselves. The output from SPSS Statistics is often voluminous. For us, finding precisely the information we need to report can sometimes be more challenging than performing the analysis itself!

STATA

This is the software we use the most. We find that it provides most of what most biostatisticians want, and close to, if not everything, a non-biostatistician should want to do. Using fairly simple syntax, which is generally consistent between functions, you can perform interactive analyses, or submit a batch of code all at once. There is also the option of doing almost everything through a point-and-click interface, which conveniently displays the code that would have done the same thing, helping you to learn new commands and options as you go. A particular virtue of Stata is that it provides succinct output where you need to ask if you want more. While this might initially seem frustrating, it helps you to focus on what you currently need to know and reduces the risk of second-guessing options based on results. Another attractive feature of Stata is its user-friendly documentation that explains its commands in both non-technical language and with the technical details that statisticians sometimes want. Stata has an active user community, with many user-written programmes available. Over time, some of these have been added to Stata itself.

SAS

SAS is especially strong in data management and when working with multiple data sets. Like Stata, it's feature-rich, but its syntax is verbose, and we find it can take more time to learn. Like SPSS Statistics and other programmes that were developed when computers were more expensive and less accessible, its output is often lengthy and sometimes includes results using multiple options.

R

The freely available software R is, at heart, a programming language that has excellent support for statistical methods. Sometimes it's the first way to use new (bio)statistical methods. One challenge with R is the paradox of choice. R has a huge number of user-written packages. While other software might provide one standard way of doing something, community-written packages for R will often present the researcher with an unavoidable choice about exactly how they want to perform their analyses. Sometimes, different package authors will have their own preferences about options and extensions. This can lead to different results, or a researcher realising part-way through their statistical analyses that another package would have been a better choice. At the same time, there has been a lot of work towards making tasks more consistent (e.g. the Tidyverse) and enhancing the quality of packages (e.g. the Comprehensive R Archive Network (CRAN) and Bioconductor). Like Stata, R encourages you to work interactively with your data, and is succinct in its output.

What next?

Biostatistics features throughout the research cycle,[4] and different statistical software makes different things possible or easier. By carefully thinking through what you want to do, you can determine the statistical analyses you'll need (although these requirements might change later if your research doesn't go to plan), and then decide what software is best for performing these analyses.

We often find ourselves recommending Stata to researchers wanting, or at least needing, to perform their own statistical analyses, as it has almost all of the methods we would recommend, encourages good practice in being code-based (but with menus and dialogue boxes to remind us of the commands when we forget, alongside some excellent manuals and books), and facilitates focused exploration of our data and statistical models.

As always, talking to a biostatistician early in your research can avoid many problems further down the line. If possible, ensuring that a biostatistician is part of your research team will optimise the match between the research question, the statistical approaches, and the statistical software used.

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INVITED FEATURE: MAORI HEALTH REVIEW SERIES

Māori Health Review: Oranga Tamariki and the Well Child Tamariki Ora review

Quintin Smith, Tyler Stevens

"Poipoia te kākano kia puawai"
"Nurture the seed and it will blossom"

Oranga Tamariki

It is well established that Aotearoa, New Zealand has high rates of child abuse compared to other OECD (The Organisation for Economic Co-Operation and Development) countries. From 2007 to 2017, 12% of homicides were of *tamariki* (children) under 12 years of age.[1] On average, a child dies every five weeks from family violence, ranking Aotearoa 7th highest for child homicide and 35th out of 41 OECD countries for child wellbeing outcomes.[2,3] Inequities in health outcomes exist outside of child abuse as well — Māori *tamariki* with meningococcal disease are hospitalised at 3.5 times the rate of non-Māori, non-Pasifika children.[4] Māori *tamariki* with skin infections are also hospitalised at 2–2.5 times the rate of non-Māori, non-Pasifika children.[4] These examples serve to highlight the inequitable outcomes Māori *tamariki* experience in both disease and abuse. With the prevalence of child abuse, there is a corresponding amount of activity in the child protection sector. Oranga Tamariki is the branch of government that oversees care for children of the state, youth offenders, and children at risk of harm from violence. In the 12 months prior to September 2021, 5100 children were entered into the care and custody of Oranga Tamariki.[5] Out of these children in state custody, 57% identified as Māori and a further 11% identified as both Māori and Pasifika.[5] These statistics serve to demonstrate the inequitable picture that makes up child protection interventions and outcomes in Aotearoa. The conclusive evidence that we have a child abuse epidemic in our country needs to be framed in the context of its inequitable representation.

It is Oranga Tamariki and its subsidiaries that are responsible for upholding the legislative duty of the New Zealand Government as the Crown partner in Te Tiriti o Waitangi (the Treaty of Waitangi) to provide equitable outcomes for Māori children and their *whānau* (families).

Controversies in the media

The ability of the State to forcibly uplift *tamariki* from their *whānau,* and the power imbalance between these *whānau* and Oranga Tamariki, has often resulted in media scrutiny, taking the form of advocacy for *whānau.* Widespread coverage of infamous uplifts since the 1970s can be easily found on the internet, with Māori *whānau* being disproportionately involved in many of these cases. In 2019, Newsroom made a documentary called "Oranga Tamariki: The New Wave of Trauma," highlighting a situation in Hawke's Bay where social workers from Oranga Tamariki repeatedly attempted to uplift a newborn from her mother, with attempts at 2:00 am, while the mother was alone in hospital.[6] Unfortunately, this documentary was subject to a High Court removal order and was taken down in December 2020. However, the media attention that it generated led to Tracy Martin, the Minister for Children at the time, to meet with local *iwi* (tribe) representatives from Ngāti Kahungunu and initiate an internal review into what had unfolded. From there, a wide-scale investigation into the protocols and practices of Oranga Tamariki occurred, culminating in nine separate claims to the Waitangi Tribunal.[7] In 2021, another Newsroom documentary was posted, this time with footage obtained from a whistle-blower within Oranga Tamariki.[8] The footage given to Newsroom showed caregivers physically assaulting a young teenager, instead of using the correct restraint techniques that they had been trained to use. Later in 2021, a Radio New Zealand article arose detailing a complex child protection case in Waikato.[9] An investigation was opened in the paediatric department at Waikato Hospital, including the excerpt below:

> *"When the child was discharged after 67 days, the youngster "screamed, cried, and fought" before being escorted by police to a car and taken into care in what one staffer called the most distressing discharge of her entire paediatric career. One report said the child did not require hospital admission for any medical reason and was not unwell. The child, the report says, was afraid of Oranga Tamariki staff and told medical staff about wanting a job in the hospital to avoid ever having to leave."*[9]

It is important to note that in this Waikato hospital case, the documents were obtained from the "dark web" during the cyber-attack that crashed Waikato District Health Board computer systems last year. However, this case, and the many others before it, shows that organisational change is strongly needed, and that further inappropriate and paternalistic action from Oranga Tamariki will only widen inequities and continue to harm the populations it is commissioned to protect.

Well Child Tamariki Ora review

Organisational change first requires identification of where issues in policy and practice lie. In 2019, Oranga Tamariki began a review process as part of the government's Child and Youth Wellbeing Strategy. The focus of the review was the Well Child Tamariki Ora (WCTO) programme, a nationwide service that provides developmental and health services to all *tamariki* under five, and it aimed to analyse the programme's sustainability and equity. Findings of the review then informed Oranga Tamariki as to how the WCTO programme could be strengthened to assist in more equitable health outcomes; service all *pēpi* (babies) and *tamariki*; and improve sustainability, performance, and efficiency across the *motu* (country).[10]

Four questions were set by Oranga Tamariki to guide the review of the current WCTO programme: 1) to what outcomes should the WCTO programme be contributing? 2) what should the content of WCTO services be? 3) how should WCTO services be delivered? and 4) what are the critical enablers that allow the WCTO to be

delivered?[9] The predominant finding of the report was the conclusive need to redesign the WCTO programme to support all *tamariki* and *whānau*; while the current programme does provide a service that contributes to the health and wellbeing of many *tamariki* in Aotearoa, it does not yet cater for equitable outcomes for Māori and Pasifika *tamariki* and whānau.[9,10]

The review found that to redesign the WCTO programme, a flexible and *whānau*-centred approach is needed. To reduce inequities, an approach that strengthens the current components of the programme to support the health and development of all *tamariki*, while nurturing Māori partnership and leadership to fulfil Te Tiriti o Waitangi commitments, must be laid out. Below are excerpts from the WCTO Review report:

> *"Like all sectors in Aotearoa New Zealand, we need to ensure Māori are co-designers and enact tino rangatiratanga and mana motuhake in the design, delivery, and monitoring of the WCTO programme. We need to enable devolved funding and commissioning approaches to support equity."*[10]

Measures of service coverage and utility are persistently lower for Māori and Pasifika peoples living in high deprivation areas. Addressing these inequities requires devolving and shifting the funding and commissioning model so that it enables local design of integrated service models with a focus on *tamariki* and *whānau*, reflects the changing demographics, and has sufficient resources to provide a flexible service as mentioned above.

> *"We require integration of local strategies to support pae ora for tamariki and whānau."*[10]

The current WCTO programme has been based off frameworks from international evidence for child wellbeing surveillance programmes. The review found that there was a need to maintain the basis of these frameworks, whilst updating and tailoring them to our context in Aotearoa, with a framework based on Kaupapa Māori and Pasifika concepts of health and wellbeing. Kaupapa Māori frameworks are a structural analysis of Māori health disparities that explore the axiological (ethical), ontological, epistemological, and methodological assumptions of Māori health disparities that many Western models of care make.[11] This is also true for Pasifika models, such as the Fonua model of care, which aims to understand the relationship between the *fonua/whenua* (land) and people, to maintain *melino* (peace/harmony).[12]

> *"We need to invest in system infrastructure."*[10]

High quality monitoring and information systems that work at a national, regional, and local level to support service delivery and achieve *pae ora* (a healthy future) are necessary. Currently, this has not yet been achieved, due to gaps in information and technology, governance, and accountability.

COVID-19 pandemic

The review also evaluated the challenges and weaknesses of the WCTO programme during the coronavirus disease 2019 (COVID-19) national lockdown period between March and May 2020.

- Strengths: WCTO services and Whānau Ora providers, including primary care providers and social care providers, provided more responsive services to *whānau* during the COVID-19 response through delivery of welfare packs and holistic assessments. Further, the review noted that pre-existing connections and rapport made the transition to virtual contact much easier, and that providers were innovative and flexible in using technology to communicate with *whānau*.
- Challenges: Some *whānau* were unable to access healthcare support during the response. For instance, some *whānau* did not accept the referral from their lead maternal carer to a WCTO programme due to concerns about the value of virtual care. For other *whānau*, financial constraints meant that basic needs and food took precedence over accessing the WCTO programme. Other barriers to virtual consults included a lack of adequate devices with audio-visual capabilities, and difficulties with internet connection, particularly in rural regions. Even when consultations could occur, providers reported that virtual consultations could not gather the same comprehensive and holistic information when compared against in-person consultations. Additionally, workforce redistribution during the COVID-19 lockdown impacted the availability of services in the WCTO programme, resulting in staff fatigue, lack of support, and inadequate facilities and resources.

Reimagining the future

The review identified four objectives for the transformation phase of a redesigned, and more appropriate, WCTO programme:

1. Te Tiriti O Waitangi — to increase and support Māori partnership in governance and leadership at all levels.
2. Achieving equity — to deliver a fair and sustainable system that achieves equitable outcomes for *pēpi*, *tamariki*, and *whānau* who are Māori or Pasifika, have disabilities, or have higher needs.
3. Healthy futures — to enable *whānau* to express and achieve their aspirations for their *tamariki*.
4. Ways of working — to strengthen the current system to deliver improved services for *tamariki* and *whānau*.

To achieve these objectives, six action areas were identified.

1) GOVERNANCE

Governance incorporates the involvement of Māori for collective *kaitiakitanga* (guardianship) and leadership in the design and delivery of all services. This needs to happen for all services under the early years' health and wellbeing system, including primary care services, dental services, the WCTO, immunisation, and maternal mental health. Strong governance incorporates Māori leadership and will drive a service delivery that achieves better health outcomes for our Māori population.

2) MODELS OF CARE

This describes the frameworks that service delivery, including WCTO, is based on to provide safe, effective, and evidence-based care for our *tamariki* and *whānau*. Some of the values around models of care that this review identified included having continuity of care, providers including the entire *whānau* and acknowledging the experience of parents and grandparents in caring for *pēpi* and *tamariki,* and having a reliable and consistent service delivery.

3) FUNDING AND COMMISSIONING

Funding and commissioning directly impact how services are paid for, contracted, and monitored. The findings of the review suggest that the commissioning model is not flexible enough to support *whānau* in changing providers, which directly impacts engagement within the WCTO programme. Another finding suggests that the total amount of funding is not adequate to achieve equitable services for our Māori and Pasifika *whānau*.

4) QUALITY, MONITORING, AND EVALUATION

Maintaining an effective and equitable programme requires a transparent outcome monitoring system. This review found that current measures focus on outputs rather than outcomes — for example, measuring the success of sudden unexplained death in infancy (SUDI) prevention through the frequency of providers giving SUDI prevention advice, rather than the actual safety of *pēpi* sleep. Alongside this, the review also found that the current reporting requirements and quality improvement protocols do not require measuring important aspects of programme quality and outcomes.

5) INFORMATION TECHNOLOGY

Quality information services play a fundamental role in providing safe and *whānau*-led services, as they enable all parties to make informed decisions about the design and delivery of healthcare. The review reported that information was not shared universally between lead maternity carers, general practitioners, WCTO services, and before-school care providers, which led to *whānau* frustration when having to repeatedly share their story. It also found that the WCTO programme's "My Health Book," which is an integrated record of each child's wellbeing, was out of date. Finally, it reported that *whānau* and communities needed better access to their health information, as this would ultimately lead to improved health literacy, engagement, and better health outcomes.

6) WORKFORCE

In order to provide a service that achieves better and equitable health outcomes for our *tamariki* and *whānau*, the make-up of the WCTO workforce must be examined. This includes a workforce that has the knowledge, skills, cultural safety, and experience to actively identify and break down the systemic barriers that create inequities. The review reported that we need a multidisciplinary and diverse team including a large range of allied health professionals and a larger Māori and Pasifika-led workforce. This includes non-regulated roles to help improve the accessibility and cultural safety of the services, as well as valuing and resourcing these roles appropriately. Non-regulated roles are not regulated under the Health Practitioners Competence Assurance Act and are deemed to have a low level of risk of harm to patients and clients, such as physicians' assistants, where oversight of practicing decisions is made by a supervising physician. Recruitment retention was another issue found in the review, as retention pressures have been increasing within the WCTO programme. Workforce burnout and high rates of employee turnover were found to contribute to this.

Conclusion

Over the last decade, controversies in the media have repeatedly highlighted the deep inequities in child protection services across Aotearoa.[6–8] Under the leadership of Aotearoa's current Minister for Children, Kelvin Davis, it appears that Oranga Tamariki is undergoing a period of introspection and policy-change. The WCTO Review Report was commissioned in 2019, published in 2020, and reportedly actioned from July 2021. However, to date, it appears that Oranga Tamariki has not yet implemented the suggested changes from the WCTO Review Report. The WCTO Review report details six key principles that will guide this organisational restructure, yet it appears to lack clarity in exactly how these will be actioned. The lack of a distinct timeline does not reflect the urgency required in making these organisational shifts, with early data showing that the COVID-19 pandemic is likely exacerbating inequities.[5]

Despite the comprehensive review, the reported findings and action areas as described in the WCTO report were generalised and broad. The action areas identified in the review to improve service delivery of the programme described remodelling and extensive redesign and shifts in funding, but lacked specific examples. It was challenging to understand the context of the report findings and exactly how the WCTO programme will be further redesigned to improve health outcomes for our *tamariki*. However, the report does give an overview of the current key issues in the WCTO programme and the key causes for the inequities in outcomes for our Tamariki.

Awareness of child health outcomes and inequities is important for medical students at all stages of their education. Students will likely see Oranga Tamariki involvement on their paediatric attachment, but beyond this, an understanding of the driving forces of inequity in child care outcomes is necessary as we progress into our clinical roles beyond medical school. In this article, we have delved into the inequities in child health outcomes in Aotearoa and the mechanism by which Oranga Tamariki plays a part in these outcomes. We have summarised the WCTO report that was published by Oranga Tamariki and have concluded that although there are well-formed guiding principles and a comprehensive understanding of the barriers to equity, there is a lack of deep and critical reflection, and that the action points defined in the WCTO report lack clarity and vision.

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- This is available at: http://resources.bmj.com/bmj/authors/bmj-house-style
- The Vancouver referencing style should be followed. Numbers within the text should be included as superscript, with references listed consecutively at the end of the article
- Abstracts and keywords are required for all research articles, including case reports

Submission

- All manuscripts should be anonymised prior to submission. The cover sheet and manuscript document should be submitted online (http://www.nzmsj.com/how-to-submit-my-manuscript.html)

Process

All submissions undergo a double blinded peer-review process. Submissions will be reviewed for spelling, grammar, and clarity. Academic articles will then also be sent for for review by an academic and/or clinician with relevant expertise in the field. Authors will be required to revise their articles during this process. Final decision for publication will be made in conjunction with our academic advisors and Editorial Board once the review and revision process is completed to a professional publishing standard.

Acceptance of an article into the review process does not constitute a guarantee of publication. It is the intention of the NZMSJ to provide authors with the benefit of external review and revision processes that are standard internationally for published journals. This is in keeping with our educational aim of assisting medical students in making the transition from writing for medical school to writing for publication in an academic journal following graduation.

Contact us

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We are currently accepting submissions for Issue 35 which will have a theme of "Health Literacy" and is due for publication in October 2022

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STONZ as a union have committed a percentage of membership income to ensuring that trainee interns (TIs) and resident medical officers (RMOs) working and training environments are evidence based.

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Clinical research is also encouraged by STONZ and can also be funded to an upper limit of $1,000.

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The Verrall Award is awarded to the best academic research article published in the NZMSJ each year.

This annual prize is valued at $500 and is named after Dr Ayesha Verrall who was instrumental in leading the student committee that founded the journal in the early 2000s.

All original academic articles (including systematic and literature reviews) will be eligible and judged by the NZMSJ team.

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