Author/s:
Schulz, Thomas Ray

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Doctor of Medical Science

"Successful elements of an improved model of care for refugees and immigrants in regional Australia".

Dr Thomas Schulz

MBBS, BSc, FRACP

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Author Affiliations

1) University of Melbourne; Student No 1033141, course number; J15TC
2) University of Melbourne; Lecturer, Staff No 074877
3) Infectious Diseases and General Physician; Royal Melbourne Hospital (RMH) and Victorian Infectious Diseases Service (VIDS) at the Doherty Centre, Melbourne, Vic
4) General Physician; Royal Women's Hospital, Parkville, Vic

ORCID ID 0000-0002-1185-0030

This thesis is submitted as a compilation of published work in total fulfilment of the requirements for the degree of Doctor of Medical Science at the University of Melbourne.

Prelude

This set of papers has originated from clinical questions that have arisen managing refugee patients, primarily at the Royal Melbourne Hospital (RMH) within the Victorian Infectious Diseases Service (VIDS) refugee, immigrant and travel clinic.

The specific questions were:

1) Should we screen refugees for Helicobacter pylori (*H.pylori*) as part of post arrival screening?

2) Does country of birth influence Hepatitis B management?

3) Can a telehealth program be developed to address the issue of many refugees settling in regional Victoria and often travelling long distances for specialist clinical care, or in many cases not receiving the quality of care that they should?

4) Are the clinical outcomes achieved utilising this telehealth program to provide Hepatitis C treatment of a standard comparable to onsite care?

5) Can a telehealth program be used to expand and improve access to interpreters, and will this be acceptable to patients and clinicians?

This set of publications aims to provide robust answers to these questions in order to improve health outcomes of refugees and immigrants settling in regional Australia.

Contents

Abstract/Overview

Australia has benefited from a long history of migration, including accepting refugees and asylum seekers (referred to as refugees within this discussion) from a wide range of countries experiencing conflict and hardship. Multiple health care challenges exist for refugees, including language difficulties, low health literacy, poor mental health and exposure to infectious diseases that may be unfamiliar to Australian health care practitioners. This is exacerbated by the growing numbers of immigrants and refugees settling in regional areas, where there are poorer health outcomes and provision of quality health care is more difficult.

The published papers included in this thesis outline a number of the challenges in the provision of high-quality health care to refugees who settle in regional Australia, and some solutions that have been successfully utilised to improve health care provision to this population. The demonstrated solutions used for refugee populations are also valid for other immigrants and locally born Australians living in regional areas.

The literature review provides the context and rationale for each of these papers with more specific references included within each paper. The literature review provides an overview of the topic and outlines the importance of the papers in addressing issues previously poorly understood or not considered.

Paper one investigates the challenges of identifying appropriate screening for newly arrived immigrants and focuses on the cost effectiveness of screening new arrivals for *H pylori.* Modelling outlines the situations where a screening program could be considered and highlights the uncertainties that exist within the assumptions used for this modelling.

Expanding on specific infectious disease challenges in immigrant populations, *paper two* examines the genotypes of hepatitis B that are encountered in immigrants from Burma and *paper three* describes genotypes amongst African immigrants. Papers two and three address the clinical relevance of genotype and country of birth in the management of hepatitis B.

The subsequent three papers examine the provision of health care to refugees and immigrants via telehealth. *Paper four* outlines the development of a tertiary hospital based Infectious Diseases telehealth program. *Paper five* measures and compares the effectiveness of healthcare delivered to regional areas via telehealth, with a focus on care for individuals with hepatitis C virus. *Paper six* then describes the extension of the use of telehealth to include the provision of interpreters.

The discussion outlines the conclusions that have been drawn from these papers, and then suggests further improvements for the care of refugees and immigrants who settle in regional areas. Reducing the gap in health care outcomes between those who live in large urban centres and those who live in regional areas is relevant to the whole population. Drawing on these findings, recommendations are outlined to reduce this gap.

Included Papers

- Paper 1
  Using stool antigen to screen for *Helicobacter pylori* in immigrants and refugees from high prevalence countries is relatively cost effective in reducing the burden of gastric cancer and peptic ulceration.
  Schulz TR, McBryde ES, Leder K & Biggs BA.
  PlosOne 2014 Sept 30;9(9):e108610

- Paper 2
  Hepatitis B amongst Immigrants from Myanmar: Genotypes and their Clinical Relevance.
  Schulz TR, Edwards R, Thurnheer MC, Yuen L, Littlejohn M, Revill P, Chu M, Tanyeri F, Wade A, Biggs BA, Sasadeusz J
  J Med Virol 2018 Feb;90(2):271-276

- Paper 3
  Genotypic profiles of hepatitis B in African immigrants and their clinical relevance.
  Thurnheer MC, Edwards R, Schulz TR, Yuen L, Littlejohn M, Revill P, Bannister E, Chu M, Tanyeri F, Wade A, Biggs BA, Sasadeusz J.
  J Med Virol. 2017 Jun;89(6):1000-1007

- Paper 4
  Telehealth: experience of the first 120 consultations delivered from a new Refugee Telehealth clinic
  Schulz TR, Richards M, Gasko H, Lohrey J, Hibbert ME & Biggs BA.
  Internal Medicine Journal 2014 Oct;44(10):981-5

- Paper 5
  Using Telehealth to improve access to Hepatitis C cure in the direct acting antiviral therapy era.
  Schulz TR, Kanhutu K, Sasadeusz J, Watkinson S and Biggs BA
  Journal of telemedicine and telecare 2020 Apr;26(3):180-185

- Paper 6
  Improvements in patient care: Videoconferencing to improve access to interpreters during clinical consultations for refugee and immigrant patients,
  Schulz, TR, Leder, KS, Akinci, I, Biggs, B, 2015,
  Australian Health Review 2015 [P], vol 39, issue 4, pp. 395-399

Declaration

This is to certify that this thesis comprises my original work, with the contributions made by co-authors as outlined below.

Paper One

I was responsible for the concept and design of the study, the writing of the manuscript and the review of the statistics. Professor Emma McBryde conducted the statistical analysis. The other co-authors critically reviewed the manuscript.

Paper Two

I was responsible for the concept and design of the study and the writing of the manuscript. Dr Thurnheer prepared the statistical analysis and Dr Edwards conducted the genotypic testing. The other co-authors assisted with review of the manuscript, and sample and data collation.

Paper Three

Dr Thurnheer prepared the manuscript and statistical analysis. I was responsible for the concept of the study and review of the manuscript and Dr Edwards conducted the genotypic analysis. The other authors reviewed the manuscript and assisted with data collation.

Paper Four

I was responsible for developing the telehealth program and the subsequent design and concept for the paper. I drafted the manuscript and prepared statistical analysis. The co-authors reviewed the manuscript and assisted with the program development.

Paper Five

I was responsible for the concept and design of the study and I drafted the initial manuscript, Dr Kanhutu provided statistical review of the data, and the co-authors reviewed the manuscript and assisted with the patient care through the period of the study.

Paper Six

I was responsible for the concept and design of the study, and the collection and analysis of the data. I drafted the initial manuscript and prepared the statistical analysis. The co-authors reviewed the manuscript and assisted with data collation.

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Professor Bev Biggs for her support with this thesis but also the leadership of the Refugee Health programme that has allowed much of this work to occur.

My Co-Authors without whom the papers would not have been possible.

Glossary

Refugee

Someone who is unable or unwilling to return to their country of origin owing to a well-founded fear of being persecuted for reasons of race, religion, nationality, membership of a particular social group, or political opinion (1).

Internally Displaced Person (IDP)

A person who has been forced to leave their home or place of habitual residence, in particular as a result of, or in order to avoid the effects of armed conflict, situations of generalised violence, violations of human rights, or natural or man-made disasters, and who have not crossed an international border (2).

Asylum seeker

An individual who has sought international protection and whose claim for refugee status has not yet been determined (2).

Migrant

Any person who is moving or has moved across an international border or within a State away from his/her habitual place of residence, regardless of the person's legal status; whether the movement is voluntary or involuntary; what the causes for the movement are; or what the length of the stay is (3).

Immigrant

A migrant who moves into a particular State or area, that is away from his/her habitual place of residence.

Telehealth

A collection of means or methods for enhancing health care, public health, and health education delivery and support using telecommunications technologies (4).

Telemedicine

(used interchangeably with Telehealth)

More specifically this is clinical diagnosis and management that is delivered by technology (4).

Interpreter

Someone whose job is to change what someone else is saying into another language (5).

Translator

A person whose job is changing words, especially written words, into a different language (5).

Literature Review

Refugees and Immigrants - number, origins, and settlement in Australia

International migration is increasing. In 2015 some 244 million people (3.3% of the world's population) were living as migrants in another country (3). At the completion of 2017 the United Nations High Commissioner for refugees (UNHCR) also reported that a total of 68.5 million people are displaced worldwide. This included a total of 40 million internally displaced people (IDP's) and 25.4 million refugees. A further 3.1 million people were seeking asylum (2). This is the highest number of displaced people ever recorded.

Displaced people have been forced by circumstance to move to a new location, whilst immigrants choose to move and are often seeking better employment, education and economic opportunities for themselves and their families.

More than two thirds of the world's current refugees originate from five countries, Syria, Afghanistan, South Sudan, Myanmar (Burma) and Somalia (2).Of the worlds displaced people 85% are hosted in developing countries (2). A far smaller number of displaced people receive formal resettlement through the United Nations in a third hosting country. In 2017 the total number resettled was just 75000, a significant reduction from the 160,000 people resettled in 2016 (2). Currently the largest number of refugees, over 3.5 million are hosted in Turkey, with large numbers also hosted in Pakistan, Uganda, Lebanon, Iran, Germany, Bangladesh and Sudan (2).

Australia has a long history of resettling refugees through United Nations programs. Over the last 10 years an average of 15,000 (range 12,000-20,000) people have been settled annually in Australia (6, 7). Amongst developed countries Australia accepts the third highest total number of refugees through these programs (after the USA and Canada)(6, 7). Many other developed countries however have much larger numbers in the process of seeking asylum (2). These countries often have land borders or close sea access that allow large numbers of immigrants to arrive and then seek asylum. During 2015 over 2 million applications for asylum were lodged worldwide, and some 720,000 people sought asylum in Germany alone (3).

The geography of Australia means that the option of seeking onshore asylum is much more difficult than in most other developed countries, particularly those in Europe. Since 2013 government policy aimed at preventing those seeking onshore asylum (ie arrival by boat) has meant that almost all refugees now apply for settlement through offshore United Nations and Special Humanitarian Programs (7, 8).

Australia is a country built on immigration and over 28% (9) of the current population were born outside the country. Amongst Western Countries this is the second highest rate (after Switzerland 29%)(3) Other countries with high immigrant populations include Germany with 20% (10), the United States 13.5% (11)and the UK over 13%.(12). The total annual Australian permanent immigration numbers vary considerably and have been as high as 210,000 people in 2013 (13). There are also large numbers of overseas residents residing in Australia on student and temporary graduate visa's and in 2019 this was over 640 000 people (14)

Refugees and asylum seekers comprise less than 10% of total Australian immigration (7, 13, 15). This is comprised of those who are accepted through the United Nations refugee program and also through special humanitarian programs. These special humanitarian programs are for those with refugee like backgrounds but who may have not been persecuted, (which is the criteria necessary to

be regarded as a refugee under United Nations conventions) and they are often used to reunite families (7).

Refugee settlement in Australia is largely in the capital cities (16-18), however some 12% of refugees and approximately 15% of all immigrants settle in regional areas (18-20). This is partly due to specific programs to encourage this (16, 21), and also because of availability of low skilled work, lower costs of housing, and positive experiences living in regional areas (16). Recent analysis by the Regional Australia Institute has demonstrated that in the 5 years before the 2016 census, in 151 of 415 regional local government areas, the locally born population is decreasing and the overseas born population increasing (22). For this and politically motivated reasons the Australian Government has again proposed that immigration and visa's be linked to a requirement for regional residency (23). The focus on regional settlement is not unique to Australia, for example in Canada refugee settlement services operate in 36 separate cities (24).

Migration Health

To understand health provision for refugees and immigrants it is necessary to consider their health status and health outcomes. It cannot be assumed that those who migrate are representative of their source country, they may be from minority groups or particular regions (25). Many immigrants can represent a highly educated subset of the population, however refugee arrivals often represent the most disadvantaged groups within a source country (26, 27).

Over many years a body of research has developed suggesting that health outcomes for migrants are generally better than for the local population for many but not all conditions (28-31). This has been known as the healthy migrant effect and was first described in Hispanic immigrants to the United States over 30 years ago (32). This has suggested that those who arrive as immigrants have better health outcomes than the locally born population of comparable age and gender. This effect does not relate to immigration directly, and is not caused by being a migrant, but rather relates to a complex set of health determinants that exist for immigrants, and is not distributed evenly across immigrant arrival type (33).

Those who arrive as skilled migrants (voluntary migration) often have high levels of education, have good language competency, and have had a health screen as part of the application for a visa (13, 33, 34).

Those who arrive as refugees (forced migration) are often fleeing conflict, do not require a language competence test to immigrate, and may have less health literacy (13, 33, 35).

The differences in health outcome for immigrants are thought to be driven by determinants of health including rates of smoking, levels of alcohol consumption and differences in diet (29, 33, 36-39). Most data however on alcohol, smoking and drug use amongst immigrants are based on self-reports, and cultural differences may mean some immigrants are less likely to accurately report consumption. Surveys also often require English language which may introduce a bias towards a more educated, and possibly more healthy sample (33). These variables together mean the causes and the true size of any difference in health outcomes amongst immigrant groups are difficult to determine.

Health screening of immigrants prior to arrival both formally and indirectly has the potential to improve pre-arrival health but also to select a healthy migrating cohort (37, 40). Most immigrants to Australia other than humanitarian arrivals must meet a health requirement. This includes being free

from ‘any disease or condition that will be a significant healthcare and community service cost to the Australian community’ (41). This acts as a barrier to immigration for those with chronic diseases.

It is also likely only those who are in good health are able to access employment in Australia and hence open the pathway to skilled migration (33). It is thought this possible healthy migrant effect may be greatest for those who come from the developing world (31, 39, 42). Australian research has suggested this relationship may be more complex, with immigrants from English speaking countries with English language competency enjoying a health advantage over those who don’t speak English (43). In Australia it is recognised that health outcomes are better in urban centres and the predominance of immigrants settling in cities may also contribute to improved health (40).

In Australia, refugee arrivals who comprise only a small component of immigration, have different health issues and health outcomes to the much larger group of immigrants who arrive on other visa types (largely skilled migrants and their families) (13, 33, 35). This is particularly the case for some mental health outcomes which are worse than physical health outcomes for those who arrive as refugees (43). Notably rates of post-traumatic stress disorder (PTSD) and depression are higher in refugee groups (44). When considering mental health it should be appreciated that assessment of mental health uses a western understanding of mental health, and that this understanding may be very different in other cultures (45).

This difference in health outcomes associated with type of immigration has also been identified in the United Kingdom with those who arrive as asylum seekers having poorer health outcomes and this difference is maintained for over 20 years after arrival (42). Overall, after long periods in the new country, health outcomes for immigrants as a whole tend to merge towards the levels of the locally born population (33, 39, 42).

Acute Health Issues

The acute health issues faced by new immigrants are different to the long term health issues (46) and are similar to the local population, other than some predominance of infectious issues. Management of acute conditions after arrival is a fairly minor consideration as the immigrant population generally arrives healthy, and screening to prevent future poor health is of greater long-term significance. Conditions that pose an infectious risk to the general population in the host country have not been noted in significant numbers (46). This finding has been repeated in multiple studies across a number of developed countries. Amongst refugee populations rates of infectious diseases are higher than in the general population, however these also do not generally pose any significant health risk to the locally born population (47-50).

Over time after migration the health issues change, with infectious diseases becoming less problematic, and rates of other chronic conditions increasing with a change in lifestyle (51). This necessitates a change in the focus of healthcare management (29). The appropriate selection of screening tests and suitable chronic disease management represent important challenges in the management of refugees and immigrants who settle in developing countries such as Australia.

Screening

Prior to arrival in Australia immigrants are required to undergo health screening. The nature of this depends on the age of the applicant, the visa type and the country of origin. All require a general medical examination, and additional testing can include testing for HIV, Tuberculosis (TB), Hepatitis B and C, and Syphilis (52). (table 1 below)

Table 1: Pre Arrival Health Screening for Immigrants to Australia (52)	
Under 2 years	Medical examination
2 or more but under 11 years	Medical examination and a TB Screening test - either Tuberculin Skin Test (TST) or Interferon-Gamma Release Assay (IGRA) if from a higher risk country for tuberculosis or applying for a refugee or humanitarian type visa
11 or more but under 15 years	Medical examination and chest x-ray
15 or more years	Medical examination, chest x-ray and HIV test
Specific groups	**Additional tests**
People who intend to work as a doctor, dentist, nurse or paramedic	Hepatitis B and C test
15 years old or older and applying for an onshore protection visa	Hepatitis B and C tests, and syphilis test
15 years old or older and applying for a refugee visa	Syphilis test
Pregnant women	Hepatitis B test
Children for adoption	Hepatitis B test and HIV test

Those who are identified as having TB will require treatment before arrival, and any suspected of having possible latent TB disease will require follow-up after arrival (52). Other conditions may require follow-up after arrival or may prejudice the application (52), and in cases where the cost associated with these conditions is high immigration may be not possible. This cost criteria does not apply for those refugees who are accepted through the humanitarian program (52).

Comprehensive post arrival health screening is recommended for all refugees arriving in Australia, regardless of pre-migration screening (which may have been incomplete or occurred many months before departure). Other countries also have screening recommendations for refugees (53-56), (Comparison examples in table 2 below) and these are partially influenced by the presence or not of pre-arrival screening (57).

With the exception of follow-up of pre-immigration screening abnormalities, there is no specific recommendation in Australia for post arrival screening for non-refugee, immigrant groups.

Table 2: Post Arrival Refugee Screening recommendations			
Test	Australia (58)	Canada (54-56)	United States (53)
Medical Examination	yes	yes	yes
Immunisation check/update	yes	yes	yes
Full Blood Count (FBC)	yes	Women and children	yes
Mental health screening	Consider	Consider	Consider
Urinalysis	yes	Not routine	yes
Test for Latent Tuberculosis (Mantoux or IGRA)	yes	yes	yes
Chest X Ray	If not done before arrival and over 11 years old, or if mantoux or IGRA +ve	Not Routine	If not before arrival

Lead testing	Not Routine	Not Routine	Yes, if less than 16 years old
Stool sample for parasites	Either empiric helminthic treatment or stool sample	Not Routine	If did not have pre-arrival empiric helminthic treatment #
Malaria testing	If from malaria area	Only if symptoms	If from malaria area and did not have treatment #
Strongyloides serology	yes	If from South East Asia or Africa	Yes *
Schistosomiasis serology	If from endemic area	If from Sub-Saharan Africa	If from Sub-Saharan Africa *
Syphilis serology	If risk factors	Not routine	yes
Chlamydia urine PCR	If risk factors	Not routine	If risk factors
Gonorrhoea urine PCR	If risk factors	Not routine	If risk factors
Hepatitis B	yes	If from countries with prevalence over 2%	If from countries with prevalence over 2%
Hepatitis C	If from high prevalence country >3% or if risk factors	If from high prevalence countries >3%	If born between 1945 and 1965 or if risk factors
HIV testing	yes	If from countries with prevalence > 1%	yes
H.pylori testing	If high risk or symptoms	Not routine	Not routine
Hearing testing	yes	Not routine	Not routine
Vision Testing	yes	yes	Not routine
Screen for dental pain	yes	yes	Not routine
Diabetes	As per national guidelines	If over 35 years old	As per national guidelines
Pap Smear	As per national guidelines	Women if sexually active	As per national guidelines
Iron Deficiency	If risk factors	FBC in women of reproductive age	Not routine
Vitamin D	If risk factors	Not routine	Not routine
Vitamin B 12	If risk factors	Not routine	If risk factors

Refugees to the United States from Africa, the Middle East and Asia receive pre arrival albendazole and if from Sub-Saharan Africa also praziquantel and malaria treatment.

* Presumptive treatment rather than serology and follow up is also a recommended option

Refugees and immigrants will generally be in relatively good health at arrival and are unlikely to see healthcare screening as a priority due to the many competing priorities, including a safe and secure place to live, English language training, child education, and reuniting with family members. Good health at arrival is in some part due to screening processes that occurred prior to arrival (54, 59, 60), this includes both official screening processes, and for asylum seekers the fact that good health is often necessary to make the journey to the new country (60).

From the perspective of the health service provision however, screening is strongly recommended to prevent the later development of significant disease (53, 56, 61-63). This potential for late disease

manifestations is most problematic for the individual, however in the case of infectious diseases can also lead to transmission within the new country (62). The risk of this transmission is low but can rarely occur (64).

The appropriate screening of refugees after arrival in their new country has attracted considerable attention (62, 63). Guidelines exist both in Australia and internationally to assist clinicians with this (55, 56, 61-63, 65). These largely focus on infectious issues however more recent versions have also included screening recommendations for non-communicable disease (55, 56, 58). Between these guidelines there is considerable variability in the testing that is recommended (53, 55, 56, 58, 66) (Table 2).

The countries from which refugees have come continues to change, largely as a reflection of international conflicts that are driving refugee movements (3, 19). In the Australian context this has seen a shift from significant numbers of refugees from African backgrounds, to more from Middle Eastern backgrounds, and in recent years particularly from Syria (figure 1). The arrivals from Africa lead to a focus on infectious diseases screening and management, however in the arrivals from the Middle East this is less of an issue and the challenge of mental health is more problematic (67, 68). A screening program therefore needs to have the flexibility to be appropriate for people from a wide variety of backgrounds and with a wide variety of disease exposures. It also needs to remain relatively simple as it will be implemented by a diverse group of health practitioners across the country.

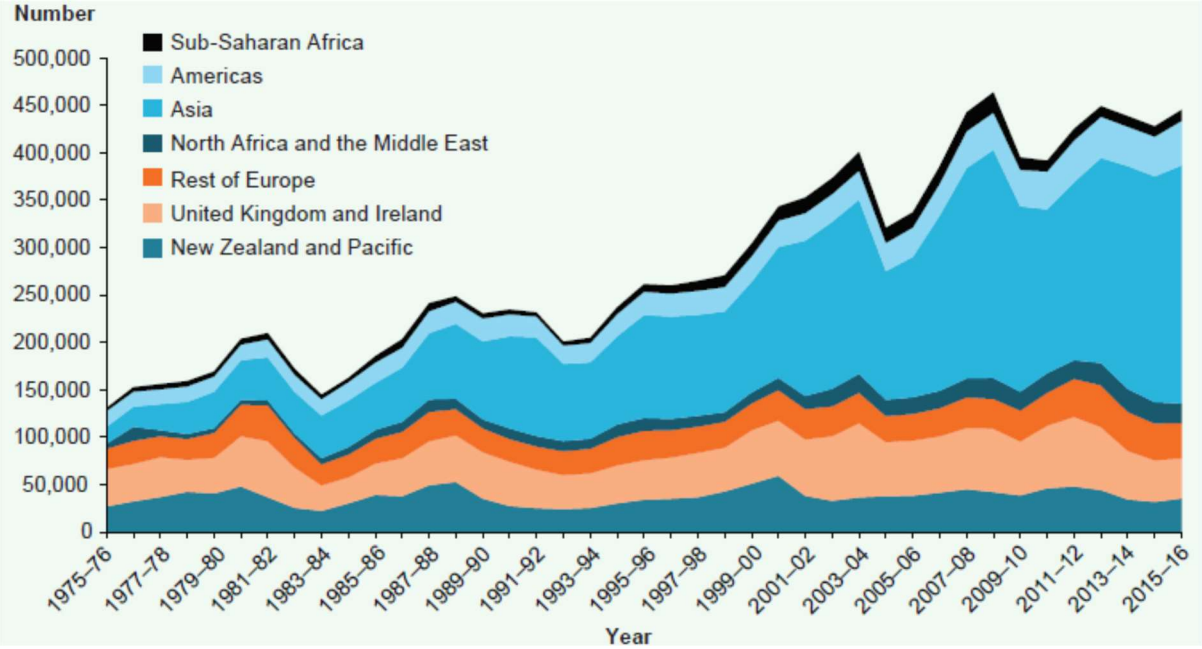

Figure 1 Migrant Arrivals to Australia by region of most recent residence AIHW 2018 (69)

Challenges

1) **Choosing what to screen for:**

Hepatitis C

Currently the Australian refugee health guidelines recommend a risk-based screening approach for Hepatitis C virus, with universal screening only for those from high prevalence countries (58). This is

slightly different to guidelines for the general Australian population that recommend screening for people who have risk factors for virus acquisition and also include screening for migrants from a range of countries (70, 71). This includes Africa and Asia, and hence includes the large majority of migrants to Australia from developing countries (72). The wide international variability in the rates of hepatitis C, (and also Hepatitis B and HIV) both between and within countries, and the fact that immigrants may not reflect the rate in their country of origin makes the development of appropriate recommendations challenging (73, 74).

Amongst the refugee and immigrant population, the rates of Hepatitis C are very variable and a recent review of migration to Europe has identified rates of between 2.2 – 5.6% amongst immigrants from Asia, Sub Saharan Africa and Eastern Europe (46) and an overall prevalence amongst immigrants of 1.9% (antibody prevalence) (73) which is higher than the prevalence in the Australian general population of 0.9% (estimated prevalence of those with virus) (75). In some European countries, estimates suggest that approximately 10% of the population with hepatitis C are foreign-born (74, 76). Much of the data that exists for hepatitis C is based on particular populations within countries and may well not represent the rate for the country as a whole (76, 77).

Successful hepatitis C screening programs for refugees have been implemented internationally, with previously unrecognised cases identified and effectively treated (78). However other reviews of migrant screening practices have indicated that a relatively small number of positive cases are detected and that a significant number of patients are subsequently lost to follow up (66) unless a comprehensive accessible system of care is in place. An additional consideration in recommending a screening program is the current very high cost of the treatment that is necessary (79). The appropriateness of screening therefore is determined by factors including baseline prevalence, and cost and effectiveness of treatment, that are changing rapidly (79, 80). Additionally the costs of morbidity associated with the disease need to be considered.

In the current Australian context it can be argued that Hepatitis C treatment is subsidised and universally available to all with the disease, and that it is very difficult to assess the real risk of individual migrants (72). The initial visit to the local doctor for refugee health screening represents a unique opportunity to engage this population who may have limited ongoing contact with the health system. A blood test is already being done and a pragmatic approach is to use this as opportunity to offer Hepatitis C screening.

Paper five that is discussed further in the telehealth section addresses methods to improve access to Hepatitis C care, especially in rural areas, and potentially reduce the number of patient's lost to follow up.

Screening for cancer

In addition to infectious disease screening, it also important to consider approaches to reduce the risk of developing chronic disease. This includes screening to reduce cancer morbidity and mortality. National recommendations suggest screening for a number of common cancers including breast cancer, cervical cancer and colon cancer, and it is appropriate that immigrants are encouraged to participate in these screening programs (71, 81).

Differences in health outcomes between migrants and locals have been noted when reviewing cancer morbidity and mortality, both internationally and in Australia (31, 82, 83) (28, 82, 84). Those cancers associated with infection, including gastric cancer, liver cancer and cervical cancer have higher rates of mortality amongst immigrants from developing countries (28, 82, 83). The majority of other common cancers, including breast, colon, prostate and lung cancer have lower rates of

detection and mortality (28, 31, 82, 83). Lung cancer rates however are very much determined by smoking rates, and Swedish and Australian studies showed higher rates of lung cancer amongst immigrants (83, 84), which may well reflect lower rates of smoking amongst the local population (38). Cervical cancer shows considerable variability in rates amongst immigrants, Hispanic immigrants to the United States have lower rates of cervical cancer compared to the native Caucasian population (82), although the mortality is higher, probably as a result of lower screening rates and later cancer detection. Immigrants to Sweden have also been shown to have higher rates of cervical cancer mortality (84).

These differences in cancer mortality remain when adjusted for gender and age of the populations (83) and socioeconomic status (31). The difference in outcomes does reduce with time after arrival, however Canadian research suggests it is 50 years before rates are similar to the local born population (31). Late cancer diagnosis can be problematic amongst immigrants, and this can lead to worse clinical outcomes (10, 82). It has been recognised that cancer screening rates are often lower amongst immigrant groups both in Australia and other developed countries (82, 85-87). With the example of bowel cancer screening, it has been demonstrated that the greatest risk for non-attendance at screening is amongst those from low-income countries (86). It is recognised that screening rates are lower in lower socio-economic areas which may be more likely to have higher levels of immigrants, however this study controlled for this and the effect amongst immigrants was still present (86).

There are a number of barriers to screening including poor health literacy, lack of education and understanding of the testing, cost (dependant on individual countries health systems), inconvenience, and in the case of breast and cervical cancer screening, the possibility that the treating doctor is a male (88, 89). For people of certain cultural and religious groups it would normally be unacceptable for a male doctor to provide these examinations in their countries of origin, and they may hence not attend male doctors in Australia for these examinations (90). This issue is particularly relevant in regional areas where the choice of treating doctor is often much more limited (91). It is recognised that with longer duration in the new country the rates of screening merged towards those of the resident population, possibly as people become more familiar with the process of medical care in their new country (85, 88).

Cancer and Infection

Recent reports from the International agency for research on Cancer suggest that worldwide in 2018 over 18 million new cases of cancer will be diagnosed (92) and it is expected that over 9.5 million people will die from cancer (92). The highest rates of cancer are in the developed world (92, 93) and in the developed world cancer is the most common cause of premature mortality (92). This is very different to the developing world were communicable diseases are much more problematic (92). Even amongst cancer diagnoses in the developing world, a much larger percentage, in some cases as high as 30% are associated with infection, whereas in developed countries this is less than 10% (94). Three cancers constitute the bulk of the burden of infection associated cancer. Cervical cancer caused by human papilloma virus (HPV), hepatocellular carcinoma (HCC) caused by hepatitis B and to a lesser degree hepatitis C, and *H. pylori* predisposing to gastric cancer (92, 95). Specific consideration therefore needs to be given to screening for these cancers in the immigrant population.

A recommendation for regular cervical cancer screening for all women is well defined and included in most countries health policies (96).

Hepatocellular carcinoma screening guidelines exist for those with hepatitis B, (and also with cirrhosis from other causes) (97, 98). These recommendations are clear and evidence based, and include high-risk groups with hepatitis B for whom cancer screening is strongly recommended (97, 99).

This should be performed in association with hepatitis B vaccination and treatment, which has been demonstrated in multiple reviews to be effective in reducing rates of infection and complications from hepatitis B (100).

Screening for liver cancer amongst immigrants is a two-stage process.

1) Initial screening for hepatitis B in those groups at risk of this infection
2) Screening those with Hepatitis B who are at high risk of developing a liver cancer.

The rate of development of liver cancer is much higher amongst those who have hepatitis B than in those who do not. Estimates suggest the relative risk of developing liver cancer is 15 to 20 times for those who have hepatitis B (101). This risk is particularly high amongst those who have cirrhosis and more than 80% of the cases of liver cancer occur in people who have cirrhosis (101).

Screening for H.pylori

A recommendation for screening to prevent the development of gastric cancer is much less clear. Gastric (stomach) cancer is a cause of approximately 1 million deaths internationally each year and is the third most common cause of cancer death worldwide (92). *H.pylori* is a leading cause of non-cardia, gastric cancer, and it is thought that 780 000 deaths are caused annually by *H.pylori* (92, 102). The bulk of gastric cancer occurs in the developing world (92) and hence migrants from the developing world represent a population for whom screening should be considered. Currently no clear guideline exists for this. Some screening guidelines have briefly commented on those from high *H.pylori* prevalence countries without being clear in recommending a screening strategy for migrants from such countries (103, 104).

Screening to prevent the development of gastric cancer can either be done as screening for *H.pylori* to potentially halt the progression to gastric cancer (105), or screening for gastric cancer itself which occurs in countries with high rates of gastric cancer such as Japan and Korea (106, 107).

Given the high rates of gastric cancer in the developing world, there exists the possibility of screening arrivals for *H.pylori* to potentially reduce this risk. This opportunity exists particularly amongst the refugee arrivals for whom screening for other infections is already occurring (58), who have been identified as a group with a high prevalence of infection (108), and has been suggested by some authors (109). The appropriateness of this screening is uncertain and the research reported in *paper one* was designed to address some of this uncertainty, particularly around the issues of costing.

Well-developed long-standing guidelines exist for assessing the appropriateness of screening programmes (110). These consider a number of possible conditions that need to be met for a program to be considered appropriate for implementation.

The case for consideration of *H.pylori* screening amongst immigrants to prevent cancer will be reviewed using the initial criteria for healthcare screening developed in 1968 (110). It should be recognised that some small modifications have been suggested to these criteria but that the core recommendations remain unchanged (111).

1. The condition sought should be an important health problem.

Gastric Cancer is the third most common cause of cancer death (92), and the prognosis from the time of diagnosis is poor (92). *H.pylori* and the associated inflammation are a key driver of the large bulk of this cancer (92, 102).

2. *There should be an accepted treatment for patients with recognized disease.*

Antibiotic treatment is effective at curing *H.pylori* and is widely available, although rates of antibiotic resistance to current first line therapies are increasing (104). Eradication of *H.pylori* has been associated with significant reductions in gastric cancer incidence in recent large meta-analyses (105, 112).

3. *Facilities for diagnosis and treatment should be available*.

Testing and treatment are widely available through non-specialist doctors and are relatively simple (113). The testing used is already well established and is also used for those with symptoms that are possibly caused by *H.pylori* (113).

4. *There should be a recognizable latent or early symptomatic stage.*

For *H.pylori* the time between contracting the infection and developing gastric cancer is generally more than 50 years (114). This allows a very considerable period for detection and eradication at a stage before significant disease progression has occurred. However it is recognised that once a significant level of histopathological change has occurred in the stomach lining, eradicating the H.pylori may not halt the progression to gastric cancer (115).

5*. There should be a suitable test or examination.*

H.pylori breath testing and stool antigen testing represent sensitive and specific tests for the detection of *H.pylori* infection although they are slightly more complicated than a blood test (116). The use of stool antigen testing may be more suitable in a paediatric context (116, 117). The use of serology is an easier alternative however the lack of specificity associated with a positive result means that this generally would not be a suitable test for a screening program (116).

6. *The test should be acceptable to the population.*

Testing with either a breath test or a stool antigen is not particularly invasive and breath testing is accepted for detection of *H.pylori* for other indications. Stool collection, whilst somewhat unpalatable, is readily accepted by patients in other contexts.

7. *The natural history of the condition, including development from latent to declared disease, should be adequately understood.*

A model has been described (118) that includes a number of histopathological changes in the lining of the stomach with progression from normal through to neoplasia. Evidence, both histopathological and from randomised trials supports this model (115, 119, 120).

8. There should be an agreed policy on whom to treat as patients.

Currently general agreement to screen those from high *H.pylori* prevalence populations exists, although the specific definition of high-prevalence populations lacks clarity. Implementation of a program of screening for immigrants from high-prevalence countries would require clearly defined high prevalence countries, and given the lack of prevalence data in many countries, and ongoing changes in prevalence, this remains a difficult task.

9*. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.*

Paper one looks to address this issue using costs associated with a screening program and using cancers prevented as a marker of program efficacy.

10. *Case-finding should be a continuing process and not a "once and for all" project.*

Implementation of a screening program would form part of immigrant screening and would be ongoing for new immigrants from high prevalence countries. Any individual however would be expected to only require a single screening episode. For refugee arrivals for whom post arrival screening is recommended this could form part of the current screening program. For other immigrant arrivals for whom currently post arrival screening is not universally recommended, this would require the implementation of an additional program to screen this group. The rates of reinfection in adults in the developed world are low, supporting the long term benefits of eradication (121).

This overview of the development of screening programs identifies the gaps in evidence that exist related to *H.pylori*. This led to the preparation of *paper one*, the cost effectiveness analysis which addresses this issue.

Beyond the selection of what to screen for, the next challenge becomes how to manage the conditions that have been identified as positive. This is particularly relevant for conditions that are chronic and will require lifelong management such as hepatitis B.

Hepatitis B Genotype

Hepatitis B is a considerable health problem amongst immigrants to the developed world. Many immigrants come from countries of medium and high hepatitis B prevalence (above 2%) (122, 123). In Europe in some countries almost all patients with hepatitis B are foreign born, which means that screening efforts should be very much targeted to this population (122). In Australia the large majority of newly identified cases of hepatitis B virus are amongst immigrants (124).

Amongst immigrants from sub-Saharan Africa high rates of hepatitis B have been identified, and refugees have been recognised as having higher rates of hepatitis B than the general immigrant population (123).

International and Australian guidelines for the management of hepatitis B outline when therapy is appropriate to be considered and what testing and screening is necessary (99, 125-127). Although these guidelines exist there is significant evidence in Australia to suggest that most people with hepatitis B are not receiving ideal management (128, 129). It is estimated only 62% of those with Hepatitis B have been diagnosed and only 15% are receiving management that is guideline concordant (129). This suggests considerable scope for improvement in the delivery of care.

The hepatitis B genotype is one of many determinants of the outcome of the disease (130). Hepatitis B genotype is not routinely tested for outside of research settings, as a knowledge of the genotype currently does not significantly alter the management of the disease. Current recommendations do not include a routine recommendation for genotype testing (99, 127).

Information about genotypic prevalence is very limited amongst the refugee and immigrant cohort, particularly in Australia. *Papers two* and *three* contribute to this with a focus on immigrants from Burma (Myanmar) and Africa. High rates of hepatitis B have been recognised in the immigrant populations from Burma and Africa in studies done in Australia and Internationally (50, 122, 131, 132).

Recent publications have raised concerns in the paediatric population that disease outcomes may vary depending on the genotype of hepatitis B (133). In the paediatric population the use of interferon as a treatment has differing success depending on genotype and in that setting a recommendation for genotype testing could be considered (133). Additional information about genotypic prevalence can assist with these decisions.

Challenges:

2) **Refugee and immigrant patient with chronic diseases requiring specialist management settle in rural and regional areas where these services are limited.**

The challenge of long-term chronic disease management is illustrated clearly in the example of hepatitis B. This is more difficult when patients live in regional areas with less access to specialists. This is the case both for the Australian born population but also for immigrants. Significant numbers of immigrant arrivals live in regional areas (19) and providing long-term chronic disease management for this patient group requires different approaches to the approaches that can be utilised in large cities.

In Australia one particularly successful example of regional settlement has been the Burmese settlement in the small town of Nhill in regional Victoria (134). In this town a local duck farmer required additional labour, and sought out the refugee community. Initially a small number moved to the town and over a period of some five years the local population has increased by nearly 10% due to Burmese arrivals to work, and their families. This has brought significant benefits to the town both economically and socially, and has been identified in external reviews as being successful by both the local, and immigrant communities (134).

This population was just one of the groups that highlighted the challenge of providing specialist care beyond large cities and stimulated the development of the telehealth program which is the focus for the next three papers (*papers four, five and six).*

Telehealth

Each year between 1500 and 2000 refugees (20) and about 30000 immigrants settle in rural Australia (18). Over 1 million people who live in rural Australia were born overseas (20). Health outcomes are worse in rural Australia (69) and access to health care including medical specialists is lower in regional areas, both in absolute terms and on a per capita basis (135).

The history of telehealth extends back over 100 years. Early examples included provision of medical advice to ships captains when passengers became unwell at sea, however recent years have seen much wider availability of the necessary technology (136). A clear definition has not always been agreed upon however the broadest definition includes any healthcare that is provided at a distance (137). The terms telehealth and telemedicine are essentially interchangeable (138).

This discussion of telehealth will focus only on examples of where a patient and a clinician conduct a consultation, the link includes both voice and video, and is occurring concurrently (called simultaneous or synchronous clinical consultations). This is the most common type of telehealth in Australia comprising 85% of telehealth programmes (139). Use of telehealth is rapidly expanding as the cost of using over the Internet-based technology decreases (138, 139). The largest change in the recent years is the significant reduction in the cost associated with this. Previously telehealth had required high cost stand-alone systems that had a very significant initial infrastructure cost and also required significant costs for ongoing maintenance and usage (136). Now the large majority of telehealth is conducted over the internet with much lower costs. Almost all computers and most handheld devices have an inbuilt microphone, speaker and camera and can potentially be used for telehealth. Internet data speeds continue to improve such that the quality of images that can be viewed over the Internet is now routinely of a level that is suitable for a medical consultation. Costs for both purchasing devices and usage of internet continue to fall as the speed of data processing increases (140) although some evidence exists that this continuous 50 year fall in costs is reaching an end (140).

Together these changes make telehealth much more accessible to a large number of patients. The most ambitious have suggested that over half of specialist consultations in rural Australia will be conducted by telehealth within ten years although this would require a large change in current practices to occur (141). The CoVID-19 pandemic has demonstrated that this is possible both for regional but also metropolitan based patients. A large Australian tertiary hospital has had a 2255% expansion of outpatient telehealth within a six week period in 2020 and now 28% of all outpatient appointments are provided using telehealth (142).

This increased access provides many opportunities for improving care amongst patients who are based beyond large cities. This development of technology has particular importance for refugee and immigrant populations as their health needs may well be more complex (19), and they may need more access to specialist care (19). Some Australian data suggest over 50% of refugee arrivals will require specialist consultation at some point in the post arrival period (19, 143). Telehealth is a possible solution to improving the quality of care available to immigrants (144, 145), and Australian recommendations also support expansion of this method of care access (19). Telehealth can save in travel time and cost which is often a deterrent to seeking health care for the refugee group (146). Telehealth also allows access to an interpreter where ever a person is located and can allow consultations to occur with only short breaks from the school or workplace (146). Telehealth may provide a more relaxing less threatening interaction than attending a hospital.

In a model where patients sit with the local general practitioner (GP) this can also provide an educational opportunity for these GPs.

A literature review of telehealth implementation has identified the need for two elements for a successful program. These are a collaborative partnership approach, and specialist consultation, (that includes financial remuneration) (145). An Australian systematic review of telehealth implementation suggested the key elements include "vision, ownership, adaptability, economics, efficiency and equipment" (139). Although the rates of Internet usage for migrant populations are slightly lower than for the general Australian population, rates of over 80% are occurring (147) and this continues to increase. It is recognised however that a knowledge of, and access to technology in this populations can still be a barrier to access to health care (148). Without support some migrants may not be able to access telehealth services. Most health services in rural and regional Australia also now have access to facilities to provide and support consultations via telehealth (139). This improved availability of telehealth along with ongoing significant settlement of immigrants in rural areas provided the impetus for the development of a telehealth program.

Paper four describes the development of a new telehealth program for refugees living in regional Victoria, including discussions of challenges faced, and solutions implemented. This paper describes the first year of the program that continues currently and has now had over 1000 appointments, and covers a broad range of infectious diseases. This program that commenced within one department has then expanded into a telehealth program that is now imbedded across most outpatient departments at a major tertiary hospital (149).

Is telehealth safe and effective?

Many studies have demonstrated benefits in cost effectiveness and patient satisfaction with telehealth programs, however research demonstrating good clinical outcomes is limited (139, 150). With new technology unintended consequences can occur, and the long-term impact of telehealth on doctor-patient relationships remains uncertain (145, 151). An international panel of experts has raised a list of possible unintended consequences with telehealth. This includes the constantly changing technology requiring ongoing training and education, possible provision of clinical care with sub-optimal levels of clinical information, and the fact that telehealth systems may not link well with other health care records. These barriers are not insurmountable but those who are actively using telehealth should be aware of these considerations (152).

Recently studies have demonstrated the clinical effectiveness of telehealth programs. A recent randomised trial of heart failure management in which the patients randomised to the telehealth care had significantly less episodes of heart failure than those in the standard of care arm although the telehealth group did have a greater total number of episodes of care (153). Studies that have used telehealth to support local practitioners to manage patients with hepatitis C have demonstrated excellent clinical outcomes (154). A meta-analysis of studies to improve the control of diabetes has shown that overall level of diabetes control assessed using glycosylated haemoglobin is lower in patients who had telehealth management (155). A meta-analysis of various interventions that included telehealth to improve asthma control has identified significantly better asthma control amongst those who had telehealth interventions in combination with case management, although in studies without case management, achievements were achieved only in perceived quality of life, and not in asthma control (156). A study of renal patients managed using telehealth, identified similar outcomes to on-site management, using a composite endpoint of death, progression to end-stage renal disease, and worsening of creatinine. Patients also had higher rates of clinical attendance and lower costs associated with this attendance (157). Use of telehealth to provide acute stroke care has demonstrated similar outcomes in terms of mortality and intracerebral haemorrhage between on-

site management and telehealth. In addition the time to achieving thrombolysis has been significantly reduced with the use of telehealth (158). A cluster randomised trial found that telehealth interventions for the management of diabetic foot ulcers were not inferior to on-site care and the telehealth managed group in fact had a lower rate of amputations (159).

Most trials looking at clinical endpoints have tended to demonstrate benefits related to telehealth however this has not been the case in all trials. A Danish randomised trial looking at diabetic foot monitoring had significantly higher mortality amongst the telehealth arm, although a clear reason for this was not identified (160). This higher mortality has not been seen in other studies (161) but is concerning and is a reminder of the need to proceed cautiously with new methods of care.

A review of the telehealth literature focussing on clinical effectiveness recommends that for monitoring of chronic conditions, communication and counselling about chronic conditions, and for psychotherapy for behavioural health there is adequate evidence of benefit, and that efforts should now focus on implementation (161).

Paper five examines the implementation of a treatment program for hepatitis C in patients living in regional Victoria, focussing particularly on the clinical cure rates achieved. The aim of this paper is to provide reassurance to those who are considering managing Hepatitis C using telehealth that this can be done safely and with clinical outcomes that are comparable to those achieved with onsite care.

Interpreters

In recent years the majority of new immigrants to Australia have come from non-English-speaking countries, and a significant proportion of the Australian population do not speak English at home (9, 15, 69). English language competency is necessary for skilled migrants to Australia, however humanitarian arrivals and the families of skilled migrants are not required to achieve English competency before a visa is granted (15). It is these groups of migrants who often have low English-language proficiency and require professional interpreters (13).

Lack of English Proficiency is associated with poor health outcomes including hospital readmissions (162, 163). Long term health outcomes have been recognised to be worse for immigrants who do not develop English language competency (43). For refugees in Australia surveys have identified that lack of access to interpreters in a timely manner is a major barrier to access to healthcare (164) and reviews of care models have also identified this as a barrier (90).

Interpreters are necessary in health care to improve quality of care and to meet legislative requirements (165, 166). Systematic reviews have shown improved clinical care across a number of clinical areas with the use of professional interpreters (167). It has been demonstrated that the use of professional interpreters is associated with significantly reduced length of hospital stay and a reduced readmission rate (168), and it has been identified that one of the key barriers to providing high-quality care for refugee and immigrant arrivals is the lack of access to interpreter services (144).

Guidelines recommend the use of interpreters for all medical consultations when lack of language competence makes this necessary and this is a legal requirement in many jurisdictions (166, 169, 170). The requirement for access to healthcare in an appropriate language is included in the Australian charter of healthcare rights (171). In the United States ensuring access to services for people with limited English proficiency is part of the Civil Rights Act (166, 172). It has been argued

that there is a moral imperative to provide an interpreter in an appropriate language if a clinician intends to provide the best health care for their patients (173).

Despite this it is well recognised that interpreters are not always provided when indicated and that improving access to interpreters is one way to address this (174). Australian research looking at utilisation of the free interpreter service by General Practitioner's suggests that as few as 1.6% of consultations for patients with low English proficiency utilise a professional interpreter (174), and that lack of access to interpreter's is associated with lower levels of access to care (175). A recent study in Emergency Departments in the United States estimated 85% of the need for interpreters was not met (176).

One way to potentially improve access to interpreters is through the use of videoconferencing (177). This is particularly useful in regional Australia where access to interpreters can be the most problematic (174, 175, 178). Recent work has demonstrated that videoconferencing for access to interpreters has higher rates of comprehension and understanding of the diagnosis compared to telephone interpreting (167). Local studies of maternal and child nurses in regional Victoria have identified telephone interpretation as problematic and recommended interpreting via videoconference as a possible solution (179).

A randomised trial looking at treatment of Chinese immigrants with depression has found that a program based on telehealth and supportive care provides effective treatment. This randomised trial used bilingual clinicians and hence avoided the need for interpreters as over 90% of the patients only spoke their native language (180). A randomised trial in this area is uncommon, and this has demonstrated that a cohort of non-English speaking patients who receive treatment via telehealth from bilingual doctors achieve good clinical outcomes. Although these patients and the treating clinicians lived in larger cities, the benefit of telehealth to this cohort was to increase their access to a pool of bilingual specialists that would not otherwise be readily available (180). Another pragmatic randomised trial comparing videoconferencing to telephone using Spanish interpreters in a paediatric emergency department has identified significantly better parent comprehension with the use of videoconferencing (181). This was done using parent surveys assessing comprehension in the week following the emergency department visit. A study of the change from the use of onsite and telephone interpreters to wider access to interpreters by using videoconference in the Emergency Department, showed reductions in length of stay and numbers of tests ordered. These changes however were also seen amongst English speakers over the same time period so may be caused by other unmeasured factors (182).

The refugee population is particularly challenging for interpreter provision as they may be from small language groups or languages that are not otherwise commonly spoken in Australia (174). The availability of interpreters from these languages may be very limited. This can be complicated as the limited pool of interpreters may be from the same small ethnic community, potentially increasing privacy concerns, both real and perceived (183). A small study of interpreters has identified that refugee patients provide additional challenges for the interpreters due to complex health needs and a need to develop trust with the interpreter (184). In addition the interpreters can experience a degree of trauma due to the traumatic nature of experiences they have to interpret and the possibility that they have also previously experienced similar trauma (184). Interpreters can also have an un-official also role as a cultural mediator particularly for refugee patients (184). Whilst this can assist the patient to navigate the complexities of the health system it can lead to a blurring of boundaries regarding the independence of the interpreter. Interpreters have recognised that overall

onsite interpreting was preferred to use of telephone, however telephone interpreting offers a degree of anonymity that was preferred by some refugee patients (184).

Victorian recommendations on improving interpreter services recommend expanded access to interpreters via videoconference (174). This can both improve access to care but also reduce health care costs. The cost of interpreters in health care is significant, however for hospital inpatient's, reductions in the length of hospital stay can potentially offset this cost (168, 174). The use of interpreters accessed via videoconference also has the potential to lower costs when compared to onsite. This has been demonstrated in California using sharing videoconferencing of interpreters across a network of hospitals (173).

This lack of access to interpreters is what led to the trial of providing access to interpreters via videoconference outlined in *paper six*. This is different to other trials of accessing video interpreters, as the interpreters used were from a range of languages. This is the reality of health care provision in Australia where immigrants are from a wide range of countries and language groups, and a large range of interpreters need to be available (90, 174). This is different to the United States where most experience exists with the use of videoconferencing of interpreters and the bulk of interpreting work is in Spanish (173, 181). When the range of language of interpreters required is small it is much less logistically challenging to be able to access an interpreter in the desired language, particularly at short notice, either onsite or via videoconference. The costs associated are also much lower when compared to less frequently used languages (173).

Paper six compares the use of interpreters via videoconference with the provision of interpreters both onsite and via telephone and offers valuable insights into the preferences of both patients and clinicians. This supports the further development of services that can embed access to interpreters via videoconference. It is thought that the greatest advantage of this would be for refugee patients based in regional areas where access to interpreters is most difficult.

This research has been subsequently included in systematic reviews of the use of videoconferencing (185). The findings have been used to develop a program of access to interpreters via videoconference at the Royal Melbourne Hospital that is now embedded as a part of outpatient care, and potentially available for most outpatient consultations. During the 2020 CoVID-19 pandemic this programme has proven very effective for the delivery of interpreter services during periods of social isolation and distancing.

Challenges

3) Australians living in regional areas have worse health outcomes

Rural Australians

Rural Australia is considered to be all the areas that are beyond the major cities and can be divided into regional areas, including both inner and outer regional areas, remote and very remote areas (69), using the Australian standard geographical classification (ASGC) remoteness area structure developed by the Australian Bureau of Statistics (ABS)(appendix 1) (186, 187). Approximately 30% of Australians live outside major cities (69) (figure 2). Often however the term regional is used to indicate all areas beyond capital cities, not only regional areas covered by the specific ABS classifications (19). This discussion will consider issues that apply to all areas that are not

metropolitan, however differences exist between the challenges in regional areas and more remote areas. Remote areas have higher rates of indigenous populations, and isolation and poor access to services are more problematic (188).

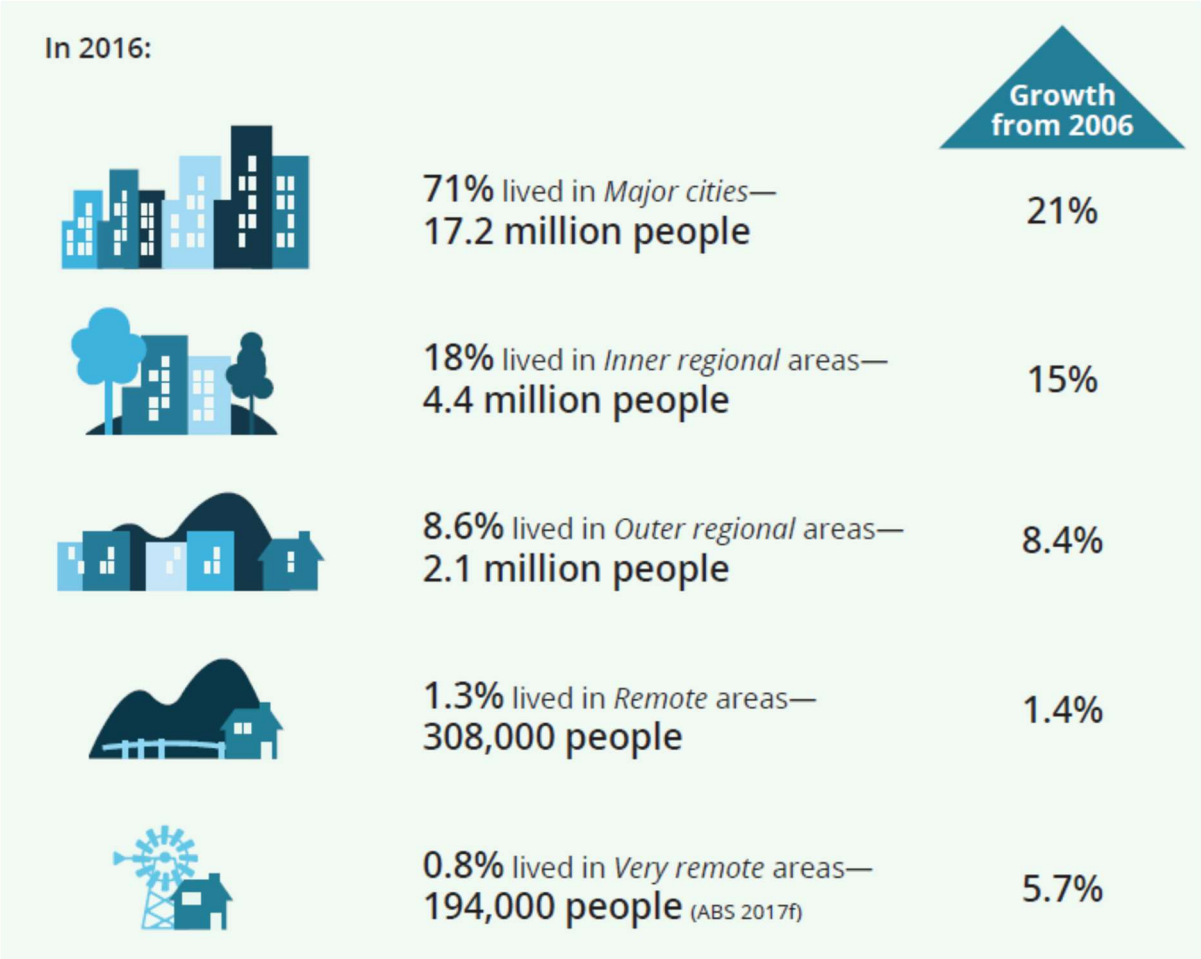

Figure 2: Where the Australian population lives and how this is changing, AIHW 2018 (69)

As previously described a significant number of refugee and immigrant arrivals to Australia settle in regional but also in remote areas (19, 22). This also occurs in many other developed countries and often policies have been implemented specifically to encourage this (16). This can be driven by the availability of work for skilled professionals that may not be accessible in metropolitan areas, and the availability of work that is not preferred by the local population such as low paid work in agriculture and food processing (20).

Settlement of refugees and immigrants in rural Australia has been occurring in significant numbers since the end of the Second World War. One of Australia's largest infrastructure developments, the Snowy Mountains Scheme, was built over a period of 25 years starting in 1949, and two thirds of the 100,000 workers were immigrants from over 30 different countries (189). Australian reports have looked at what contributes to successful regional settlement for the refugee population (175, 190, 191). Factors identified include access to employment and training opportunities , the availability of housing, the support and goodwill of the host community (190), and the availability of settlement services and suitable infrastructure (191).

Rural Australia is currently experiencing considerable shifts in population. Coastal areas are experiencing growth of an often older population, and many smaller inland towns having declining populations (20). The most recent census suggested that in many parts of rural Australia the population would actually be shrinking without the arrival of migrant groups (22). Figure 3 shows the change in population in different local government areas. The areas of considerable interest are in light yellow, covering a large geographic area, and are areas where the locally born population is decreasing and the overseas born population is increasing. Much of Australia's overall population growth is in the capital cities and in Victoria almost all population growth is in Melbourne or adjacent areas whilst population decline has occurred in non-coastal areas (18, 192). (figure 3)

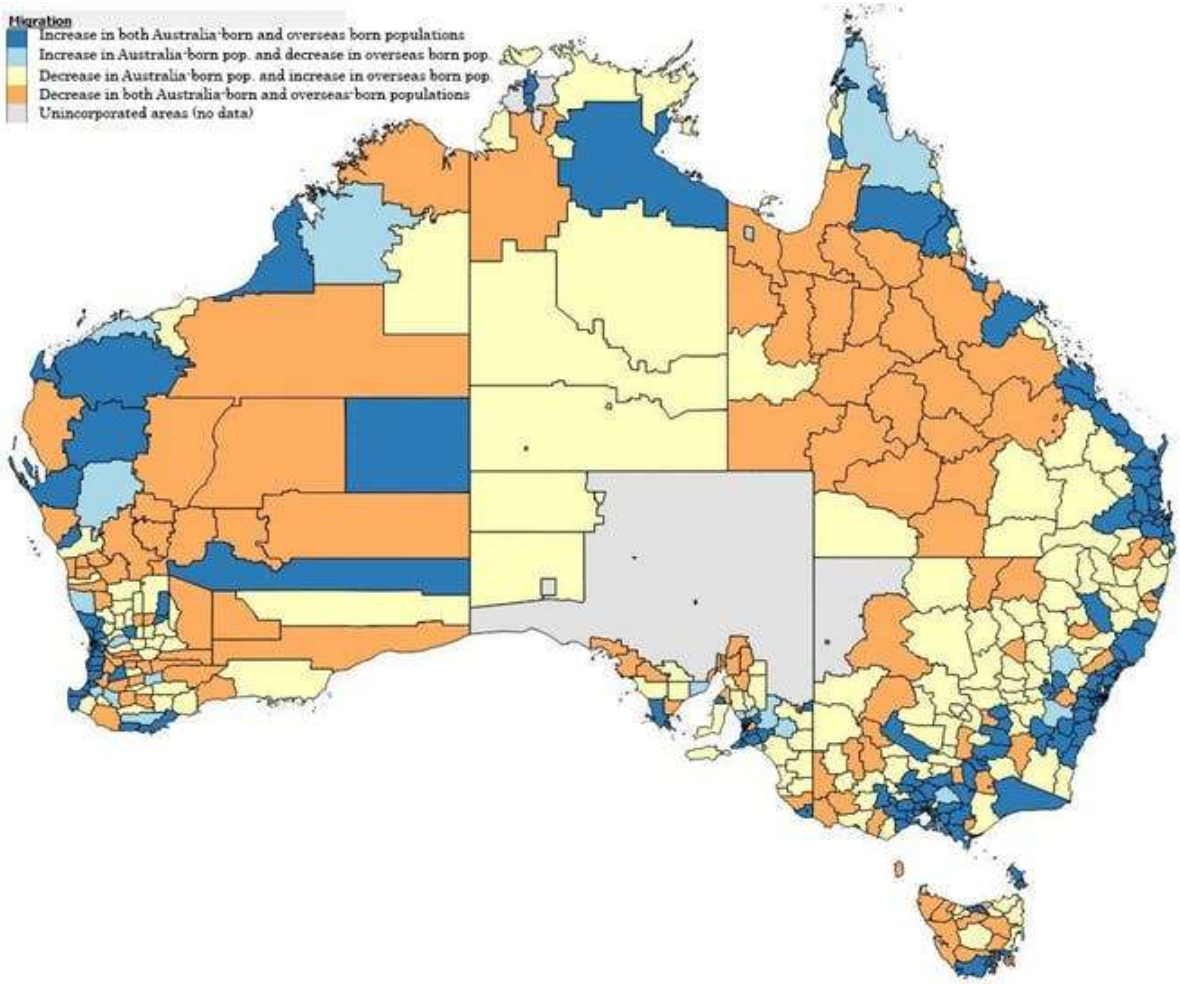

Figure 3: Impact of migration on the population of Regional Australia (Figure from the Regional Australia Institute based on Australian Census figures from 2011 and 2016)

Health of immigrants in regional areas

The average age of the overseas born population in Australia is higher than the local born population, and more are over 65 years old (19% compared with 12 % (193)). This is a reflection of Australia's long history of being an immigrant country, that most people migrate as adults and that many migrants have now lived in Australia for long periods of their lives. As people age, their health care needs increase which highlights the importance of ensuring that overseas born Australians in regional areas are able to access health care.

Overall residents of regional areas have higher cancer screening rates than urban residents, (87, 194, 195) although this may not be the case in more remote areas (194). This is also true for the overseas born population living in regional Australia with studies demonstrating screening rates for bowel, breast and prostate cancer that are higher than for overseas born urban residents (87) although this may not hold true for prostate cancer (196). The rate of screening however is higher for Australian born than for overseas born residents of both regional Australia and urban areas (87). Amongst the refugees who settle in regional Australia a post arrival screening programme using local general practitioners has successfully achieved good attendance and completion rates (197).

Worse healthcare outcomes in rural and remote Australia

Healthcare outcomes in regional Australia are significantly worse than in major cities (69). Those living in regional Australia have higher rates of smoking, higher rates of excess alcohol consumption, higher rates of obesity, and lower levels of physical activity (69). This difference is more pronounced in remote areas (69). People living in remote areas have an age-adjusted death rate 1.5 times higher than those living in cities, and a considerable amount of this excess death rate is due to preventable causes of death (69). Life expectancy is lower in regional and remote areas compared to major cities with an increasing gap in the most remote areas, most starkly a 15 years difference in life expectancy (82 years v 67 years) exists between those living in very remote areas and those living in major cities.

Considerable social differences exist between these populations, with much higher rates of tertiary education in major cities, and much higher rates of the Indigenous population living in remote areas (69). The non-metropolitan population is older, the median age of the population in regional and remote Victoria and NSW being 43 years , compared to 36 years in Melbourne and Sydney (198). Provision of health care is also different with less specialists (91, 135) and allied health professionals, both in absolute terms and on a per capita basis working in regional and remote Australia, and more hospital presentations for possibly preventable health conditions (69). Other differences in health care outcomes in regional Victoria include more emergency department admissions, more malignant cancers, poorer dental hygiene and more unintentional injuries (192). Significant differences exist in cancer mortality between urban and regional Australians with large numbers of preventable cancer deaths identified, particularly amongst males (199).

The Australian Atlas of healthcare variation which looks specifically at the differences in health care by region has noted higher rates of hospital admissions for a number of common conditions in regional areas, in particular in outer regional and remote areas. These conditions include cellulitis, chronic obstructive airways disease (COAD), urinary tract infections, complications of diabetes, and heart failure (200). Some conditions such as Hepatitis C are identified at higher rates in regional areas however the rates of treatment are significantly lower (201).

Less access to high quality treatment

The difference in treatment appropriateness and clinical outcomes has been identified across many conditions in regional Australia and is concerning. It is very difficult to justify why treatment and outcome should be different based on the patient's postcode (table 3)(69). The included table focuses only on the differences in treatment appropriateness and clinical outcome for common medical conditions in Australia in adults, reported during the last decade. This does not include differences in psychological and mental health outcomes and studies focussing only on indigenous health outcomes are not included. These studies show significantly worse outcomes for cancer care, heart conditions, infectious diseases and a range of chronic medical conditions in regional and

remote areas (table 3). Together these studies demonstrate a very significant difference in health outcomes, and these differences remain despite multiple adjustments within the studies to attempt to remove confounding variable that were thought to be possibly significant. These outcome differences have been recognised for many years and demand thoughtful responses, as issues may not be the same in all regional areas (202, 203).

Table 3. Management and outcome differences in rural and remote Australia

Area of Healthcare	Outcome	Quantitation	Reference
Infectious Diseases	Less appropriate antibiotic use	Inappropriate endocarditis prescribing in regional and remote compared to urban hospitals 8.2% v 2.7%	Bishop 2019 (204)
Infectious Diseases	Less appropriate Sepsis prescribing	Inappropriate prescribing for gram positive sepsis in regional and remote compared to urban hospitals 12% v 6%, Inappropriate empiric sepsis treatment 26% v 12%	Bishop 2019 (204)
Hepatitis C Treatment	Lower rate of starting Hepatitis C treatment	Rate of starting treatment is significantly lower for regional and remote areas compared to urban (outer regional areas rate of 0.58 compared to cities)	Scott 2018 (201)
All Cancers	Excess deaths in rural Australia (2001 – 2010)	Estimated 8878 extra deaths in rural areas over 10 years. Age standardised mortality rate of 1.11 for men and 1.07 for women.	Coory 2013 (199)
5 main cancers (Breast, Colon, Lung, Ovarian and rectal)	Significantly worse survival in all 5 cancers	Lower 5 year survival for 5 common cancers in rural areas in NSW (increased HR of death)	Chen 2015 (205)
Oncology (Breast)	More mastectomy, less radiotherapy	OR 1.66 if over 100km from a radiotherapy centre	Collins 2017 (206)
Oncology (Breast)	Longer interval between symptoms Longer delay between mammogram and diagnosis	OR 1.50 for outer regional areas and 2.46 for remote areas OR 1.71 inner regional, 4.17 for outer regional and 3.62 for remote areas	Youl 2016 (207)
Oncology (Prostate)	Worse 5 years survival	87.7% vs 91.4% in rural areas compared to urban areas	Baade 2011 (196)
Oncology (Bowel)	Worse survival and less patients receive optimal clinical management	Systematic review of 43 papers showed poorer outcomes in regional, rural, and remote areas	Ireland 2017 (208)

Oncology (Bowel)	Worse survival	HR 1.35 for death in stages A – C cancer in remote areas of South Australia in multivariate analysis	Beckmann 2016 (209)
Oncology (Neuroendocrine tumours)	Lower median survival	Survival of 1613 v 2935 days comparing remote location with large regional centres	Hafeez 2017 (210)
Haematology (lymphoma)	Worse 5 year survival of patients with diffuse large B cell lymphoma	HR for death of 1.14 in multivariate analysis of patients in rural Qld compared to urban areas	Wright 2018 (211)
6 main chronic diseases (Diabetes, Ischaemic heart disease, stroke, hypertension, airways disease, renal disease)	Higher mortality correlated with increasing remoteness	RR of death in very remote areas 1.6 times cities, for other rural areas RR of 1.3, 1.4 and 1.5 compared to cities with increasing remoteness	Chondur 2014 (212)
Cardiovascular Mortality	Higher mortality	MRR of 1.03 – 1.15 in regional and remote areas after adjusting for socio-economic status compared to metropolitan areas	Jacobs 2018 (213)
Acute Myocardial Infarct (AMI)	More myocardial infarcts and an increasing rate	Between 1996 – 2013 a 28% reduction in AMI in urban areas but an 8% increase in regional areas of NSW	Davies 2017 (214)
Ischaemic Heart Disease (IHD)	Systematic review of studies of IHD outcomes	All seven studies measuring IHD mortality showed higher rates in non-urban areas	Alston 2017 (215)
Heart Failure	Higher 30 day and 1 year mortality	Adjusted OR of death at 30 days 1.25 and HR of death at 1 year 1.13 between urban and rural in WA	Teng 2013 (216)

- HR = Hazard Ratio
- RR = Relative Risk
- OR = Odds ratio
- MRR = Mortality risk ratio
- Results included meet statistical significance of at least 0.05.

Not all health outcomes are worse in rural areas. Recent studies looking at the use of anticoagulants have shown similar usage rates across different areas of remoteness. Newer medications that require less monitoring are experiencing good uptake in remote areas (217). A study of palliative care in rural Australia has identified similar levels of access and minimal differences in care (218), and a study of heart failure outcomes has not identified worse outcomes (219). A study of dialysis in non-indigenous populations has identified higher rates of peritoneal dialysis in patients with increasing levels of remoteness, but no difference in the mortality within the patients on peritoneal dialysis, (220) suggesting this may be a suitable choice for patients in areas that have less access to haemodialysis.

The subsequent papers outlining the development of the telehealth program (*paper 4*), an assessment of the quality of clinical outcomes delivered via the telehealth program (*paper 5*) and the use of this to improve access to interpreters (*paper 6*), can contribute to the solutions to regional health outcomes. The solutions that can be implemented for refugees and immigrants in regional Australia may also be applicable to the local population.

Summary of Challenges

Australia is a country with a long history of migration and this continues with new arrivals from many different countries every year. The majority of these arrivals are skilled immigrants and their families but there is also a significant number of refugees arriving annually.

When refugees and immigrants arrive, they will bring different health challenges to the local population. It is important to consider what conditions to screen for and how to manage the health conditions that are more prevalent amongst migrants.

A significant number of immigrant arrivals will settle outside the major cities where it is well recognised that health care outcomes are worse and the availability of health services is less.

It is necessary to consider how to provide high quality healthcare to the refugees and immigrants who settle in rural Australia.

The subsequent research papers contribute to addressing these challenges.

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PLOS ONE

Using Stool Antigen to Screen for *Helicobacter pylori* in Immigrants and Refugees from High Prevalence Countries Is Relatively Cost Effective in Reducing the Burden of Gastric Cancer and Peptic Ulceration

Thomas R. Schulz[1,2], Emma S. McBryde[1,2,4], Karin Leder[1,3], Beverley-Ann Biggs[1,2]*

1 Victorian Infectious Diseases Service, Royal Melbourne Hospital, Parkville, Victoria, Australia, **2** Department of Medicine, University of Melbourne, at the Doherty Institute, Melbourne, Victoria, Australia, **3** Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, Victoria, Australia, **4** Centre for Population Health, Burnet Institute Prahran, Victoria, Australia

Abstract

Objectives: Refugees and immigrants from developing countries settling in industrialised countries have a high prevalence of *Helicobacter pylori* (*H. pylori*). Screening these groups for *H. pylori* and use of eradication therapy to reduce the future burden of gastric cancer and peptic ulcer disease is not currently recommended in most countries. We investigated whether a screening and eradication approach would be cost effective in high prevalence populations.

Methods: Nine different screening and follow-up strategies for asymptomatic immigrants from high *H. pylori* prevalence areas were compared with the current approach of no screening. Cost effectiveness comparisons assumed population prevalence's of *H. pylori* of 25%, 50% or 75%. The main outcome measure was the net cost for each cancer prevented for each strategy. Total costs of each strategy and net costs including savings from reductions in ulcers and gastric cancer were also calculated.

Results: Stool antigen testing with repeat testing after treatment was the most cost effective approach relative to others, for each prevalence value. The net cost per cancer prevented with this strategy was US$111,800 (assuming 75% prevalence), $132,300 (50%) and $193,900 (25%). A test and treat strategy using stool antigen remained relatively cost effective, even when the prevalence was 25%.

Conclusions: *H. pylori* screening and eradication can be an effective strategy for reducing rates of gastric cancer and peptic ulcers in high prevalence populations and our data suggest that use of stool antigen testing is the most cost effective approach.

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* Email: babiggs@unimelb.edu.au

Introduction

Estimates suggest that half of the world's population is infected with *H. pylori*. Sero-prevalence studies in lower and middle income countries show rates of exposure above 80% [1]. *H. pylori* infection is usually acquired in childhood [1]. Colonisation persists for decades and is potentially lifelong, leading to chronic gastrointestinal inflammation, and stomach and duodenal ulcers.

H. pylori is also a major causative agent in the development of gastric cancer [1], and cancer occurs in 0.1–3% of those chronically infected [1]. Gastric cancer is the second most common cause of cancer death worldwide leading to 736,000 deaths annually [2], including 11000 in the United States [3]. The mean 5 year net cost of a patient with gastric cancer is over $50000 [4], and the five year survival rate is less than 20% [5]. Eradication of *H. pylori* has been shown to reduce progression to precancerous changes in the stomach [6], and to reduce the risk of developing gastric cancer by approximately one third [7].

Refugees and immigrants settling in western countries often have high rates of *H. pylori* infection (72–93%) [8,9], as compared to the local population [8]. In Canada, overseas birth and immigration after 20 years of age were both shown to be risk factors for *H. pylori* infection [10]. Mexico, the largest source country for US immigration, has an *H. pylori* prevalence of 60% in serological surveys of 20 year olds [11]. More than 80% of African refugee children in Australia have positive stool antigen tests on arrival [9].

Approximately 12.5% (38.5 million) of the US population were born overseas, of whom 85% come from low or middle income countries [12]. Currently, neither *H. pylori* nor gastric cancer

screening are recommended for this group if asymptomatic, with most guidelines recommending testing based on symptoms. However, it is recognised that detection based on symptoms can miss a significant burden of *H. pylori* infection [8] and gastric cancer [13].

A number of testing modalities exist for the detection of *H. pylori*. Serology is widely available and has a sensitivity of 92% (25% IQR 85–96%) and specificity of 83% (25% IQR 73–92%) depending on the test kit used [14]. Antibody levels decline slowly after eradication of *H. pylori* infection so a positive serology result may reflect past rather than current infection. Stool antigen testing is relatively inexpensive, monoclonal enzyme immunoassay (EIA) testing has a sensitivity of 94% (95% CI 93–95%) and specificity of 97% (95% CI 96–98%) [15]. Breath testing is a rapid, non-invasive test with a high sensitivity (95%) and specificity (98%) but is more expensive [16]. Gastroscopy with biopsy and culture remains the gold standard for *H. pylori* detection but is costly and more logistically challenging.

In this study we hypothesized that screening for and eradication of *H. pylori* in high prevalence populations would be cost-effective. Our objectives were to model the effect of various *H. pylori* screening strategies on the incidence of gastric cancer and ulcer disease in populations with different prevalence's of infection, and to compare the relative cost-effectiveness of each strategy (including savings accrued through prevention of gastric cancer and reduced burden of ulcer disease).

Methods

Costs of test and treat strategies were compared to no screening and to empiric treatment strategies, both of which require no testing. Nine different screening and follow-up strategies were investigated (Figure 1).The empiric treatment approach was included as a comparator and may have a role in very high prevalence populations.

Costs were calculated as total costs for each strategy and benefit as the total cost of the outcome prevented. Primary benefits were the prevention of gastric cancer and the prevention of peptic ulcer disease, compared to no screening or treatment. Net costs were total costs minus savings accrued due to benefits of screening (ulcers and gastric cancers prevented).

The likelihood of a particular testing outcome was based on sensitivity and specificity values for the tests used (Table 1). Models were developed using decision analysis trees with the endpoints being total and net cost of the strategy and number of gastric cancers and ulcers prevented. Costs and treatment efficacy were based on published estimates (Table 1 & 2).

Each model included the cost of the physician visits, which were assumed to be only for *H. pylori* management and not as part of other care or screening. It was assumed tests or empiric treatment (with a proton pump inhibitor (PPI), clarithromycin and amoxicillin), would be ordered during this initial visit. Strategies with a single time-point for testing were assumed to require up to two physician visits, with the second visit being needed only for those who required treatment because of positive testing. Strategies involving retesting were assumed to require up to three physician visits. Non-medical and indirect costs were not included, in keeping with other comparable modelling papers [5]. While a small proportion of individuals remain *H. pylori* positive after two courses of treatment, (the second course of treatment with PPI, bismuth, tetracycline and metronidazole) and require subsequent further testing and treatment, this scenario was not included. It is recognized that certain strains of *H. pylori* have higher risk of progression to gastric cancer [17]. As immigrants arrive from a multitude of countries from which strain prevalence varies or is not known, a standard risk of progression to cancer was used.

Costs were calculated in US dollars for 2011. Costs from earlier years were adjusted for inflation to bring them to 2011 values (Table 2). Analyses were performed for each strategy at three prevalence values (25%, 50% and 75%) with net costs per cancer prevented calculated for each strategy (Table 3). Total costs and numbers of cancers and ulcers prevented with each strategy (expressed per 1000 patients managed) were also calculated (Table 4).

Sensitivity analysis was performed on the most cost-effective strategy in the initial analysis (stool testing with retesting of those treated). The outcome measure of interest was the net cost per

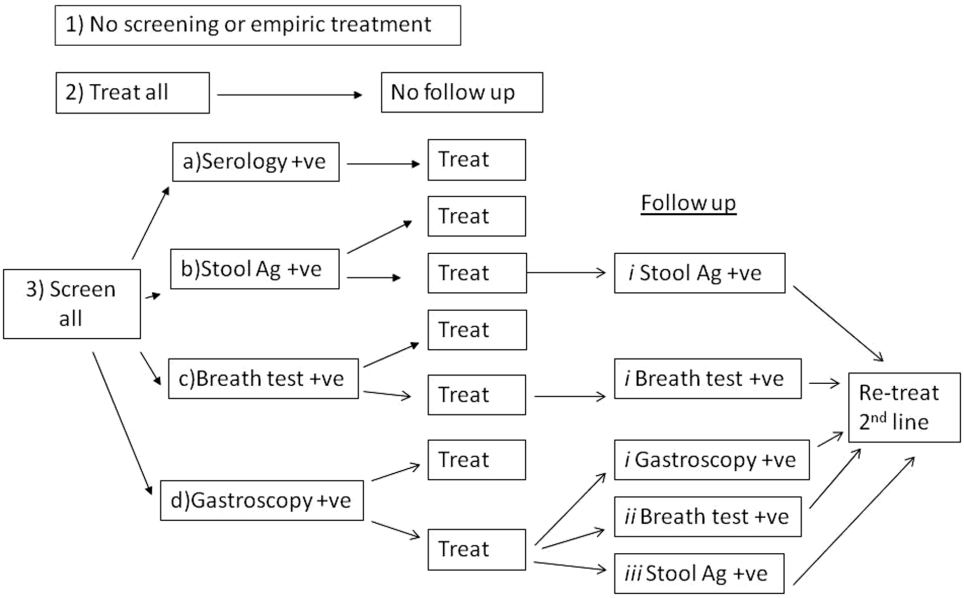

Figure 1. *H. pylori* management strategies included in the analysis.
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Table 1. Testing and treatment parameters used including estimated ranges around each parameter.

Parameter	*Best estimate*	*Lower range*	*Upper range*	*Distribution*	*Reference*
Testing for *H.pylori*					
Breath test					
Sensitivity (%)	95.3	92.2	97.5	95%CI[a]	[16]
Specificity (%)	97.7	94.8	99.3	95%CI	[16]
Serology					
Sensitivity (%)	92	85	96	IQR[b]	[14]
Specificity (%)	83	73	92	IQR	[14]
Stool Antigen					
Sensitivity (%)	94	93	95	95%CI	[15]
Specificity (%)	97	96	98	95%CI	[15]
Gastroscopy with biopsy					
Sensitivity (%)	95	90	99		[36]
Specificity (%)	99	95	100		[36]
Treatment of *H. pylori*					
HP7 efficacy	77%	27%	97%	full range	[29,37]
2nd line treatment efficacy	90%	85%	95%		[38]
Sequential therapy efficacy	93%	91%	95%	95%CI	[37]
Benefits of *H.pylori* eradication					
Reduction in gastric cancers	RR[c] 0.56	RR 0.4	RR 0.8	95%CI	[7]
Reduction in duodenal ulcers	RR 0.37	RR 0.26	RR 0.53	95% CI	[22]
Other					
Incidence of Peptic Ulcer disease	0.19%	0.10%	0.19%		[39]
Prevalence of Peptic Ulcer disease	1.50%	0.12%	1.50%		[39]
Incidence of duodenal ulcer if H. pylori +ve	5%	0.18%	17%	95% CI	[21]
Treatment adverse effects (all)					
Comparison	8%				[22]
Treatment	22%				[22]
Cancer Survival (%)					
1 year	41	39	42	95%CI	[5]
2 year	26	25	28	95%CI	[5]
3 year	21	19	22	95%CI	[5]
4 year	18	16	19	95%CI	[5]
5 year	16	14	17	95%CI	[5]

[a]CI = 95% Confidence Interval.
[b]IQR = Interquartile range.
[c]RR = Relative Risk.
doi:10.1371/journal.pone.0108610.t001

cancer saved. The parameters tested were cost of managing one cancer, cost of a physician visit, cost of medication for eradication, cost of managing one peptic ulcer and lifetime risk of gastric cancer. The change in net cost per cancer saved was estimated against the proportional change in each of the five parameters. A probabilistic model was developed in which the model parameters were drawn from their full uncertainty distributions, as given in Table 1. The distributions were assumed to be normal with the mean equal to the best estimate and upper and lower range equal to the 95% area under the curve of the normal distribution. For each of 10,000 iterations, a parameter was drawn from each uncertainty distribution and results calculated; including costs, number of cancers averted, number of ulcers averted false negatives and positive results. Sensitivity to change in parameters was estimated using multivariable regression, with cost per cancer saved as the continuous outcome variable and the parameters above as the predictor variables. Linear relationships were assumed and the parameters were not transformed. Figures represent the effect on cost per cancer prevented if each parameter was increased by 1% of the original estimate used.

Results

For all three prevalence rates tested, the most cost effective approach relative to others was testing with stool antigen, with treatment for those who tested positive followed by retesting and further treatment if the initial treatment failed (Figure 2, 3, 4).

When the prevalence was assumed to be 75%, the estimated net cost per cancer prevented was $111800 (strategy 3b*i*) (Table 3). For every 1000 people managed under this strategy we expect that

Table 2. Costs of testing and treatment for *H.pylori,* and costs of adverse outcomes associated with *H.pylori* in US dollars.

Costs (in US$)	*Original figure (US$)*	*Converted to 2011 (US$)*	*Reference*
Testing and Treatment			
Physician visit	86	86	[40]
Serology	29	30	[41]
Breath test	133	140	[41]
Stool antigen	21	22	[41]
Eradication therapy	355	373	[41]
Gastroscopy with biopsy	550	636	[21]
Peptic ulcer annual cost			
Peptic Ulcer Costs	866	1582	[42]
Gastric Cancer costs			
Mean cost of gastric cancer care (5 year net in 2004)			
Men	44203	52712	[4]
Women	41899	49965	[4]

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3.0 gastric cancers and 22.8 ulcers would be prevented (Table 4). At 50% prevalence the net cost per cancer prevented was estimated to be $132300, with prevention of 2.0 cancers and 15.2 ulcers per 1000 people managed. At 25% prevalence the net cost per cancer prevented was estimated to be $193900, with prevention of 1.0 cancer and 7.6 ulcers per thousand people managed (Tables 3 & 4).

Treating all individuals without screening was also a relatively cost effective strategy in a high prevalence (75%) population, with a net cost per cancer prevented of $116600 (Table 3), although the overall number of cancers (2.5/1000 treated) and ulcers (18.2/1000 treated) prevented was lower than with a strategy involving retesting and further treatment (Table 4). At a lower prevalence estimate of 25% (Table 4) the cost of treatment became a very significant burden with the treat-all strategy because most of the population would receive unnecessary treatment. At 25% prevalence the strategy with the lowest cost of testing (stool antigen testing) offered the lowest overall cost, and post treatment testing and retreatment improved the net benefit.

The use of serology was more expensive at all prevalence levels tested and breath test, although having slightly better sensitivity and specificity than stool antigen, was considerably more expensive. Any strategy that involved the use of gastroscopy had considerably higher net costs per cancer prevented (Table 3) and total costs (Table 4). The net costs were slightly lower than the total costs indicating that the cost savings from preventing gastric cancer and ulcer disease contributed only a small component of the cost/benefit of each strategy.

Table 3. Net cost per cancer prevented (US dollars) for each strategy at varying prevalence rates of *H. pylori*.

Net cost per cancer prevented		**Prevalence**	
Management Options	*25%*	*50%*	*75%*
1) No screening	0	0	0
2) Treat all	477800	206900	116600
3) Screen and Treatment			
a. Serology			
No follow up	294700	169900	128300
b. Stool Ag			
No follow up	219200	142700	117100
i) Follow with stool Ag and retreat	193900	132300	111800
c. Breath test			
No follow up	360200	213800	165000
i) Follow with breath test and retreat	334600	216400	177000
d. Gastroscopy			
No follow up	972000	520600	370200
i) Follow up gastroscopy and retreat	939900	577200	456300
ii) Follow with breath test and retreat	820200	460100	340100
iii) Follow with stool Ag and retreat	794400	433900	313700

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Table 4. Total cost (US dollars) and number of gastric cancers and ulcers prevented for each strategy for every 1000 people managed.

Prevalence	**25%**	**25%**	**25%**	**50%**	**50%**	**50%**	**75%**	**75%**	**75%**
Management Options	Total cost	Cancers prevented	Ulcers prevented	Total cost	Cancers prevented	Ulcers prevented	Total cost	Cancers prevented	Ulcers prevented
1) No screening	0	0	0	0	0	0	0	0	0
2) Treat all	458700	0.8	6.1	459000	1.7	12.1	459000	2.5	18.2
3) Screen and Treat									
a. Serology									
No follow up	280500	0.8	5.6	366600	1.6	11.2	452700	2.3	16.7
b. Stool Ag									
No follow up	226200	0.8	5.7	330700	1.6	11.4	435100	2.4	17.1
i) Follow with stool Ag and retreat	258000	1.0	7.6	393200	2.0	15.2	528300	3.0	22.8
c. Breath test									
c. Breath test No follow up	343000	0.8	5.8	449700	1.6	11.6	556400	2.4	17.3
i) Follow with breath test and retreat	404800	1.0	7.6	569800	2.0	15.3	734900	3.0	22.9
d. Gastroscopy									
No follow up	834300	0.8	5.8	942200	1.6	11.5	1050000	2.4	17.3
i) Follow up gastroscopy and retreat	1014800	1.0	7.6	1296700	2.0	15.3	1578600	3.0	22.9
ii) Follow with breath test and retreat	894400	1.0	7.6	1060900	2.0	15.3	1227400	3.0	22.9
iii) Follow with stool Ag and retreat	865900	1.0	7.6	1005000	2.0	15.2	1144100	3.0	22.8

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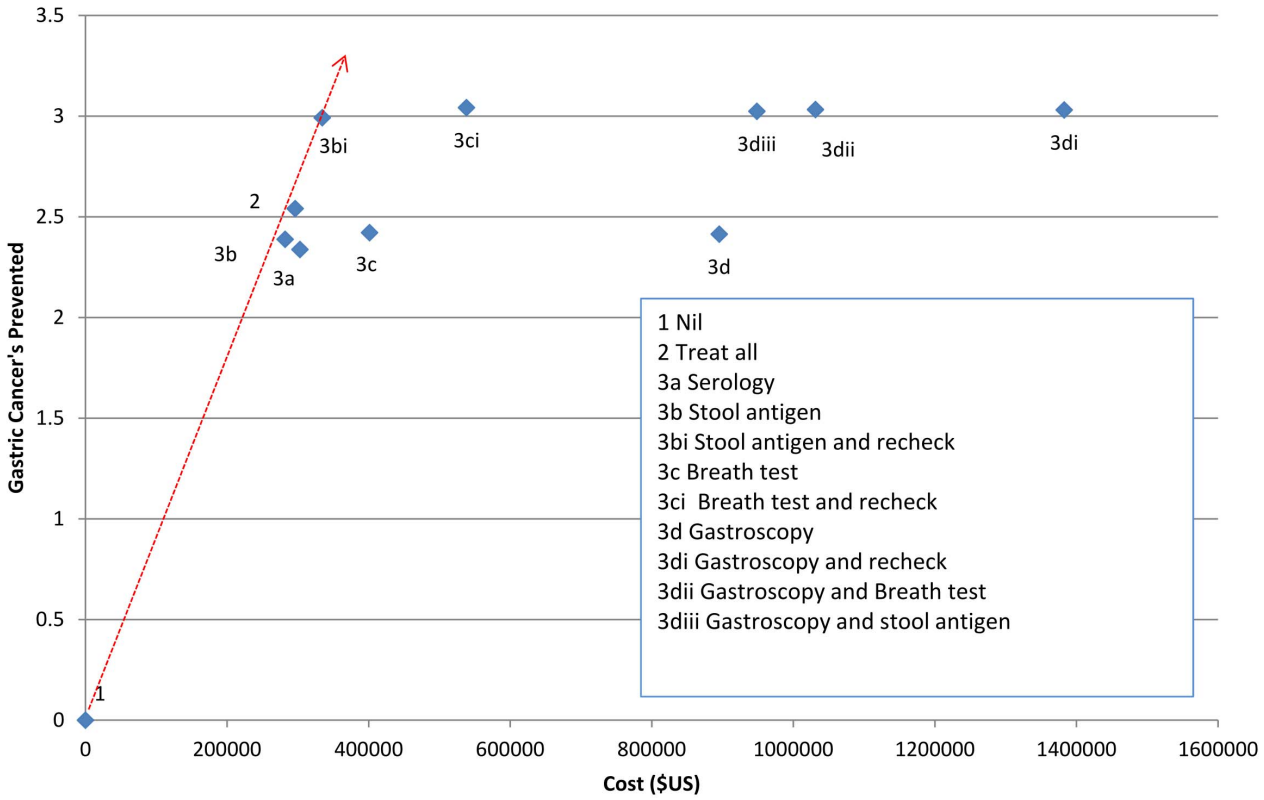

Figure 2. Net cost per number of cancers prevented for different strategies for screening and treatment of *H. pylori* in a population with a 75% prevalence of *H. pylori infection* shown as an Incremental Cost Effectiveness Ratio (ICER). Red line indicates lowest net cost per cancer prevented.
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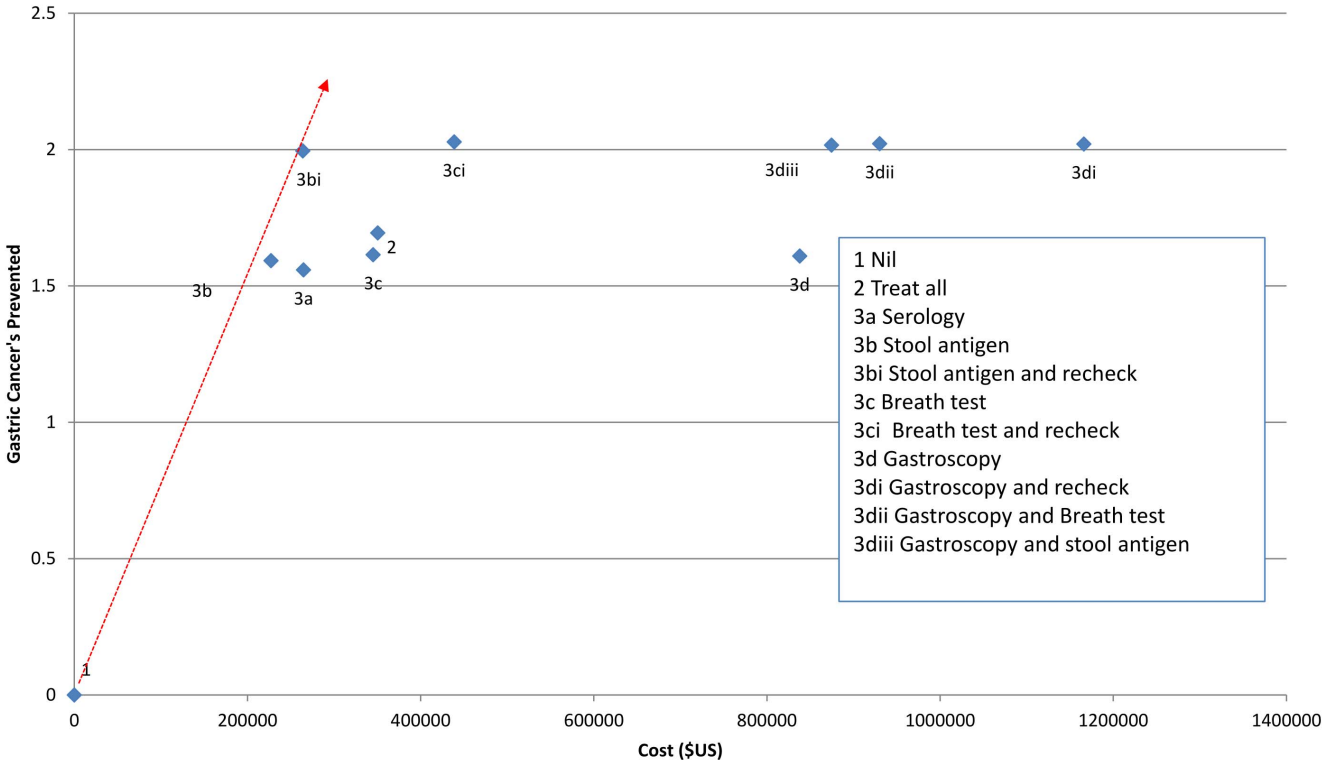

Figure 3. Net cost per number of cancers prevented for different strategies for management of *H. pylori* in a population with a 50% prevalence of *H. pylori infection* (ICER). Red line indicates lowest net cost per cancer prevented.
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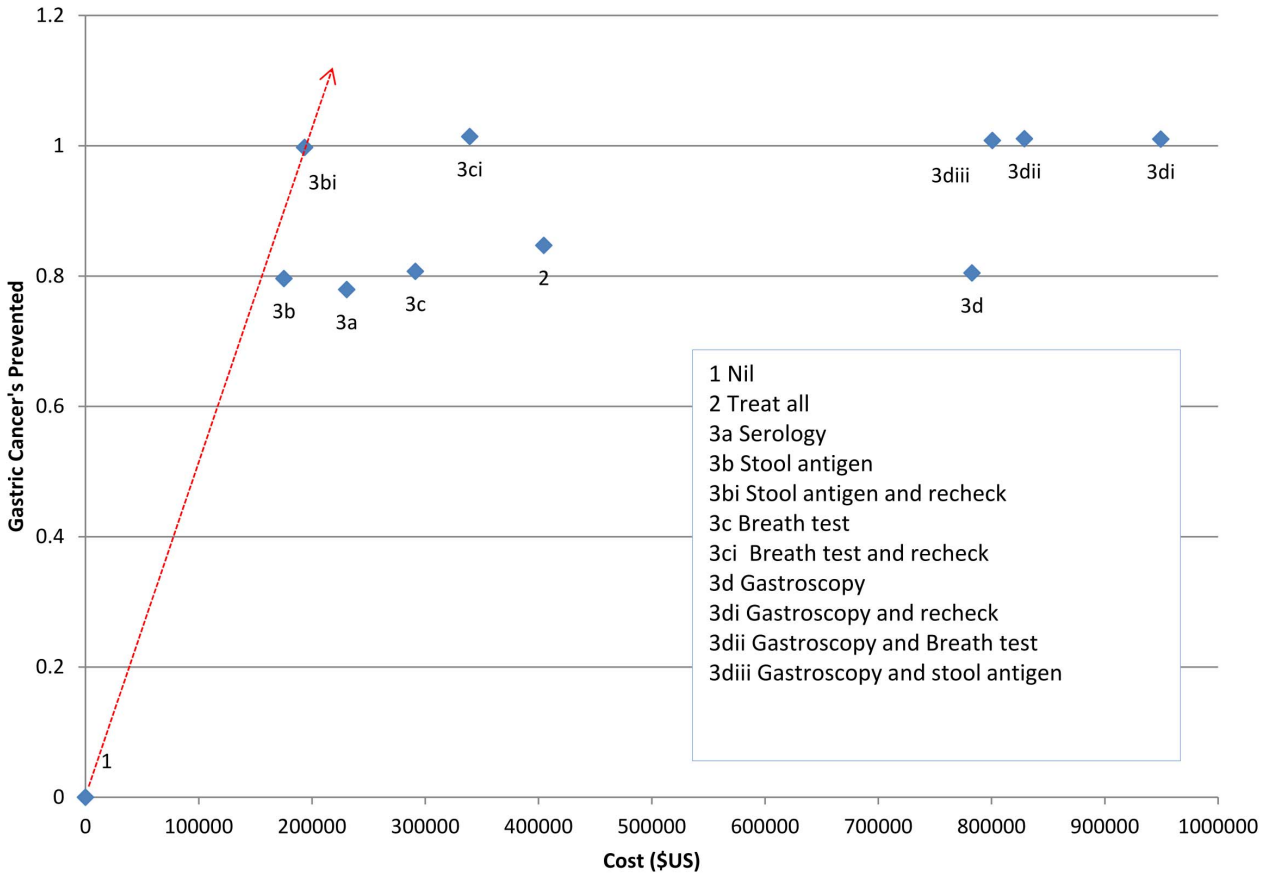

Figure 4. Net cost per number of cancers prevented for different strategies for screening and treatment of *H. pylori* in a population with a 25% prevalence of *H. pylori infection* (ICER). Red line indicates lowest net cost per cancer prevented.
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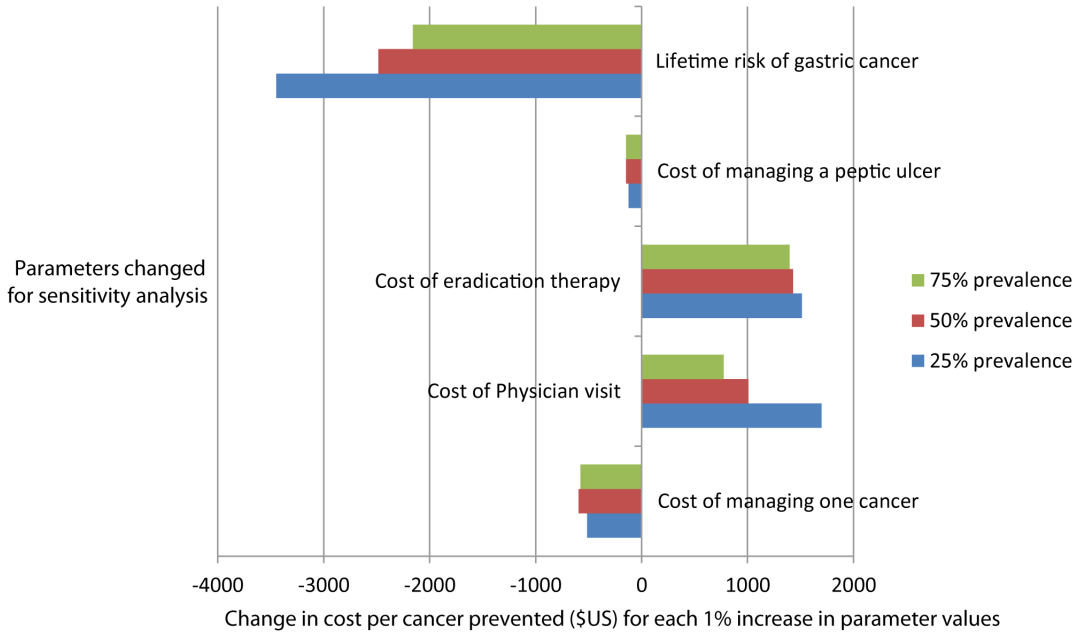

Figure 5. Sensitivity analysis for the most cost effective strategy (stool antigen with retesting). Horizontal bars represent the estimated net effect on cost per cancer prevented in US Dollars with a 1% increase in the listed parameters.
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Figure 5 shows the sensitivity analysis for each of three prevalence values, using strategy 3bi, the optimal strategy. Parameters that represent the consequences of untreated *H.pylori* (peptic ulcer and gastric cancer) have negative values because as these costs rise, the value of eradicating *H.pylori* increases, the cost-effectiveness increases, and the net cost per cancer averted decreases. The parameters associated with the cost of the strategy have positive values, since as costs rise for any intervention, the cost per cancer averted rises. The cost of eradication therapy was the greatest cost associated with the strategy at high prevalence, while the risk of gastric cancer contributed significantly to the benefit of the strategy. Any increase in the estimated lifetime incidence of gastric cancer results in a significant decrease in the net cost per cancer prevented.

Discussion

Screening and treatment of *H. pylori* in high-risk populations has been suggested as a means of reducing the burden of gastric cancer and peptic ulceration [8,18] and been shown to be cost effective [19] however this is not routinely undertaken in Western countries [18]. Immigrants from developing countries represent a group with a high prevalence of *H. pylori* and hence a target group for screening strategies. Our modelling has shown that the costs associated with most of the available 'test and treat' strategies are not prohibitive. In particular, the use of a cheap and easily available stool antigen test has the potential to significantly lower the overall costs of screening, and deserves consideration in populations with high prevalence's of *H. pylori*. Notably the number of cancers and ulcers prevented is similar with stool antigen testing and retesting, breath test and retesting or any strategy involving gastroscopy and retesting. This indicates that the additional cost of more expensive screening strategies does not confer any significant additional benefit and reflects the similar sensitivity and specificity of these testing modalities.

Previous international modelling has shown that universal screening of 20 year olds for *H. pylori* is a cost effective way of reducing gastric cancer in a Chinese population [20]. Screening in lower prevalence populations has also been shown to be cost effective although the cost is significantly higher per quality adjusted life year (QALY) [5].

Our model may underestimate the benefits of screening and treatment as we did not include prevention of dyspepsia through *H. pylori* treatment and the associated reduced doctor visits for dyspepsia management, and potential for reduced hospital admissions [21]. The benefits of test and treat strategies may also be an underestimate as the cost of gastric cancer treatment may be considerably more than the cost estimates used in this analysis in patients over the age of 65 years [3]. The use of physician assistants or clinic nurses to order the initial testing would also lead to cost savings, and the use of more effective first line therapies could improve cost effectiveness. However, the frequency of treatment side effects, which reportedly occur in 22% of treated patients and 8% of placebo patients [22] needs to be considered and these additional side effects may increase costs.

H. pylori has been part of our gastrointestinal flora for 60000 years [23] so a recommendation for eradication should be made with caution. *H. pylori* prevalence rates have been falling in developed countries at the same time as allergic disease, reflux and obesity have been increasing [24]. Some randomised trial evidence demonstrates a small increase in weight after *H. pylori* eradication [25]. *H. pylori* eradication is also associated with a rise in prevalence of Barrett's Oesophagus [26], and increasing oesophageal cancer rates [27]. Concern that *H. pylori* eradication can lead to increased risk of gastro-oesophageal reflux disease (GERD) has not been confirmed in a large systematic review [28]. In any event this concern about oesophageal pathology is of small magnitude compared with the potential reduction in gastric cancer rates.

Antibiotic resistance to *H. pylori* is increasing and efficacy of standard treatment for *H. pylori* in many countries is now less than 80%, primarily due to clarithromycin resistance [29]. This is concerning for the implementation of a screening program. Other options that can be more effective include sequential therapy with PPI and amoxicillin for 5 days followed by PPI, clarithromycin and metronidazole for 5 days) [29], and longer courses (10–14 days) of quadruple therapy, including bismuth, tetracycline, metronidazole and a PPI [30].

Screening or empiric treatment for refugees and immigrants for infectious conditions is currently recommended for a number of pathogens. Empiric treatment for helminthic infections is cost effective and recommended in some settings [31]. Treatment costs for latent tuberculosis (TB) are over US$28000 (17,956 pounds) per episode of TB prevented [32]. TB in the United States now has a mortality less than 5% [33], compared to gastric cancer's 5 year mortality of 84% [5]. Screening and treatment for Hepatitis B virus is common in many immigrant groups, and is cost effective even at a population prevalence of less than 2% [34].

Stool sampling is currently routinely recommended for helminth detection for refugee groups arriving in many developed countries [35], and faecal antigen testing for *H. pylori* could be incorporated with stool testing for other pathogens, an additional important cost saving measure.

The current American College of Gastroenterology and also European guidelines do not recommend a general screen and treat strategy for *H. pylori* infection to reduce the risk of gastric cancer; and do not specifically address the issue of high risk populations [6,36]. Asia Pacific guidelines, representing countries with a higher *H. pylori* prevalence, do recommend general screening for *H. pylori* in high risk populations although the strategy is not clearly defined [18].

Our data provide important evidence on which to base future recommendations.

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Author Contributions

Conceived and designed the experiments: TS EM KL. Performed the experiments: EM. Analyzed the data: EM TS. Wrote the paper: TS KL BB EM.

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RESEARCH ARTICLE

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Hepatitis B among immigrants from Myanmar: Genotypes and their clinical relevance

Thomas R. Schulz[1,2] | Rosalind Edwards[3] | M Christine Thurnheer[1] | Lilly Yuen[3] | Margaret Littlejohn[3] | Peter Revill[3] | Melissa Chu[4] | Firuz Tanyeri[4] | Amanda Wade[5] | Beverley-Ann Biggs[1,2] | Joseph Sasadeusz[1]

[1] Victorian Infectious Diseases Service, at the Doherty Institute, The Royal Melbourne Hospital, Melbourne, Victoria

[2] Department of Medicine/ RMH, at the Doherty Institute, University of Melbourne, Melbourne, Victoria

[3] Victorian Infectious Diseases Reference Laboratory, at the Doherty Institute, Melbourne, Victoria

[4] Department of Medicine, University of Melbourne, Parkville, Victoria

[5] Department of Infectious Diseases, University Hospital, Geelong, Victoria

Correspondence
Joseph Sasadeusz, Victorian Infectious Diseases Service, at the Doherty Institute, The Royal Melbourne Hospital, 792 Elizabeth Street, Melbourne 3000, Victoria.
Email: J.Sasadeusz@mh.org.au

Hepatitis B virus (HBV) from 76 adult immigrants in Australia from Myanmar was characterized to determine the prevalence of different HBV genotypes and subgenotypes. A mutational analysis was then performed to determine the presence of clinically significant mutations and correlate them to clinical outcomes. Initial genotyping revealed 68 patients with genotype C (89.5%) and eight patients with genotype B (10.5%). Phylogenetic analysis revealed the large majority of the genotype C infections were of subgenotype C1 (67/68). Sequencing of the HBV polymerase gene (and overlapping surface gene) revealed no mutations associated with antiviral resistance. HBV surface gene mutations were detected in 10 patients with subgenotype C1. HBV BCP/PC sequencing was obtained for 71/76 (93%) patients. BCP and/or PC mutations were identified in 57/71 (80%) of PCR positive patients. Treatment had been commenced for 15/76 (18%) patients, a further 26 untreated patients were in a stage of disease where HBV treatment would be considered standard of care. It was identified that genotype C1 is the predominant sub-genotype in this population. Genotype C is known to be associated with increased risk of development of HCC. This highlights the need for screening for HCC given the potential for the development of liver cancer. It was also identified that people with HBV were potentially not receiving optimal therapy in a timely fashion.

KEYWORDS
hepatitis B virus genetics, immigrant, Myanmar

1 | INTRODUCTION

Chronic Hepatitis B virus (CHB) infection affects approximately 248 million people worldwide.[1] CHB prevalence is highest in eastern Asia and Africa[1] and chronic infection leads to death in up to 25% of those infected due to hepatocellular carcinoma (HCC) and liver cirrhosis.[2,3]

In Australia, an estimated 218,000 people (1% of total population) are living with CHB, the majority (56%) of whom were born overseas[4] predominantly from the following regions: Asia/Pacific 38%, Europe 10%, Africa/Middle East 7%, and The Americas: 0.8%. People from culturally and linguistically diverse (CALD) backgrounds, particularly Asia-Pacific or Sub-Saharan Africa, are listed as one of the priority populations in the Australian National Hepatitis B Strategy[5] and as such are an important group to focus on for screening and therapy.

Myanmar (Burma) has suffered 50 years of military dictatorship, as well as ongoing civil war. As a result minority groups have fled to refugee camps along the borders of India, Bangladesh and Thailand, as well as to Malaysia. High rates of CHB have been identified amongst immigrants from Myanmar in both Australia (9.7%)[6] and the USA (9.4%).[7] It is estimated that the seroprevalence of CHB in

Myanmar is about 8%, making it an area of high prevalence.[8,9] Almost half of the population of Australians from Myanmar (24 000) arrived after 2006, and 80% are under 45 years of age.[10] There are 135 distinct ethnic groups recognized in Myanmar. The largest groups are Burmese (Bamar) (68%), Shan (9%), and Karen (Kayin) (7%).[11] Many of the immigrants from Myanmar living in Australia have come from the Thai-Myanmar border and are of Karen ethnicity.[6]

Many clinical and molecular-based studies in Australia have predominantly focussed on CHB in Chinese and Vietnamese immigrants. These studies have found that genotypes B and C predominate in South East Asia and China. Genotype C is known to be associated with an increased risk of development of HCC.[12] Co-infection with more than one genotype is possible, and in Asia co-infection with both genotype B and C is common.[13] Some Hepatitis B virus (HBV) recombinants are now endemic in certain geographic regions, and have been assigned their own genotype or subgenotype, most notably the recombination between isolates of HBV genotypes B and C[14] resulting in HBV subgenotype B2, which contains the precore and core genes of an HBV genotype C, and is found throughout Asia.[14]

Within Myanmar genotype C has been identified as the predominant genotype, both amongst local residents and those migrating from Myanmar.[8,15,16] Genotype C is associated with a later seroconversion from Hepatitis B e-Antigen (HBeAg) positive status to HBeAg negative, anti-HBe positivity and more advanced liver disease.[17] Other studies however, have focused on populations such as from Korea with largely genotype C2, and it is unknown if this is also the case with genotype C1.[18] Basal core promotor (BCP) and/or precore (PC) mutations have been shown to be associated with increased progression to cirrhosis and/or HCC.[19] Routine use of genotyping may assist in the selection of patients for treatment, as has been recommended for Asian patients with genotype B or C virus, and may identify patients at higher risk of progression of liver disease and HCC.[20]

The aim of this study was to characterize HBV isolates from Myanmar-born immigrants living in Victoria, Australia. We aimed to determine the prevalence of different HBV genotypes/subgenotypes, and also perform a mutational analysis to determine the presence of clinically significant mutations which may influence clinical outcomes. This information was correlated with patient clinical information including disease stage and treatment status.

2 | METHODS

This was a retrospective, observational study. Ethics approval was received from the Royal Melbourne Hospital Human Research and Ethics Committee.

2.1 | Patient samples

Stored serum was obtained for 84 patients from Myanmar from three separate sites in Victoria—University Hospital, Geelong, Isis Primary Care (Hoppers Crossing), and the Royal Melbourne Hospital hepatitis and travel/refugee clinics. All samples had been sent to the Victorian Infectious Diseases Reference Laboratory (VIDRL) as part of routine clinical care.

2.2 | Clinical data

Where possible sociodemographic and clinical data were collected retrospectively from medical charts together with pathology results, and were entered into a standardized case report form (CRF). The following sociodemographic parameters were collected: date of birth, gender, ethnicity, country of origin, and age. Pathology results included aspartate aminotransferase (AST), alanine amino transferase (ALT), bilirubin, albumin, platelets, HBeAg status, and HBV viral load (IU/mL). Information on clinical management (treatment yes/no, drug used for treatment, imaging studies including transient elastography results) was recorded where available. Data were censored on 30th December 2013.

Clinical information was compiled in a separate Excel© (Microsoft, Redmond, WA) database for further analysis. Disease stage was determined using recognized staging systems.[21,22] These were immune tolerant stage (HBeAg positive, viral load > 20 000 iu/mL, ALT <45 iu/L), immune clearance (HBeAg positive, viral load > 20 000 iu/mL, ALT >45 iu/L), immune control (HBeAg negative, viral load < 2000 iu/mL, ALT < 45 iu/L, and immune escape (HBeAg negative, viral load > 2000 iu/mL, ALT >45 iu/L). Statistical analysis was performed using STATA SE12© (StataCorp, College Station, TX). Fisher's exact test was used to compare categorical data of multiple groups. Kruskal Wallis test was used for numerical data comparison, assuming non-normal distribution of the data.

2.3 | HBV DNA extraction, PCR, and sequencing

HBV DNA was extracted according to previously published protocols.[23]

To determine genotype/subgenotype, a 893–bp fragment of the reverse transcriptase (RT) region of the polymerase gene (and corresponding overlapping region of the surface (S) gene) was amplified and sequenced using primers Seq2 5′-TTG GCC AAA ATT CGC AGT C-3′ and 2996 5′-GCG TCA GCA AAC ACT TGG C-3′.To determine the presence of basal core promoter (BCP) and precore (PC) mutations, amplification and sequencing of a 356 bp fragment of the BCP/PC region was performed using primers PC5 5′-TCG CAT GGA GAC CAC CGT GA-3′ and PC2 5′-GGC AAA AAC GAG AGT AAC TC-3′.

Amplification and sequencing was conducted as per previously published protocols.[23]

HBV consensus sequences for the polymerase and BCP/PC genes were constructed using the DNA sequence analysis program SeqScape (ABI Prism, Applied Biosystems, Foster City, CA). HBV genotype and unique HBV mutations were identified using a web-based analysis program, SeqHepB, as previously described.[24,25]

TABLE 1 Demographic data and pathology results

	All	B (not subtyped)	B5	B7	C1	C8
Total	76*	1	3	4	67	1
Male sex	48	1	2	2	42	1
Age (years, median)	36	28	41	35	36	40
Pathology results (median)						
Viral load (IU/mL)	3248	NA	469	451	3768	22823
ALT (IU/L)	29	24	42	23	29	22
AST (IU/L)	28	34	34	22	27	32
Bilirubin (umol/L)	10	9	6	10	10	17
Albumin (g/L)	42	45	43	43	42	40
Transient elastography						
Yes	24	0	0	2	22	0
Median stiffness (kPa)	6			5	6	
Treatment						
Entecavir	10			1	8	1
Tenofovir	1				1	
PegINF	4		1		3	
Serology						
HBeAg pos	20	0	1	1	17	1
HBeAg neg	56	1	2	3	50	0
HBeAb pos	31	0	1	2	28	0
HBeAb neg	12	0	1	1	9	1
HBeAb NA	33	1	1	1	30	0
HBe seroconverted**	31	0	1	2	28	0

*For 6/84 patients no genotype information was available, one individual (ISI073) was removed from study as country of origin uncertain, one patient has insufficient serum, these eight patients were excluded from the analysis.
**Defined as HBeAg neg and HBeAb pos.

2.4 | Phylogenetic analysis

The HBV polymerase sequences obtained were compared to a set of published reference sequences from GenBank representing all the human HBV genotypes (>50 subgenotypes) and multi-aligned using the Clustal W algorithm in Bioedit (BioEdit v7.2.6.1)[26]

Neighbour-joining phylogenetic trees were constructed using the MEGA software, version 5.0[27] and evaluated by bootstrap resampling with 1000 replicates.

3 | RESULTS

3.1 | Demographics and clinical characteristics

Serum was collected from 84 patients, and genotypic analysis was able to be performed on samples from 76 patients. Clinical data has been presented only for those for whom a genotype was available. Eight patients were excluded; six as they were PCR negative, one had no serum available and one for whom the country of origin was uncertain.

TABLE 2 Stages of disease

	Number (*N* = 76)	HBeAg pos/neg	HBeAb pos/neg/NA	Viral Load (IU/mL) median (IQR)	ALT (IU/L) median (IQR)
Immune tolerance	10	10/0	0/5/5	1.75×10^8 ($1.8\text{-}3.2 \times 10^8$)	32 (16-60)
Immune clearance	3	3/0	0/0/3	149 (137-10827)	25 (25-49)
Immune control (low replicative)	25	0/25	14/1/10	532 (222-703)	30 (21-43)
Immune escape (reactivation)	23	0/23	11/1/11	6717 (3122-15092)	24 (19-30)
On treatment	15	7/8	6/5/4		36 (22-65)

NA, Not available; IQR, Interquartile range.
Those with incomplete data have been classified as the closest match. Viral loads are not included for patients who started treatment.

There were 48 males (63%) and 28 females (37%) included in the analysis (Table 1). Date of birth was available for 64/76 (84%), with a median age of 36 years. The median age amongst the largest genotypic group (C1) was also 36. Most were of Karen ethnicity (66/76, 87%), two were of Burmese ethnicity, and for eight patients the ethnicity was unknown. Viral loads were available for 71/76 (93%) of the samples. Amongst those who had transient elastography ($n = 24$), the median score was 6 kPa (range from 3.3-21.3 kPa). Cirrhosis was identified in one patient (stiffness 21.3 kPa). This patient was on treatment with entecavir and did not have clinical or biochemical markers to suggest cirrhosis.

Disease staging (Table 2) showed 10 patients in the immune tolerance phase, three patients undergoing immune clearance, 26 patients in the immune control phase and 23 patients in the immune escape phase. An additional 15 patients were being treated with antiviral therapy; 10 with entecavir, four with pegylated interferon and one with tenofovir (Tables 1 and 2).

3.2 | Genotyping

Initial genotyping revealed 68 patients with genotype C (89.5%) and eight patients with genotype B (10.5%). Phylogenetic analysis revealed the large majority of the genotype C infections were of subgenotype C1 (67) and one case of C8. Of the genotype B infections, four were B7, three were B5, and one could not be subgenotyped. Amongst those with genotype C1 disease, the median age of those with HBV eAg positive disease was 29 in the immune tolerance phase and 34 years in the immune clearance phase. The median age of those with immune HBV eAg negative disease was 41 in the immune control phase and 39 years in the immune escape phase.

3.3 | Mutational analysis

Sequencing of the HBV polymerase gene (and overlapping surface gene) revealed no mutations associated with antiviral resistance. Fifteen patients were on treatment, ten of these had genotyping done on blood samples taken before treatment was commenced and three in the early months after treatment commencement. One patient treated with entecavir had genotyping done after 18 months of treatment when they had been non adherent for many months and one patient had a previous 12 months course of Pegylated interferon three years before the sample used for genotypic analysis. HBV surface gene mutations were detected in 10 patients with subgenotype C1 (Table 3), and these included stop codons at positions sW172 (one patient),[28] sW182 (three patients), and sL216 (five patients), as well as mutations sP120T (one patient) and sG145R (two patients) that are known to be associated with HBIg or vaccine escape mutants.[29,30]

HBV BCP/PC sequencing was obtained for 71/76 (93%) patients. BCP and/or PC mutations were identified in 57/71 (80%) of PCR positive patients (Table 3). The most common mutations identified were the PC G1986A with BCP A1762T and/or G1764A (25/57, 44%), the BCP mutations alone (20/57, 35%) and the PC mutation alone (7/57, 12%). A PC start mutation was identified in two patients and a one nucleotide insertion in PC at amino acid 12 was identified in three patients (Table 3).

4 | DISCUSSION

Our results revealed predominantly HBV genotype C in this opportunistic sample of Victorian immigrants from Myanmar. This accounted for 89% of the population, making this a remarkably homogenous virological population.[12] In particular we identified that the genotype subtype C1 is the predominant sub-genotype in this population. This has also been identified in those with HBV living in Myanmar.[8] HBV isolates from immigrants from Myanmar living in Victoria would likely reflect the HBV from immigrants from Myanmar to Australia as a whole. Genotype C is known to be associated with increased risk of development of HCC.[12] Interestingly the median age of patients with both HBeAg positive and HBeAg negative disease is very similar to studies of Korean patients with genotype C2, showing a mean age of 31 and 40 years respectively.[31] It is therefore interesting that a high proportion of individuals remain HBeAg positive at a relatively advanced age. This suggests that seroconversion may be a relatively late phenomenon in this genotype and population.

Of the samples that were successfully amplified for BCP/PC sequencing, a high proportion (80%) harbored BCP and/or PC

TABLE 3 Frequency of BCP/PC mutations according to sub-genotype

BCP	PC	PC start	Insertion in PC	B5 ($n = 3$)	B7 ($n = 4$)	B? ($n = 1$)	C1 ($n = 67$)	C8 ($n = 1$)	Total ($n = 76$)
A1762T and/or G1764A					1		18	1	20
	G1896A				1		6		7
		M1 L/T					2		2
			1nt (aa12)				2		2
A1762T and/or G1764A	G1896A				1	1	23		25
A1762T and/or G1764A			1nt (aa12)				1		1
Total					3	1	52	1	57

mutations. In HBV genotype C, the A1762T/G1764A dual mutations have also been associated with an increased risk of HCC.[12] These results highlight the importance of following HCC screening recommendations in the population of immigrants from Myanmar, who are likely to have genotype C virus. The median transient elastography score was 6.0 kPa and only one patient had a transient elastography score suggestive of cirrhosis (21.3). This suggests that the majority of individuals had mild liver disease and is counter to prior reports suggesting genotype C infections being associated with more advanced liver disease although larger studies of liver fibrosis in this genotype are needed to confirm this.

It is notable that 15/76 (18%) of patients were on treatment which would be expected amongst a population with HBV.[32] Of note a further 26 untreated patients were in a stage of disease where HBV treatment would be considered standard of care (three patients in immune clearance and 23 patients in the immune escape phase).[33] It is unclear how long these individuals had been in these active phases of disease but suggests that at least some individuals may have had unrecognized active disease for prolonged periods.

This has been well recognized as a significant problem within Australia, with epidemiological data suggesting the majority of patients with HBV are not receiving appropriate monitoring and management.[32] It has been recognized that under treatment of patients with HBV is widespread, both in the community and tertiary hospitals[32,34,35] and this finding suggests further efforts are necessary to ensure patients are identified early and receive timely optimal care. This is particularly important given the association of Genotype C virus with HCC and advanced liver disease.

Limitations to the study include that the sample size was small and numbers for non C1 genotypes did not allow for between groups statistical comparisons. In addition data was collected retrospectively, some information was incomplete, and most patients did not have a formal assessment of fibrosis stage. However, these findings are important as they have implications for patient monitoring and treatment. They particularly highlight the need for screening for HCC given the potential for the development of liver cancer in genotype C1 disease. They also illustrate the issue of people with HBV potentially not receiving optimal therapy in a timely fashion.

In summary, patients from Myanmar who migrate to Australia are predominantly infected with genotype C (especially C1) virus and may not be receiving timely therapy. This highlights the need to increase efforts to bring these individuals into the cascade of care. In addition, in order to better guide clinical care and decrease the morbidity and mortality of HBV, improved clinical guidelines need to be informed by further studies into the natural history of various specific genotypes and subtypes of HBV.

ORCID

Beverley-Ann Biggs http://orcid.org/0000-0002-2961-9793

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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RESEARCH ARTICLE

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Genotypic profiles of hepatitis B in African immigrants and their clinical relevance

Maria Christine Thurnheer[1] | Rosalind Edwards[2] | Thomas Ray Schulz[1,3] | Lilly Yuen[2] | Margaret Littlejohn[2] | Peter Revill[2] | Elizabeth Bannister[2] | Melissa Chu[4] | Firuz Tanyeri[4] | Amanda Wade[5] | Beverley-Ann Biggs[1,3] | Joseph Sasadeusz[1]

[1] Victorian Infectious Diseases Service, The Royal Melbourne Hospital, at the Doherty Institute, Melbourne, Victoria 3000, Australia

[2] Victorian Infectious Diseases Reference Laboratory, at the Doherty Institute, Melbourne, Victoria 3000, Australia

[3] Department of Medicine/ RMH, University of Melbourne, at the Doherty Institute, Melbourne, Victoria 3000, Australia

[4] Department of Medicine, University of Melbourne, Parkville, Victoria 3050, Australia

[5] Department of Infectious Diseases, University Hospital, Geelong, Victoria 3220, Australia

Correspondence
Joseph Sasadeusz, Victorian Infectious Diseases Service, The Royal Melbourne Hospital, at the Doherty Institute, 792 Elizabeth Street, Melbourne Victoria 3000, Australia.
Email: j.sasadeusz@mh.org.au

Hepatitis B virus (HBV) from 40 adult African immigrants in Australia was characterized to determine the prevalence of different HBV genotypes and subgenotypes. A mutational analysis was then performed to determine the presence of clinically significant mutations and correlate them to clinical outcomes. Initial sequencing analysis revealed 13 with genotype A (32.5%), 13 with genotype D (32.5%), and 14 with genotype E (35%). Serology showed that 37 were HBeAg negative. Phylogenetic analysis identified a high prevalence (25%) of HBV subgenotype A1 in our cohort, a subgenotype which has been associated with more aggressive clinical disease. BCP/PC sequencing was obtained for 38 patients. BCP and/or PC mutations were identified in 36/38 (95%). The median viral load of all patients was 2995 IU/mL and most of the pathology results were within the normal range. Only one patient had an increased APRI score of 1.1 suggestive of cirrhosis. We present novel information on the HBV genotypes amongst the African population in Australia along with clinical correlates. The high prevalence of A1 subgenotype in this population supports the current Australian recommendation to commence hepatocellular carcinoma screening in Africans with chronic HBV from 20 years old.

KEYWORDS
Australia, chronic hepatitis B, hepatocellular carcinoma, mutation, sequencing, serology

1 | INTRODUCTION

Chronic Hepatitis B virus (HBV) infection affects approximately 248 million people worldwide.[1] HBV prevalence is highest in Africa and Eastern Asia and chronic infection will lead to death in up to 25% of those infected due to hepatocellular carcinoma (HCC) and liver cirrhosis.[1–3]

In Africa, some 75 million people have chronic HBV where it is considered hyper endemic, with a seroprevalence of >8%.[2,4,5] In this setting, the virus is predominantly transmitted either vertically through mother to child transmission or horizontally during early childhood.[6] Current evidence regarding the geographic distribution of HBV genotypes includes that genotype D is found in North Africa, genotype E is found in Western and Central regions, and genotype A is in Eastern and Southern regions.[5] Genotypes E and A1 are unique to Africa, except in cases where there is migration history such as slave trade or refugees.

In Australia, an estimated 218 000 people (approximately 1% of the total population) are living with chronic HBV, the majority (56%) of who were born overseas.[7] (Asia/Pacific: 38%, Europe: 10%, Africa/Middle East: 7%, Americas: 0.8%). In the past two decades, there have been increasing numbers of refugees arriving from Sub-Saharan Africa to Australia and also to other parts of the world.[8,9] People from culturally and linguistically diverse (CALD) backgrounds (particularly Asia-Pacific or Sub-Saharan African background) are listed as one of the priority populations of the Australian National Hepatitis B Strategy and as such are an important group to consider and prioritize.[10]

Preliminary work from an ongoing study of HBV in African children in Australia documented the presence of genotypes A, D, and E in this

population group.[11] Phylogenetic analysis revealed the presence of sub genotype A1 which is associated with aggressive clinical disease,[12] as well as a high prevalence of HBV variants encoding mutations in the basal core promoter (BCP) and/or precore (PC) gene associated with hepatitis B e antigen (HBeAg) negativity, with the majority of subjects having sero-converted to anti-HBe (HBeAb) despite their young age.[11] The identification of BCP variants in particular is important, as recent studies have shown the presence of these mutations is associated with increased likelihood of progression to advanced liver disease, particularly cirrhosis.[13,14]

In this study, we aimed to characterize HBV isolated from adult African immigrants and refugees living in Victoria, Australia by determining the prevalence of different HBV genotypes/sub genotypes, and then performing a mutational analysis to determine the presence of clinically significant mutations and correlating them to clinical outcomes.

2 | MATERIALS AND METHODS

Ethics approval was received from the Royal Melbourne Hospital human research and ethics committee.

2.1 | Patient samples

Stored serum samples were obtained from 42 African patients from three separate sites in Victoria—University Hospital (Geelong), Isis Primary Care (Hoppers Crossing), and the Royal Melbourne Hospital hepatitis and travel/refugee clinics.

2.2 | Clinical data

Sociodemographic and clinical data were collected retrospectively from medical charts together with pathology results, and were entered into a standardized case report form (CRF). The sociodemographic parameters collected were date of birth, sex, ethnicity, country of origin, and age. Data were censored on 30th December 2013. Regions of origin were defined according to the geographic location of the country of origin. Pathology results collected included aspartate aminotransferase (AST), alanine amino transferase (ALT), bilirubin, albumin, gamma glutamyltransferase (GGT), alkaline phosphatase (ALP), platelets, HBeAg status, and HBV viral load (IU/mL). AST to platelet ratio index (APRI) scores were calculated as a marker of hepatic fibrosis where concurrent results for platelet counts and AST were available (29/40 patients), using the following formula: ((AST (IU/L)/AST upper limit of normal (ULN) (IU/L))/platelet Count (10^9/L))*100. (40IU/L was used as ULN for AST values).

The presence or absence of clinical signs of cirrhosis (including ascites, encephalopathy, and splenomegaly) were recorded where available. Information on clinical management (current treatment yes/no, drug used for treatment; imaging studies including transient elastography results) was recorded where available.

Clinical information was compiled in a separate database for further analysis. Statistical analysis was performed using STATA SE12© (StataCorp, College Station, Texas, USA). Fisher's exact test was used to compare categorical data of multiple groups. Kruskal Wallis test was used for numerical data comparison, assuming non-normal distribution of the data.

2.3 | HBV DNA extraction, PCR, and sequencing

HBV DNA was extracted from 200 µL serum using the QIAamp DNA Minikit (QIAGEN, Hilden, Germany) according to the manufacturer's instructions. Extracted DNA was eluted in a final volume of 50 µL of supplied elution buffer. To determine genotype/subgenotype, a 893 bp fragment of the reverse transcriptase (RT) region of the polymerase gene (and corresponding overlapping region of the surface (S) gene) was amplified and sequenced using primers Seq2 and 2996 (Table 1). To determine the presence of BCP and PC mutations, amplification, and sequencing of a 356 bp fragment of the BCP/PC region was performed using primers PC5 and PC2 (Table 1).

Amplification was carried out using HotStarTaq *Plus* DNA Polymerase (QIAGEN, Hilden, Germany) at a concentration of two units/reaction, 10 × PCR Buffer (containing 15 mM MgCl2), 0.16 µM dNTPs, and 0.2 µM of each primer. For the BCP/PC PCR, the final concentration of $MgCl_2$ was slightly higher at 2 mM. Amplification conditions were as follows: denaturation at 95°C for 5 min, followed by 50 cycles of denaturation (94°C for 30 s), annealing (55°C for 30 s) and extension (72°C for 40 s), then a final extension step of 72°C for 10 min. Prior to sequencing, amplified products were purified using ExoSAP-IT (USB® Products Affymetrix, Inc.) according to the manufacturer's instructions.

Sequencing was carried out using the Big Dye® Terminator v3.1 Cycle Sequencing Kit (Applied Bio systems, Foster City, CA), according to the manufacturer's instructions. Full genome amplification was carried out as previously described using HotStarTaq *Plus* DNA Polymerase (QIAGEN, Hilden, Germany) and primers P1 and P2 (Table 1).[15] After purification, sequencing was performed using nine overlapping primers—SeqP1, 903, 865, 1798, 2254, JM, 2996, OSX1, and SeqP2 (Table 1).

HBV consensus sequences for the polymerase and BCP/PC genes, as well as the full genomes, were constructed using the DNA sequence analysis program *SeqScape* (ABI Prism, Applied Bio systems, Foster City, CA). HBV genotype and unique HBV mutations were identified using a web-based analysis program, *SeqHepB*, as previously described.[16,17]

2.4 | Phylogenetic analysis

The HBV polymerase sequences obtained were aligned using Clustal W and Bio edit (www.mbio.ncsu.edu/BioEdit/bioedit.html). Consensus sequences were compared to a set of published reference sequences (GenBank) representing the 10 human HBV genotypes (A–J, approx. 50 sub genotypes) (Fig. 1). Neighbour-joining phylogenetic trees were constructed using the MEGA software, version 5.0[18] and evaluated by bootstrap resampling with 1000 replicates.

TABLE 1 HBV primers used for PCR and/or sequencing[a]

Name	Position	Sequence (5'-3')
Seq2	330–318	TTG GCC AAA ATT CGC AGT C
2996	1175–1193	GCG TCA GCA AAC ACT TGG C
PC5	1604–1623	TCG CAT GGA GAC CAC CGT GA
PC2	1940–1959	GGC AAA AAC GAG AGT AAC TC
P1	1821–1841	*CCG GAA AGC TTG AGC TCT TCT TTT TCA CCT CTG
CCT AAT CA		
P2	1806–1825	*CCG GAA AGC TTG AGC TCT TCA AAA AGT TGC ATG
GTG CTG G		
SeqP1	1821–1841	TTT TTC ACC TCT GCC TAA TCA
SeqP2	1806–1825	AAA AAG TTG CAT GGT GCT GG
865	2301–2320	TTY GGA GTG TGG ATT CGC AC
903	2337–2362	GTT GAT AAG ATA GGG GCA TTT GGT GG
1798	3237–3257	CCA CTG CAT GGC CTG AGG ATG
2254	412–433	GAA GAT GAG GCA TAG CAG CAG G
JM	3114–3134	TTG GGG TGG AGC CCT CAG GCT
OSX1	807–827	TTT TCT TTT GTC TTT GGG TAT
OS1	2846–286	GCC TCA TTT TGT GGG TCA CCA TA

[a]Numbering from *Eco*R1 site.
*Non-HBV sequence underlined.

3 | RESULTS

3.1 | Study population, clinical characteristics

Of the 42 patients recruited, two had insufficient viral load for amplification and subsequent genotyping and these two patients were not included in the analysis.

The clinical characteristics of the 40 patients included in the study are presented in Table 2. Most patients were male (28, 70%), the median age was 36 years (IQR 30–45 years), and the majority (26, 65%) originated from East Africa or Horn of Africa (14 from Sudan, 6 from Somalia, 4 from Ethiopia, 2 from Eritrea, Table 2). Five originated from West Africa (1 from Ghana, 3 from Liberia, 1 from Nigeria) and five were from the Central and Southern regions of Africa (1 from Burundi, 1 from Zimbabwe and 3 from DR Congo). No information on the country of origin was available for four patients. According to clinical classifications, none of the patients had stigmata suggestive of chronic liver disease.

The median viral load of all patients was 2995 IU/mL (IQR 583–34333 IU/mL). Most of the pathology results were within the normal range, and APRI score results for most of the 29 patients with available results for both platelet counts and AST lay below the threshold for increased risk for severe fibrosis or cirrhosis (Table 3). One patient had an increased APRI score of 1.1 suggestive of cirrhosis (>1.0 indicative of cirrhosis).[19] He was a 26 year old man from Liberia, infected with HBV Genotype E, with a high viral load of 9 254 000 IU/mL, increased AST and ALT levels (79 IU/L and 89 IU/L respectively) and a normal platelet count of 184×10^9/L. He was HBeAb positive and HBeAg negative. No results for transient elastography were available for this patient.

Only seven patients were receiving antiviral treatment (Table 3). Entecavir was the most commonly used drug (5/7 patients), one individual received tenofovir and one person had a history of treatment with Pegylated Interferon (Peg IFN). The median viral load measured whilst on treatment was 470 IU/mL (IQR 263–1331 IU/mL).

Results for transient elastography were available for 6/40 patients, the mean result for median stiffness was 4.3 kPa. One patient had a high result of 15.5 kPa, suggestive of advanced fibrosis. He was a 37 years old man from Zimbabwe, infected with HBV genotype E. His viral load was 469 000 IU/ml. Pathology results revealed increased hepatic enzymes (ALT 107, AST 66, Bilirubin 11, GGT 107, and ALP 123). He was negative for HBeAg and positive for HBeAb. No APRI score was calculated for this patient as synchronous pre-treatment AST and platelet results were not available and he was commenced on treatment after the sample collection.

3.2 | Genotyping

Initial sequencing analysis of the 40 patients revealed 13 with genotype A (32.5%), 13 with genotype D (32.5%), and 14 with genotype E (35%). Recent reclassification of genotype A sub genotypes has grouped A3, A4, and A5 together as quasi-subgenotype A3, and A6 reclassified as A4.[20] In our cohort, based on sequencing of the polymerase region, subtyping of genotype A viruses revealed 10 patients with subgenotype A1 (25%) 2 patients (5%) with quasi-subgenotype A3 and one with subgenotype A4 (2.5%) (Fig. 1).

A recent reclassification of sub genotypes of genotype D, concluded that there are six (D1-D6) sub genotypes, not eight as previously thought.[21] The low inter-subgenotype divergence between

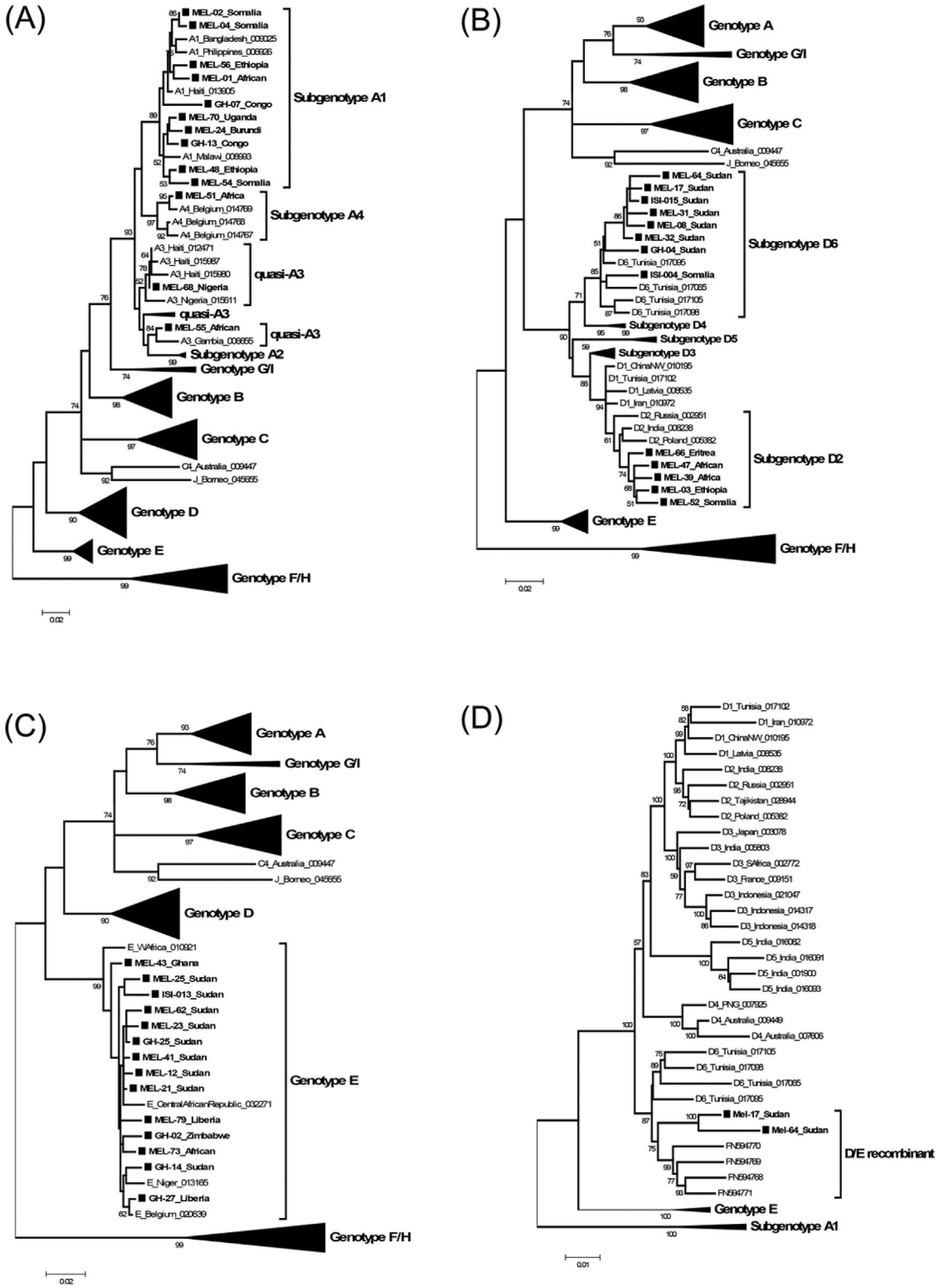

FIGURE 1 Phylogenetic trees of a 761 bp fragment of the HBV surface gene, including 143 reference sequences (Accession numbers given in supplementary table S1). Sequences isolated from this study identified by black square and country of origin. The percentages of replicate trees in which the associated taxa clustered together in the bootstrap test (1000 replicates) are shown next to the branches (>50% shown). (A) Genotype A sequences. (note: quasi-A3 was previously sub genotypes A3, A4, and A5. A4 was previously sub-genotype A6, see text for explanation). (B) Genotype D sequences. (note: D3 was previously sub-genotypes D3 and D6. D6 was previously sub-genotype D7). (C) Genotype E sequences. (D) Phylogenetic tree of HBV full genome sequences, constructed by the neighbour-joining method, showing the D/E recombinant sequences clustering with the isolates from Niger[9]

TABLE 2 Clinical data

	All	Viral sub genotypes							P^b
HBV (sub)genotype	*n* (%)	A1	A4	Quasi A3	D2	D6	D/E recomb[a]	E	
Total	40	10	1	2	5	6	2	14	
Male sex	28 (70)	6	1	1	4	4	1	11	0.845*
Age years (Median)	36	39	37	27	31	41	42	37	0.462**
Region of origin									
East Africa/Horn of Africa	26 (65)	6	0	0	5	5	2	8	0.108*
Eritrea	2								
Somalia	6								
Ethiopia	4								
Sudan	14								
West Africa	5 (12.5)	0	0	2	0	0	0	3	
Ghana	1								
Liberia	3								
Nigeria	1								
Central and Southern Africa	5 (12.5)	3	1	0	0	0	0	1	
Burundi	1								
Zimbabwe	1								
DR Congo	3								
Unknown	4 (10)	1	0	0	0	1	0	2	

[a]Recomb = recombinant.
[b]Comparing genotypes.
*Fisher's exact test (categorical data, small sample size).
**Kruskal Wallis (numerical data, non-normal distribution).

D3 and D6 suggests that they belong to one subgenotype. In addition, subgenotype D7 (from Tunisia, Algeria, and Morocco) then becomes subgenotype D6, and subgenotype D8 (from Niger) is considered a genotype D/E recombinant not a separate subgenotype.[20] In our cohort, based on sequencing of the polymerase region, subtyping of genotype D isolates revealed five patients (12.5%) with subgenotype D2 and eight patients (20%) with either subgenotype D6 or D/E recombinants (Fig. 1). These recombinant viruses have also been identified in a cohort of African children living in Australia.[11]

Full genome amplification and sequencing of two of these isolates revealed clustering with isolates from Niger,[22] thus confirming the presence of D/E recombinant viruses (Phylogenetic analysis for full genome sequencing not shown). Full genome analysis could not be obtained for the remaining six isolates due to low viral load, therefore we can only classify them as subgenotype D6, clustering with isolates from Tunisia.

3.3 | Geographic distribution

The geographic distribution of the isolated genotypes is shown in Table 2 and Fig. 2. Twenty-six patients originated from the East African/Horn of Africa region, and these patients were infected with either genotype E, D6, D2, D/E recombinant, or A.1.[6,8,15,16] The five patients from West Africa were infected with genotype E and quasi-subgenotype A3.[8,23] No genotype A1 was isolated from this region. The five individuals from Central and Southern Africa were infected with genotype A1, A4, or E (one each).[23] Comparison of genotype distribution showed no statistically significant variation among the different regions, most likely attributable to the limited number of patients.

3.4 | Mutations associated with antiviral resistance or basal core promoter/precore regions

Six patients were on antiviral therapy at the time of testing (five on entecavir, one on tenofovir) and one patient had received PegIFN for 11 months in 2011. None of these patients had viruses with mutations associated with antiviral resistance in their pre-treatment samples. No sequencing of on-treatment samples was performed. One patient had an rtA181T mutation in the polymerase (associated with resistance to lamivudine, telbivudine and adefovir) in the absence of antiviral therapy. The same patient had an sP120T mutation in the surface which is associated with HBV immunoglobulin or vaccine escape mutants.

BCP/PC sequencing was obtained for 38 patients. BCP and/or PC mutations were identified in 36/38 (95%) (Fig. 3). Two patients did not have the classic BCP or PC mutations; however, one patient had a 1 nucleotide (nt) insertion in PC at amino acid (aa) 5 whereas the other had a 1nt deletion in PC at aa12.

3.5 | HBe serology

Serology results are shown in Table 3: Only a minority of 3/40 patients were HBeAg positive whereas 37 were HBeAg negative. A high number of 34/37 patients with no detectable HBeAg were HBeAb positive (HBe

TABLE 3 Pathology results

Pathology results	All (IQR)	A1	A4	Quasi A3	D2	D6	D/E	E	P[a]
Viral load (U/mL)	3143 (652–34333)	2117	2084154	122810	1448	534	8778974	3680	0.152*
ALT (U/L)	26 (18–40)	22	37	54	22	21	38	33	0.784*
AST (U/L)	31 (24–37)	36	36	37	30	25	31	30	0.838*
GGT (U/L)	24 (19–52)	20	26	44	25	23	30	36	0.310*
Bilirubin (μmol/L)	10 (7–12)	11	9	10	7	9	8	11	0.220*
ALP (U/L)	78 (62–100)	71	107	81	64	76	79	86	0.639*
Albumin (g/L)	39 (36–41)	37	39	42	41	38	38	39	0.216*
Platelet count (10^9/L)	195 (165–228)	161	156	203	215	206	214	200	0.446*
APRI score (29/40 patients)	0.4 (0.3–0.5)	0.5	0.6	0.4	0.3	0.5	0.3	0.3	0.304**
Transient elastography	7	2	0	0	2	0	1	2	
Median stiffness (kPa)	4.3 (3.9–6)	4.5			2.6		4.3	10.5 (max 15)	
Treatment yes	7	2	0	0	1	1	1	2	0.880*
Tenofovir	1	1							
Entecavir	5	1				1	1	2	
PegINF	1				1				
Viral load on treatment	470 (263–1331)								
Serology									
HBeAg pos	3	1	1	0	1	0	0	0	0.059*
HBeAg neg	37	9	0	2	4	6	2	14	
HBeAb pos	34	9	0	2	4	5	2	12	0.319*
HBeAb neg	3	1	1	0	1	0	0	0	
HBe seroconverted	34	9	0	2	4	5	2	12	0.530*

Median values with interquartile ranges (IQR).
All values are medians unless stated, IQR is the interquartile range.
[a]Comparing genotypes.
*Fisher's exact test (categorical data, small sample size).
**Kruskal wallis (numerical data, non-normal distribution).

seroconverted), for the remaining three HBeAg negative patients no results for HBeAb were available. The three patients with positive HBeAg and negative HBeAb results had mutations in the BCP region only.

4 | DISCUSSION

Hepatitis B is thought to have been present in Africa for thousands of years and possibly much longer.[24] The predominant genotype is thought to be A1 with probably a more recent establishment of Genotype E.[23] Genotype D is also prevalent in Northern Africa and the Middle East.[25]

We have described the prevalence of various genotypes of HBV amongst a population of African immigrants to Australia. Our data demonstrated a wide variety of genotypes with a particularly high prevalence of genotype A1 (25%) and genotype E (35%). Genotypes tended to cluster in specific geographical areas with Genotype A1 predominating in the Horn of Africa and Central Africa whereas Genotype E predominating in the Horn of Africa. There was however significant overlap of genotypes in geographical regions.

Phylogenetic analysis identified a high prevalence (25%) of HBV subgenotype A1 in our cohort. In young males, A1 has been associated with more aggressive clinical disease, with a 4.5 times higher relative risk of developing HCC compared to non-A genotypes.[5] Subgenotype A1 HBV encodes mutations in the BCP and PC region that decrease core protein translation and reduce HBeAg expression,[26] although the mechanism for the rapid onset of HCC in subjects infected with this strain remains unclear.[27] It was notable that no HCC occurred amongst this small sample, the majority of whom had mild liver disease and were HBeAg negative, although longitudinal follow up of these patients is required to monitor their cancer risk.

The current recommendations for HCC screening in patients with Hepatitis B suggest Africans over 20 years old should have regular screening and this finding supports this recommendation.[28] The high prevalence of genotype A, which is known to be responsive to interferon, may suggest this as a suitable therapeutic option in this population. The use of interferon in Genotype A infection can potentially remove the need for lifelong nucleoside/tide therapy, especially in young individuals of child-bearing age.

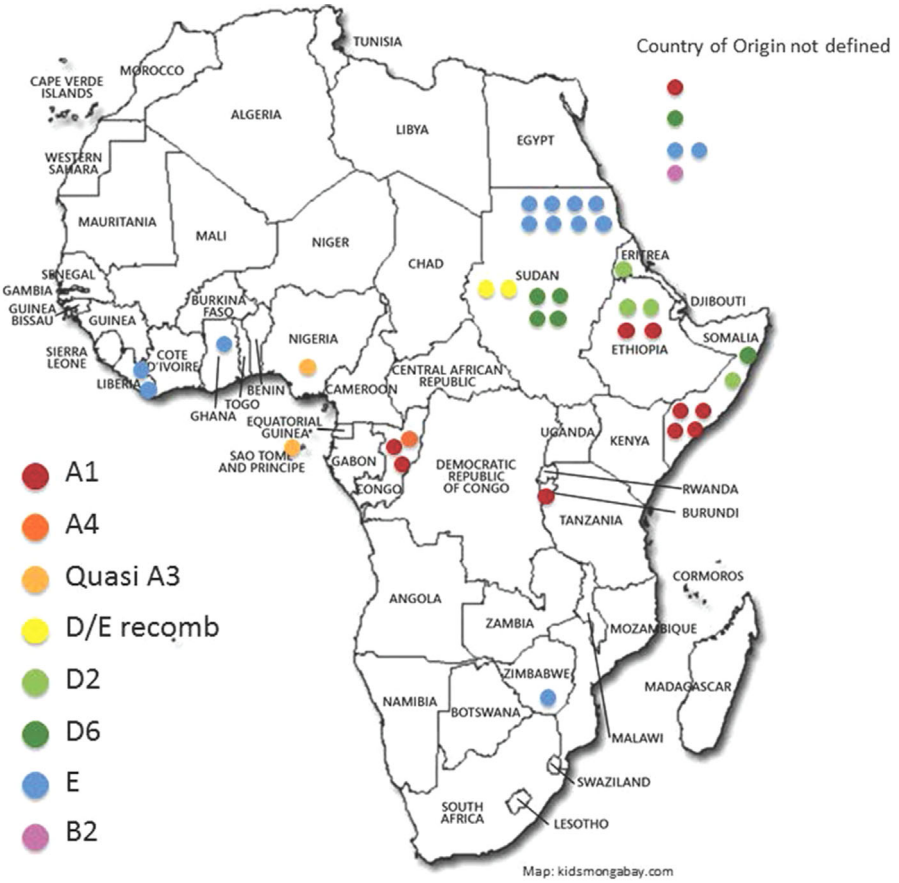

FIGURE 2 Hepatitis B genotype/subgenotype distribution by African country of origin

Although, the high rate of HBeAg negativity observed in an African paediatric HBV population suggested the possibility of more advanced liver disease in this cohort,[11] particularly as they entered adulthood, our data demonstrated mild liver disease in the vast majority of individuals with only one case of documented cirrhosis and one of possible cirrhosis. It was notable that both these cases were Genotype E.

Consistent with this high rate of HBeAg negativity, a high incidence of BCP and/or PC mutations were observed amongst all genotypes. Mutations in these regions have been associated with increased progression to cirrhosis and/or HCC,[14,29] again supporting guidelines for early age of onset for screening in Africans with chronic HBV. The high rates of these mutations also raises the possibility that routine use of genotyping may assist in the selection of patients for treatment, as has been recommended for Asian patients with genotype B or C virus.[13]

Limitations to this study include that the sample size was small and the numbers of each genotype did not allow for accurate between groups statistical comparisons. Data was also collected retrospectively, some information was incomplete and the majority of the patients were from countries in the Horn of Africa.

In conclusion, these findings have important implications for patient monitoring and treatment, particularly with increasing immigration from

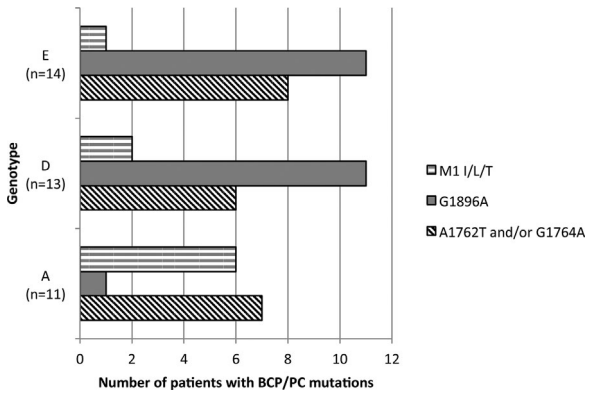

FIGURE 3 Graph of the number of patients where HBV BCP/PC mutations were detected according to genotype. Note that multiple mutations were detected in 16 patients

the Sub-Saharan region. They also highlight the need for further study into the disease course of the various genotypes of HBV, particularly those with high prevalence in African populations.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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INTERNAL MEDICINE JOURNAL

Telehealth: experience of the first 120 consultations delivered from a new Refugee Telehealth clinic

T. R. Schulz,[1,2] M. Richards,[1,3] H. Gasko,[2] J. Lohrey,[4] M. E. Hibbert[2] and B.-A. Biggs[1,2]

[1]Victorian Infectious Diseases Service and [3]VICNISS Healthcare Associated Infection Surveillance System, Royal Melbourne Hospital, [2]Department of Medicine, Melbourne Academic Centre, Doherty Institute, The University of Melbourne, and [4]Arcitecta, Melbourne, Victoria, Australia

Key words
telehealth, telemedicine, refugee, immigrant.

Correspondence
Beverley-Ann Biggs, Department of Medicine, Melbourne Academic Centre, Doherty Institute, The University of Melbourne, Vic. 3010, Australia.
Email: babiggs@unimelb.edu.au

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Abstract

Background: In 2011, the Australian Government introduced Medicare item numbers for telehealth consultations. This is a rapidly expanding method of healthcare provision.
Aims: We assessed the demographic and disease profile of refugee patients attending a new telehealth clinic, and calculated the patient travel avoided. We examined technical challenges and assessed the performance of two videoconferencing solutions using different bandwidth and latencies.
Methods: We audited the first 120 patients attending the telehealth clinic. During consultations, the patient was with the general practitioner (GP) and linked by internet videoconference using VIDYO, GoToMeeting or Skype, to the specialist at a tertiary referral hospital. Travel avoided was calculated and technical problems were assessed by the participating specialist. Bandwidth and latency variations were examined within a university broadband testing facility.
Results: The two most frequently managed conditions were hepatitis C and latent tuberculosis. Twenty-nine different GP were included and 42 consultations required an interpreter. Nearly 500 km of travel and 127 kg of CO^2 production was avoided per consultation. Technical issues were faced in 25% of consultations, most frequently sound problems and connections dropping out. A bandwidth of at least 512 kbps and latency of no more than 300 ms was necessary to conduct an adequate multipoint videoconference.
Conclusions: Telehealth using videoconferencing adds a new component to care of refugee and immigrant patients settling in regional areas. Telehealth will be improved by changes to improve simplicity and standardisation of videoconferencing, but requires ongoing Medicare funding to allow sufficient administrative support.

Introduction

Nearly one-third (30%) of the Australian population live in areas other than major cities[1] and many require access to specialist healthcare. As the delivery of healthcare becomes more specialised, the mismatch between the location of specialists and the population requiring services is increasing. This is particularly evident for the approximately 20 000 refugees that settle each year in Australia,[2] of whom half require specialist consultation.[3] The use of telehealth (consultation through videoconference in which the patient and specialist are in separate locations) is an important modality in the delivery of specialist care to these patients.[4]

Patient convenience is much improved, and reduced travel with telehealth leads to very considerable cost savings, both in the cost of the travel and the opportunity costs of other activities that are not performed while attending clinic.[5,6] Until recently, telehealth was mainly used within the public sector, especially in Queensland.[7] In 2011, the Australian Government introduced Medicare funding for clinical consultations between specialists and patients through telehealth,[8] either at a general practitioner's (GP) practice, from home or from an aged care facility. This led to a large increase in the provision of telehealth services in both the public and private sectors, and in the first 2 years of the scheme, nearly 100 000 telehealth consultations were reimbursed through Medicare.[9]

We present our experience of the first 120 clinical consultations delivered by a new infectious diseases telehealth clinic at a tertiary hospital and patients in the regional and rural Victoria, many of whom were recent refugee arrivals. We assess the benefits and challenges, and make recommendations for improving the utility and

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efficiency of videoconferencing in medicine. We calculate the reduction in carbon output that results from reduced patient travel.

Methods

The Victorian Infectious Diseases Service based at the Royal Melbourne Hospital (RMH) is a tertiary referral infectious diseases service providing inpatient and outpatient care for a broad range of patients within the subspecialty of infectious diseases. A new outpatient telehealth clinic was commenced in early 2012 to complement the current six outpatient clinics. Referrals to the clinic were from GP, and also from other RMH doctors requiring follow up of patients residing in regional areas.

During the telehealth consultation, the patient sat at the GP practice with their GP and/or a practice nurse. They communicated with the specialist through videoconference over an internet connection. Low cost internet videoconferencing systems were used, including VIDYO™ (VIDYO Inc., Hackensack, NJ, USA), GoToMeeting™ (Citrix, Santa Clara, CA, USA) and Skype™ (Skype Technologies S.A., Luxembourg City, Luxembourg). We used Logitech™ C910 cameras (Logitech International S.A., Lausanne, Switzerland), hospital desktop computers with an XGA screen (extended graphics array screen with 1024 × 768 pixels) and a ClearOne™ Chat 50 external speaker microphone (ClearOne Salt Lake City, UT, USA). Hardware at the GP's end was varied, and although guidelines were provided, including using Windows (Microsoft, Redmond WA, USA) or Mac (Apple Inc., Cupertino, CA, USA) OS/X operating systems, there were no fixed hardware requirements. Professional interpreters were used when necessary, and accessed in various ways including onsite, through telephone and through videoconference (three-way videoconference with patient, specialist and interpreter at separate locations).

Patient demographic information was stored in a de-identified Excel spreadsheet (Microsoft™) kept on a password-protected computer for the purposes of this audit. To provide future advice to GP regarding suitable bandwidth and latency for multipoint videoconferencing, we conducted a trial at the University of Melbourne broadband testing facility (Institute for a Broadband-Enabled Society) to assess bandwidths of between 128 kbps and 5 Mbps at a latency of 50 milliseconds (ms). Latency of between 50 ms and 1000 ms were also trialled at fixed bandwidth of 1 Mbps. Clinicians and researchers read medical scripts and independently rated both the sound and picture quality. A 5-point rating scale was used with a score of 3 or above indicating that the parameter was considered at least adequate for a clinical consultation. The project was approved by the Melbourne Health Human Research Ethics Committee.

Results

One hundred and twenty telehealth consultations were conducted between May 2012 and June 2013. Consultations included initial and follow-up assessments, and patients were seen either in combination with a review in-person, or entirely through telehealth. Twenty-nine different GP conducted at least one telehealth consultation with their patient and a specialist. During 76% (91/119) of the consultations, the GP was with the patient. In the other consultations, a practice nurse was present.

The median age of the patients was 39 years, and 63% were male (75/119) (Table 1).

A total of 145 conditions was managed during the 120 consultations.

The most frequently managed conditions were hepatitis C (59 consultations) and latent tuberculosis (42). Other conditions regularly managed included helminthic infections (10 consultations), human immunodeficiency virus (8), eosinophilia (7) and hepatitis B (6). Interpreters were required for 42 consultations. Most frequently, this was a professional interpreter accessed over the phone (15 consultations), through videoconference (10) or onsite (7). Family members interpreted for eight consultations and the GP for three. The most frequently used languages were Nepali (18 consultations) and three languages from Burma (Burmese, Haka Chin or Karen, for 18 consultations).

Software choice was based on GP and specialist preference, Skype was used on 59 occasions, VIDYO on 42 occasions and GoToMeeting on 19 occasions.

Technical difficulties as rated by the specialist were experienced in 25% (30/118) of consultations, although this significantly improved with experience, and in the second 60 consultations, information technology (IT) was rated an issue in only 8% (5/60) of consultations. Professional IT support was available onsite; however, the professional IT was not always immediately accessible. The most frequent IT issues were problems with lack of adequate sound quality, echo, the connection dropping out and difficulties downloading software at the GP's end.

Inadequate sound quality and echo problems were resolved by using a separate phone line if necessary. Loss of connectivity was most frequently caused by lack of adequate available bandwidth. Technical issues at the GP's end were improved when a connection was scheduled with new practices prior to the patient being present to troubleshoot potential problems.

The median distance of patient travel saved for a return trip (using road distance from GP practice to tertiary

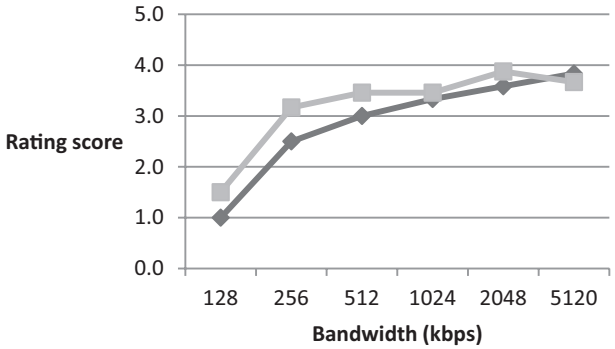

Figure 1 Rated quality of a multipoint videoconference at varying bandwidths (score of 3 or more represents an adequate consultation). (—◆—), Picture quality; (—■—), sound quality.

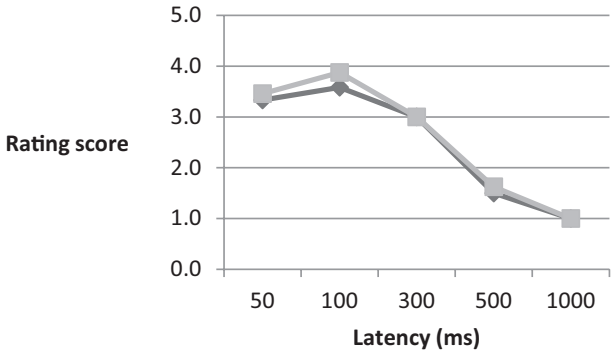

Figure 2 Rated quality of a multipoint videoconference at varying latencies. (—◆—), Picture quality; (—■—), sound quality.

hospital) was 494 km, and a total of over 54 000 km of travel was avoided. It is calculated that 15 200 kg of CO^2 (127 kg of CO^2 per return trip)[10–12] was not released into the atmosphere (assuming all kilometres travelled were by car and for the purpose of the consultation only), based on standard figures from the Australian Greenhouse Office, the Australian Bureau of Statistics and the 'carbon neutral' carbon calculator. This also represented a large time and cost saving for the patient.

The results of the trial of varying bandwidth and latency are shown in Figures 1 and 2. The trial was completed successfully on two (VIDYO and Skype) of the three software products used. We demonstrated that a bandwidth of below 512 kps was inadequate for picture quality and below 256 kps inadequate for sound quality for multipoint videoconference. A maximum latency of 300 ms was necessary for an adequate multipoint videoconference; above this latency, both sound and picture quality were rated as inadequate.

Table 1 Demographic and summary information

Patient and consultation variables	
Median age (years)	39 (IQR 32–49)
Number of males	75
Number of females	44
Consultations with GP with patient	91
GP who conducted at least one consultation	29
Consultations with practice nurse with patient	28
Median return distance from GP practice to tertiary hospital (km)	494 (IQR 188–648)

GP, general practitioner; IQR, interquartile range.

Discussion

We have demonstrated that a successful telehealth clinic can be developed within a tertiary hospital for the provision of infectious diseases clinical care to complex patients attending GP clinics throughout Victoria. Although technical issues were encountered initially, these were largely able to be resolved and significant clinical and patient benefits were realised. We were able to manage a wide range of complex medical conditions, and demonstrated that the inclusion of interpreters was feasible.

We found that telehealth can be used for follow up of discharged hospital inpatients, and regularly scheduled outpatient appointments. Mostly telehealth consultations were in addition to in-person consultations. Some patients however were able to be managed solely through telehealth without the need for in-person review. Those consultations requiring limited clinical examination and a focus on discussion of symptoms, results and prognosis, were particularly well suited to telehealth.

As medical consultations contain an inherent level of unpredictability, it is necessary to be able to arrange to see the patient in-person should unexpected medical complications develop, or the internet connection be inadequate for the required clinical interaction.

The inclusion of an interpreter into a telehealth consultation allows for improved healthcare access for vulnerable groups in the community such as refugees. Accessing onsite interpreters in rural areas is very difficult,[13] and we have demonstrated that the interpreter can sit with the specialist at the central location or with the GP and provide effective interpreting for the consultation.

Our clinic uses low cost internet videoconferencing offering much greater potential savings than telehealth clinical care delivered through expensive hardware-based systems.[5] As internet speed improves, this will become a possibility at most homes and GP practices in Australia.

The inclusion of the GP in the consultation had a direct benefit in having a clear and immediate transfer of

information between specialist and GP, and a potential opportunity for the education of GPs. Including a GP in the consultation increased cost, and made scheduling more complex.

The reduction in carbon output is an important consideration and the high levels of carbon output associated with healthcare delivery have been recognised in other studies both in Australia[14] and internationally.[15]

We confirmed the findings of others that adequate internet bandwidth (speed) is necessary for videoconferencing,[16] particularly with complex patients and if a multipoint consultation is to occur.

The requirement for a bandwidth of at least 512 kps for a multipoint consultation is higher than some recommendations for two-point videoconferencing that have considered a bandwidth of 256 kps adequate.[17] Our demonstration of the need for both upload and download speeds of at least 512 kps to have adequate picture and sound quality reinforces the considerable benefit of improving internet speeds to homes and businesses throughout Australia. Many homes and smaller businesses in Australia (including general practices) use an ADSL2+ (Asymmetric Digital Subscriber Line) internet connection that will generally have a peak bandwidth for download well in excess of 512 kps. However, the upload bandwidth (speed) may at times fall below this.[18] Wireless connections can also be used; however, we would recommend that both upload and download speeds are adequate to ensure a satisfactory consultation. Reliability and latency can also be problematic with an ADSL2+ connection. It is expected that with an Australian fibre optic broadband network both upload and download bandwidths would be significantly higher than this, even without a fibre optic connection to the actual premise.[19]

While telehealth has many advantages, the difficulties should not be underestimated. The high number of technical issues in the initial part of this study could be a significant barrier to uptake. Many busy clinicians would not persist with telehealth if IT issues were so frequently encountered.[20] Consideration should be given to a period of formal training for clinicians and ideally the availability of immediately accessible onsite IT support. The lack of interconnectedness between different software and the lack of an accepted and widely used standard videoconferencing system means clinicians are required to use different software depending on whom they are connecting to. This may be a barrier to wider provision of quality telehealth services. Simplicity and reliability are crucial to success, and until making a videoconference call is as seamless and easy as making a telephone call, full integration into routine clinical services may not occur.

The difficulty of organising an appointment at a time that is suitable for specialist, GP and patient and then to have all arrive in a timely manner should not be underestimated. The inclusion of an interpreter can then introduce a further layer of complexity. Internationally, the issue of scheduling has been successfully addressed using a central agency responsible for all telehealth bookings.[21] Furthermore, the requirement to have a patient sign a Medicare assignment form rather than the acceptance of a verbal agreement added additional administrative workload.

Conclusion

Overall, we found that telehealth enhances access to tertiary hospital-based specialist care. The availability of much faster and more reliable internet, particularly faster upload speeds, has the potential to turn most computers into high-quality videoconference units. Establishment of a telehealth service is achievable by following accepted guidelines and clinicians, and administrators should consider this development a component of routine care. This should be pursued as a way to improve healthcare access for all in regional areas including refugees, one of the most vulnerable groups in Australian society. Although IT issues can be problematic, they can be resolved and a regular telehealth clinic has proven a successful addition to our infectious diseases service.

Key recommendations and conclusions

1 Provide resources for administrative support for telehealth, either as a central service or at individual locations.
2 Use telehealth as one component of overall patient care and ensure the opportunity for in-person review is always available.
3 Move towards an accepted standard system for videoconferencing.
4 Ensure a consistent bandwidth of at least 512 kbps, for upload and download, with a latency of 300 ms or less to allow adequate sound and picture quality for multipoint videoconferencing.
5 Continued Medicare item number support for telehealth to account for the increased administrative complexity.
6 Encourage software (and hardware) vendors to improve the ease of use for clinicians, until videoconferencing is as simple as using the telephone.

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Using telehealth to improve access to hepatitis C treatment in the direct-acting antiviral therapy era

Thomas R Schulz[1,2], Kudzai Kanhutu[1,2,3], Joseph Sasadeusz[1], Sally Watkinson[1] and Beverley-Ann Biggs[1,2]

Abstract

Introduction: One-third of the Australian population lives outside major cities and this group has worse health outcomes. Telehealth is becoming an accepted way to improve patient access to specialist healthcare. Over 200,000 Australian's have hepatitis C virus (HCV) and new treatments are very effective and well tolerated. We aim to demonstrate that HCV treatment utilising telehealth support for care delivery has cure rates similar to onsite care in clinical trials. We also report length of consultation and calculate reductions in travel and carbon output.

Methods: Patient demographic, clinical, and treatment outcome data were collected prospectively from hospital software and analysed retrospectively. This was an audit of all patients treated for HCV in one year from a single tertiary hospital that included telehealth in their care delivery.

Results: Sustained virological response was achieved in 51/52 (98%) patients with completed treatment courses, and 51/58 (88%) of those who had a planned telehealth consultation as part of their management. A median of 634 km of patient travel was saved per telehealth consultation.

Discussion: We found that a telehealth-supported outreach programme for patients in regional Australia with HCV produced similar outcomes to clinical trials. There was a considerable saving in time and cost for the patients and significant environmental benefit through the reduction in carbon footprint associated with travel to distant specialist health services. We conclude that telehealth facilitated outreach is a feasible and effective way to access HCV treatment and cure in regional Australia.

Keywords

Hepatitis C, telehealth, outreach, immigrant, direct-acting antiviral

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Introduction

Hepatitis C virus infection (HCV) is a significant health problem in Australia affecting over 200,000 people, or 1% of the population.[1] Many infected individuals do not live in major cities,[2] and so access to care is more limited and health outcomes are worse.[2,3,4] Most HCV is acquired through injecting-drug use.[4,5] In Australia, over 28% of the population were born in other countries,[6] including many immigrants originating from countries with reported high rates of HCV.[6,7] The regional population also has higher rates of obesity and alcohol consumption, which are associated with poor liver health.[8]

Prior to 2016, only approximately 20,000 individuals had received HCV treatment.[4,5] This was mainly because the available treatment options, interferon and ribavirin, had suboptimal cure rates and high levels of toxicity. However, direct-acting antiviral therapy (DAA) has revolutionised HCV treatment demonstrating high efficacy and low toxicity. Since March 2016, this has been subsidised by the Australian

[1]Victorian Infectious Diseases Service, The Royal Melbourne Hospital, at The Doherty Institute, Melbourne Australia
[2]University of Melbourne, Department of Medicine/RMH, at The Doherty Institute, Melbourne, Australia
[3]Health Informatics Society, Melbourne, Australia

Corresponding author:
Professor Beverley-Ann Biggs, University of Melbourne, Department of Medicine/RMH, at the Doherty Institute, 792 Elizabeth Street, Melbourne Victoria 3000, Australia.
Email: babiggs@unimelb.edu.au

Government for the treatment of all adults with HCV.[4,5] By the end of June 2017 over 43,000 people had commenced with DAA treatment.[9] Without treatment, a significant number of people living with HCV are expected to develop major morbidity including cirrhosis and hepatocellular carcinoma.[10]

Tertiary hospital specialist centres have been at the forefront of treatment delivery to this cohort, but the wide geographic distribution of Australia's population has meant that patients often have to travel considerable distances, and as a result many have not yet accessed care.

The increasing availability of internet-based videoconferencing platforms has provided unprecedented capacity to manage patients remotely. A computer with a webcam and speaker, and a reasonable speed internet connection is all that is necessary to conduct a consultation.[11] Telehealth is well-accepted by patients and can improve healthcare efficiency.[12] The Victorian Infectious Diseases Service (VIDS) currently provides medical consultations via telehealth for rural and regional patients. This clinic was initially established for refugees and immigrants who, on arrival in Australia, settled in regional areas. [11] It has now expanded to include patients with HCV who can be seen in conjunction with local general practitioners (GPs).

Previously described successful hepatitis C management via telehealth has involved specialists providing advice to treating clinicians at remote sites, rather than direct clinical consultations with patients[13] or intensive review.[14] More recently, a large increase in the use of telehealth for HCV care has been described[15] and an international database analysis has shown good clinical outcomes using telehealth.[16] Our study outlines the outcomes of HCV treatment supplemented with the use of telehealth to both increase access to care and reduce patient travel.

The purpose of this study was to determine the virological outcomes of telehealth-supported HCV management and to compare these with results achieved in clinical trials.

The primary outcome was the rate of sustained virological response (SVR) achieved 12 weeks after completion of therapy (SVR12) amongst patients treated for HCV who had telehealth included as part of their management.

Secondary outcomes were the patient travel distance saved through the use of telehealth consultations and the reduction in carbon output that this was expected to have.

Materials and methods

The study was part of a quality audit of the hepatitis outreach service. Data were collected prospectively and analysed retrospectively. Ethics approval was received from the Royal Melbourne Hospital (RMH) Human Research and Ethics Committee.

This study was conducted in conjunction with the VIDS integrated hepatitis C service (IHCS) at the RMH. The IHCS provides outreach services to smaller regional cities through both regular visits by infectious disease specialists providing onsite clinics, and a nurse who works in an outreach capacity and provides support for HCV patients, including facilitating telehealth consultations. The nurse ensures appropriate patient workup occurs before the specialist appointment. All regional HCV patients seen via the IHCS are considered for telehealth management. Any patients referred to the service with decompensated cirrhosis were redirected for specialist onsite gastroenterology management.

All patients who had a telehealth appointment from the RMH for the management of HCV in the 12 months from 1 March 2016 and who were on treatment were included. This study included patients with multiple genotypes and also some patients with compensated cirrhosis. Patients either commenced treatment at outreach clinics and then had ongoing follow-up via telehealth or had treatment commenced during a telehealth consultation with ongoing follow-up through either telehealth or through outreach clinics. Patients were not required to have any onsite visits. Patients were commenced on treatment at the first specialist visit based on patient preparedness and the availability of sufficient clinical information. Patients then had a first follow-up appointment 4–6 weeks after commencement of treatment. Treatment selection was based on Australian Clinical Practice Guidelines.[4,5] The patient treatment outcome was determined by a blood test for the presence of HCV performed at least 12 weeks after completion of therapy (SVR12).

During telehealth consultations, patients attended their local GP's clinic while the specialist was located at the RMH. Although the patient attended the GP's clinic, a health practitioner was not always present with them during every consultation. The IHCS nurse was available for telephone advice and support in addition to the specialist consultations.

Clinical data were collected from the clinical software (CAReHR®) used within the clinic for patient management.

Also measured was patient travel kilometres saved through not attending the clinic in person and the reduced carbon production due to reduced travel (assuming the Australian average for passenger cars of 258 g of carbon produced per kilometre).[17] Travel data were based on the patient's home address postcode and the address where the telehealth consultation took place. Duration of the consultation and any

technical difficulties were recorded by the tertiary hospital specialist.

Results

In the 12 months from March 1, 2016, 58 patients were treated for hepatitis C via telehealth. The mean age was 51 years and 76% of patients were male. The most common genotype was genotype 1 (36 patients) and then genotype 3 (20 patients). The majority (34) had their treatment commenced at an onsite visit and 24 had treatment commenced during a telehealth consultation. One patient of Afghan descent required the use of a telephone interpreter during the telehealth consultation.

Thirteen patients had previously failed treatment with pegylated interferon and ribavirin and one patient who was lost to follow-up also had previous DAA treatment (boceprevir). No patients were hepatitis B surface antigen positive.

Eleven patients had cirrhosis based on a Fibroscan® score above 12.5 kPa but none had decompensated cirrhosis. Patients with cirrhosis had liver ultrasound performed for hepatocellular carcinoma (HCC) screening, and gastroscopy referral where indicated. After completion of treatment when ongoing HCC screening was required, this was organised through the local GP with the support of the IHCS. Gastroscopy was performed by gastroenterologists, where available locally, or alternatively through referral to a tertiary hospital.

Treatment included sofosbuvir/ledipasvir for 34 patients and 24 patients had sofosbuvir and daclatasvir. Twenty patients had genotype 3 diseases, and all received a combination of sofosbuvir and daclatasvir. Genotype 3 patients were treated for 12 weeks, or for 24 weeks if patients had cirrhosis or had previously failed treatment. Thirty-six patients had genotype 1 disease, 33 of whom received sofosbuvir/ledipasvir and three received sofosbuvir and daclatasvir (due to drug interactions). Six patients with genotype 1 HCV, viral loads of less than 6 million IU, and no cirrhosis had short course 8-week treatment. The other 30 genotype 1 patients had 12 weeks of treatment. The single patient with genotype 2 HCV received 12 weeks of sofosbuvir and daclatasvir, and the single genotype 6 patient received 12 weeks of sofosbuvir/ledipasvir. Two patients had co-infection with HIV, both of whom achieved an SVR.

Based on clinical trials using intention to treat analysis, the expected SVR rates for hepatitis C genotype 1 treated with 8–12 weeks of sofosbuvir and ledipasvir is 95–99%[18,19] in previously untreated patients, and 94% in previously treated patients.[20,21] For genotype 3, SVR rates of 86–97%[22] are reported after treatment with sofosbuvir and daclatasvir. In our cohort, SVR was achieved in 51 patients. One patient had a relapse and one patient withdrew from treatment for personal reasons. One patient did not start the prescribed treatment and four were lost to follow-up.

The SVR rate amongst this cohort for those who had blood tested for HCV at least 12 weeks after completion of treatment was 51/52 (98%; comparable to a per protocol analysis). Amongst all those who had a planned telehealth consultation as part of their management 51/58 (88%) achieved an SVR (Table 1). Of those patients who commenced treatment 51/57 (89%) achieved an SVR (comparable to a modified intention to treat analysis in a randomised trial). All 11 cirrhotic patients achieved an SVR (eight with genotype 1 and three with genotype 3). Only one patient (genotype 3, not cirrhotic, no previous treatment, treatment commenced onsite) has had a known relapse after completing a full treatment course (12 weeks of sofosbuvir and daclatasvir). The relapse was with genotype 3 virus.

Table 1. Patient outcomes

	Number of patients	Sustained virological response (%)	Failed treatment (%)	Lost to follow-up/ceased/ did not start (%)
All	58	51 (88%)	1 (2%)	4 (7%)/1 (2%)/1 (2%)
Male	44	39 (89%)	0	4 (9%)/1(2%)/0
Female	14	12 (86%)	1 (7%)	0/0/1(7%)
Genotype 1	36	35 (97%)	0	1(3%)/0/0
Genotype 2	1	1 (100%)	0	0
Genotype 3	20	15 (75%)	1 (5%)	3(15%)/0/1 (5%)
Genotype 6	1	0 (0%)	0	0/1(100%)/0
HIV co-infection	2	2 (100%)	0	0
Cirrhosis	11	11 (100%)	0	0
Previous failed treatment	13	11 (85%)	0	2 (15%)/0/0
Started treatment at onsite visit	34	30 (88%)	1 (3%)	2 (6%)/1 (3%) /0
Started treatment via telehealth	24	21 (88%)	0	2 (8%)/0/1 (4%)

The patient had ongoing risk factors for reinfection but unfortunately a stored sample was not available for comparison viral sequencing. Patients who were lost to follow-up had received multiple attempts at contact by both the local site staff and the IHCS, using phone and written communication.

The median travel avoided for each telehealth consultation was 634 km (mean 626 km) and each patient had a median of three (mean 3.06) visits during their treatment course, of which a median of two (mean 2.4) were telehealth consultations. For one year, an estimated 86,720 km were saved through seeing patients via telehealth. This will have reduced the carbon output by a total of 22.37 tonnes, assuming that the trips avoided would otherwise have been completed by car.[17,23,24]

Technical difficulties occurred in less than 10% of consultations and the mean telehealth consultation duration was 15 min or less (83% of visits were for treatment continuation and 17% for treatment initiation).

Discussion

Health outcomes for those living in regional Australia are worse than for those living in major cities.[3] This is also the case in regional areas of other developed countries.[25] The availability of specialists in regional areas is lower than in capital cities[8] and it has been demonstrated that fibrosis scores are higher in regional HCV patients, suggesting later access to care.[26] Telehealth is one way of reducing barriers to care and ensuring that a person's place of residence does not negatively impact on their health outcomes. The use of telehealth is expanding rapidly both in the number of users and in the range of areas of healthcare in which it is used.[27] With the introduction of novel modes of healthcare delivery, it is important to demonstrate similar health outcomes to the current method of care.

The availability of DAAs has revolutionised HCV care and made cure a reality for many patients.[28] Studies of real-world treatment outcomes for HCV patients using DAAs managed with onsite care have shown similar outcomes to clinical trials.[28,29] Our successfully treated real-world patient cohort has demonstrated comparable virological outcomes (SVR) for telehealth-managed HCV patients using DAAs compared with onsite management in clinical trials. It is notable that the cure rate was the same for patients who had treatment commenced at an onsite visit and those who had treatment commenced via telehealth. The comparison with clinical trials offers a reference point to results that can be achieved under ideal conditions. The comparison with clinical trials has also been used in other HCV studies of real-world care[29–31] although direct statistical comparison may not be considered appropriate and has not been performed in this study.[32]

This telehealth cohort included those with cirrhosis, those with previous treatment failure, and a small number with HIV co-infection. Patients were treated as per Australian guidelines.[4,5] The results presented suggest that efforts to improve access to DAA therapy using telehealth can be achieved without compromising quality patient outcomes.

Telehealth also had significant logistical and financial benefits for patients by reducing their travel burden. Telehealth has additional benefits for clinicians in either reducing the amount of travel that is necessary or increasing the number of patients who can be managed at onsite visits if they are partially managed using telehealth (as was the case in this study). In this study, patient travel savings were calculated using the home address postcode and the location of the tertiary hospital. It is appreciated that the patients may have incurred a small travel cost in going to their local doctor for the telehealth appointment, although most commonly patients lived in the same postcode as their GP. Many professional medical groups now support the use of telehealth for clinical care delivery.[33,34]

An additional potential advantage of telehealth is direct involvement of local staff at the time of specialist consultation. This offers the opportunity to directly communicate treatment plans but also to implement locally directed management of comorbidities such as alcohol use and obesity that are problematic for liver health. Although local medical staff were not present during all telehealth appointments they were readily contactable when required.

The low rate of technical complications reflects that this is an established telehealth programme. Earlier studies had demonstrated a higher rate of technical complications in the initial phase of this telehealth programme.[11] This suggests that after an initial period of programme development, a telehealth programme using internet-based videoconferencing platforms can operate reliably with few technical complications.

This study had limited participant numbers and was based at one health service, therefore results may not be generalisable to other centres. The use of telehealth is dependent on patients having access to the internet, either at home or at their local health service. All patients who utilised telehealth through our health service were included in the study and all patients from regional areas were offered telehealth consultation, although it is possible that the referring clinicians chose only a subset of their HCV population for referral to a programme that included telehealth.

The World Health Organization (WHO) has identified the health impacts of climate and environmental change as one of the leading priorities for global

action.[35] The use of telehealth has the potential to significantly reduce the carbon footprint associated with the provision of healthcare.[36] It has been estimated that the carbon footprint associated with a telehealth consultation is between 40–70 times less than that of an onsite consultation with greater benefit for longer distances.[36] This reduction in carbon footprint has a potential societal benefit that extends beyond the individual patient.

The use of telehealth to improve access to specialist care offers one way of improving outcomes for regional patients with HCV. This is already occurring in other parts of Australia.[15] This complements other recent changes to HCV care including improved support for GP prescribing and the development of nurse-led models of care.[4,5]

Conclusion

Providing HCV management via telehealth to patients in regional areas is feasible and effective and should be considered for broader use in other regional areas as one way to improve access to HCV treatment and cure.

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Improvements in patient care: videoconferencing to improve access to interpreters during clinical consultations for refugee and immigrant patients

Thomas R. Schulz[1,4] MBBS, BSc, FRACP, Physician

Karin Leder[1,2] MBBS, FRACP, PhD, MPH, DTMH, Head of Infectious Disease Epidemiology

Ismail Akinci[3] BA, NAATI, Chief Executive Officer

Beverley-Ann Biggs[1,4,5] MBBS, PhD, MRCP, FRACP, FRCP, FACTM, Professor

[1]Victorian Infectious Diseases Service, Royal Melbourne Hospital, Level 5 Doherty Institute, 792 Elizabeth Street, Melbourne, Vic. 3000, Australia. Email: Thomas.Schulz@mh.org.au
[2]Department of Epidemiology and Preventive Medicine, School of Public Health and Preventive Medicine, Monash University, 99 Commercial Road, Melbourne, Vic. 3004, Australia. Email: karin.leder@med.monash.edu.au
[3]All Graduates Interpreter Services, Suite 8.02, 343 Little Collins Street, Melbourne, Vic. 3000, Australia. Email: admin@allgraduates.com.au
[4]University of Melbourne, Department of Medicine at the Doherty Institute, Level 5 792 Elizabeth Street, Melbourne, Vic. 3000, Australia.
[5]Corresponding author. Email: babiggs@unimelb.edu.au

Abstract

Objective. To demonstrate the suitability of accessing interpreters via videoconference for medical consultations and to assess doctor and patient perceptions of this compared with either on-site or telephone interpreting.

Methods. We assessed the suitability and acceptability of accessing interpreters via videoconference during outpatient clinical consultations in two situations: (i) when the doctor and patient were in a consulting room at a central hospital and the interpreter sat remotely; and (ii) when the doctor, patient and interpreter were each at separate sites (during a telehealth consultation). The main outcome measures were patient and doctor satisfaction, number of problems recorded and acceptability compared with other methods for accessing an interpreter.

Results. Ninety-eight per cent of patients were satisfied overall with the use of an interpreter by video. When comparing videoconference interpreting with telephone interpreting, 82% of patients thought having an interpreter via video was better or much better, 15% thought it was the same and 3% considered it worse. Compared with on-site interpreting, 16% found videoconferencing better or much better, 58% considered it the same and 24% considered it worse or much worse.

Conclusions. The present study has demonstrated that accessing an interpreter via videoconference is well accepted and preferred to telephone interpreting by both doctors and patients.

What is known about the topic? Many immigrants and refugees settle in rural Australia. Access to professional on-site interpreters is difficult, particularly in rural Australia.
What does this study add? Interpreters can be successfully accessed by videoconference. Patients and doctors prefer an interpreter accessed by videoconference rather than a telephone interpreter.
What are the implications for practitioners? Doctors can utilise videoconferencing to access interpreters if this is available, confident that this is well accepted by patients and preferred to telephone interpreting.

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Introduction

Australia is a multicultural society, with 26% of the population born overseas.[1] Over 20 000[2] people are accepted as refugees each year on humanitarian grounds and, in 2012, over 100 000 immigrants settled in Australia from non-English speaking countries.[3] Overall, 19% of the Australian population does not speak English at home and 4% speaks English very little or not at all.[1] This presents enormous challenges for the provision of health services, particularly in rural areas.

In Victoria, approximately 6000 refugees are settled each year in urban and regional areas. Many more asylum seekers are currently in the community waiting for processing of asylum claims. Most undertake health screening with local general practitioners (GPs) and approximately 50% require referral to a specialist for assessment and further management.[4] These clinical consultations usually require interpreters. Guidelines recommend the use of professional interpreters for medical consultations and studies have shown that access to professional interpreter services can improve patient care.[5,6]

Interpreters can be difficult to access, even in urban areas. Some hospitals provide in-house interpreting for commonly encountered languages. This service does not cover less common language groups and is generally only available within business hours. Smaller hospitals, healthcare facilities such as community health centres and general practices have no on-site interpreter services readily available. Instead, doctors can access interpreters via a booked on-site or telephone interpreter. Family members are not recommended for use as interpreters,[5–7] although it is recognised that this does occur occasionally.[7,8]

Videoconferencing is a technical advance that could be useful when on-site interpreters are not available, but to date has not been used routinely in Australia. In the present study we evaluated the use of videoconferencing with interpreters for clinical consultations between specialists at a tertiary hospital and recently settled refugee patients attending rural GPs. The aim of the study was to determine the level of satisfaction of doctors and patients with this technology, as well as its practical limitations.

Methods

The Travel and Immigrant Health Clinic in the Victorian Infectious Diseases Service (VIDS) at the Royal Melbourne Hospital has over 800 attendances annually. Approximately 40% of patient visits require an interpreter.

On-site interpreters are used when possible, although most languages required in this clinic are not covered. Alternatively, interpreters are accessed through All Graduates interpreter service, a private contract organisation. All Graduates interpreters are provided either on-site or via the telephone.

We assessed the suitability and acceptability of accessing interpreters via videoconferencing during clinical consultations in two situations: (i) when the doctor and patient were in a consulting room at a central hospital and the interpreter sat remotely (Fig. 1, Model 3); and (ii) when the doctor, patient and interpreter were each at separate sites (Fig. 1, Model 4).

For this study, All Graduates provided a videoconferencing service, with interpreters situated at a central site.

Patients requiring interpreters were identified before the clinic visit and a request was made to All Graduates for an interpreter via videoconference. On the clinic day, the interpreter attended the centrally located All Graduates office at the specified appointment time.

The doctor commenced the videoconference after the patient gave informed consent to take part in the study. Consecutive (not simultaneous) medical interpreting was used for all episodes, with the doctor pausing to allow the interpreter to speak to the patient.

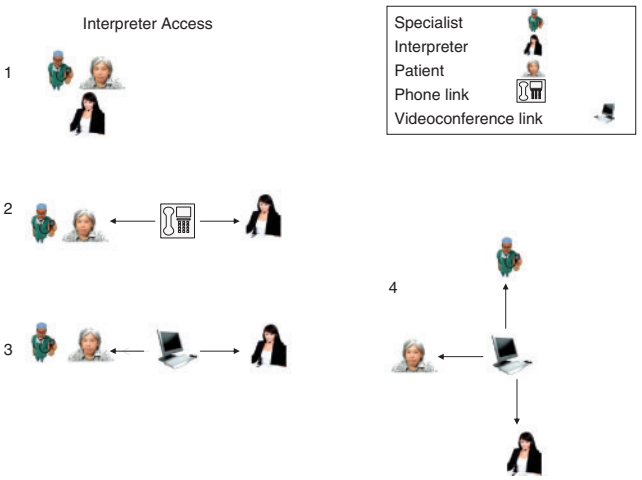

Fig. 1. Models of care for the use of interpreters in clinical consultations. Models 1 and 2 are currently used models. Models 3 and 4 are novel models evaluated in the present study.

We used Logitech C910 (Logitech International, S.A., Lausanne, Switzerland) cameras attached to hospital desktop computers with a standard screen size, a ClearOne Chat 50 (ClearOne, Salt Lake City, UT, USA) external speaker microphone and either Cisco Jabber (Cisco Systems Inc, San Jose, CA, USA) or VIDYO (VIDYO Inc, Hackensack, NJ, USA) software. These are voice-over Internet protocol (VoIP) videoconferencing systems akin to commonly recognised programs such as Skype, with a secure platform that is suitable for medical consultations.

Separate doctor and patient questionnaires were completed immediately after the clinic consultation. The questionnaires were based on a previously used questionnaire[9] and involved demographic questions, five-point Likert scale responses and open-ended questions. The study and questionnaires were approved by the Human Research Ethics Committee of the Royal Melbourne Hospital as part of quality assurance activities. Patient questionnaires were completed with the assistance of the interpreter after the clinical consultation had finished. The study was conducted over a 1-year period from July 2012.

Results

Interpreter bookings were made on 65 occasions and were provided on 56 of these occasions (86%). On eight of these occasions the interpreter was present for two patients and on three occasions for three patients. Patients did not attend on 20 occasions, and on one occasion the patient did not want to use an interpreter (Fig. 2).

Questionnaires were completed for 50 clinical consultations. Forty-three of these involved the doctor and patient in the clinic room and the interpreter at a remote site (Fig. 1, Model 3). Seven consultations involved a three-way clinical consultation with the doctor, patient and interpreter at separate locations (Fig. 1, Model 4). Doctors completed 50 surveys and patients 47 surveys.

The start of a consultation was delayed due to late arrival of an interpreter on four of 50 (8%) occasions. Some interpreters

were booked for and completed questionnaires with more than one patient during a single session.

The median age of patients was 31 years (range 19–70 years) and 51% were female. Patients had been in Australia for a median of 11 months (range 2 months–8 years) and eight separate languages were used. The most commonly used language was Burmese (16 episodes); other languages spoken by immigrants from Burma included Karen (11 episodes) and Haka Chin (10 episodes; Fig. 3). Only 60% of episodes of interpreting were provided in the patient's first language. Overall 79% of patients (37/47) were born in Burma.

Most patients (45/47) had previously used an interpreter when attending a doctor.

When asked to compare videoconference interpreting with on-site interpreting, seven of 45 patients (16%) found videoconferencing better or much better, 26 (58%) considered it the same and 11 (24%) considered it worse or much worse (Fig. 3; response missing in two cases).

When comparing videoconference interpreting with telephone interpreting, 32 of 39 patients (82%) thought having an interpreter via video was better or much better, six (15%) thought it was the same and one person (3%) considered it worse (Fig. 4; response missing in eight cases).

Most patients (46/47) agreed or strongly agreed that they were satisfied overall with the use of an interpreter by video; however, nine of 47 patients (19%) agreed or strongly agreed with the statement that they were concerned the interpreter may have missed something.

Doctors' responses for comparing videoconferencing with an on-site service showed they found it better or much better on two of 50 occasions (4%), the same on 27 occasions (54%) and worse or much worse on 20 occasions (40%; Fig. 5).

Compared with phone interpreting, doctors thought video interpreting was better or much better on 44 occasions (88%), the same on two occasions (4%) and worse or much worse on three occasions (6%; Fig. 5).

Problems with information technology (IT) were identified by patients during seven of 47 consultations (15%) and by doctors during 11 of 50 consultations (22%). IT issues were identified by doctors in three of eight (37%) consultations using VIDYO and in eight of 42 (19%) consultations using Cisco Jabber. Problems with IT included echo (2/11), inability to log in (3/11), poor picture quality (3/11) and sound dropping out (2/11).

The seven three-way clinical consultations had IT issues on two occasions (echo), and for these two patient questionnaires could not be completed.

Discussion

Advances in technology enable new models for doctor–patient care, and videoconferencing where patients and doctors are physically remote is rapidly gaining acceptance. In the present

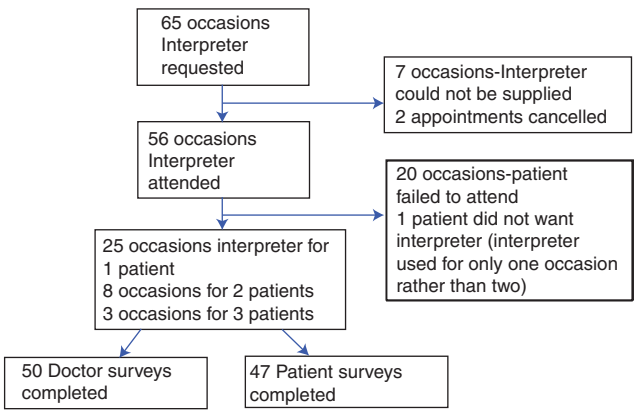

Fig. 2. Outcome of each planned occasion of use of interpreter via videoconference.

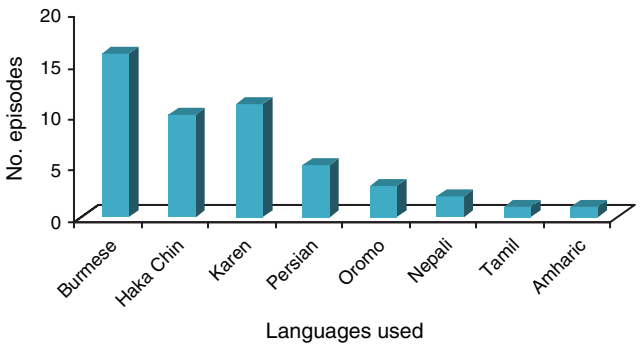

Fig. 3. Languages used by interpreters.

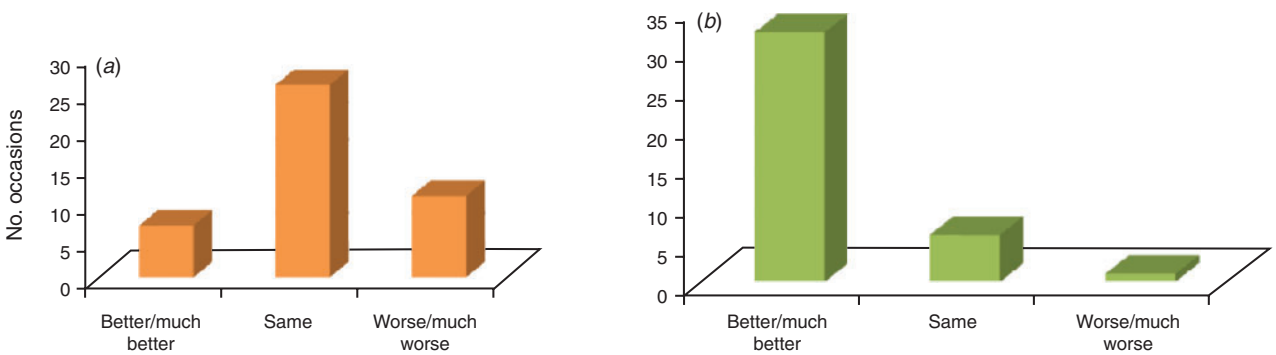

Fig. 4. Patients' comparisons of using an interpreter via videoconference with (*a*) in-person and (*b*) telephone interpreters.

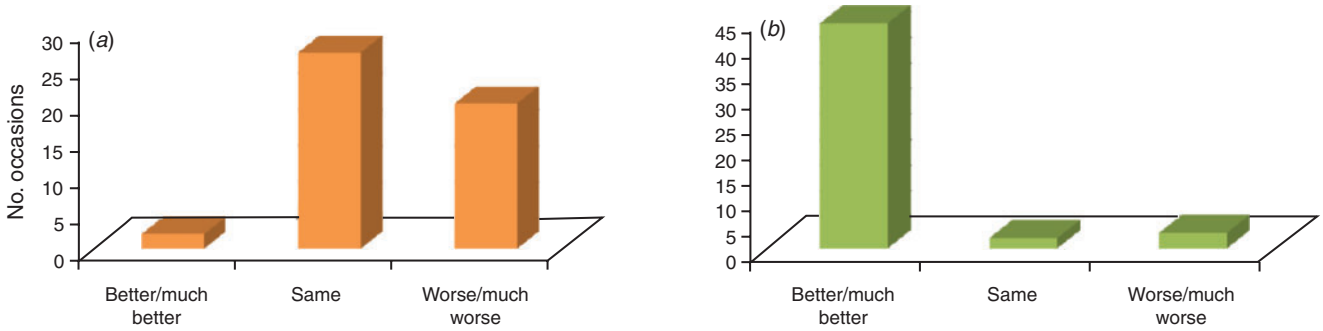

Fig. 5. Doctors' comparisons of using an interpreter via videoconference with (*a*) in-person and (*b*) telephone interpreters.

study we added two new components to the model for consultations requiring interpreter services, with the interpreter sitting at a separate site from the patient and doctor, and the patient, doctor and interpreter all physically separated and connected by three-way videoconferencing.

The study demonstrated that videoconferencing with interpreters is well accepted by both patients and doctors as a means of medical interpretation. Patients and doctors overwhelmingly preferred videoconferencing to phone interpreting, although most patients and doctors still preferred a professional on-site interpreter. These findings are in keeping with international studies using largely Spanish interpreters that have indicated a preference for on-site interpreters,[9,10] and shown an acceptance of remote methods of interpreter access such as video[11] and phone if an on-site service is not available.[12,13]

Advantages of videoconferencing compared with on-site interpreters are ease of interpreter access for uncommon languages, especially in rural areas, and access to interpreters at short notice and out of standard clinic hours.[10] Compared with phone interpreting, interpreters via videoconference can use non-verbal cues to improve interpreting and assess patient body language, and surveys have found that rapport is better established with patients when visual communication is available.[14] The ability of the patient to see the interpreter may make them feel more comfortable in this setting.[13]

Technical issues were present in 23% of consultations. These issues would need to be resolved to consider this method as a part of routine practice because they interfered with normal clinic flow. That doctors more frequently identified IT issues than patients is most likely because many issues (such as difficult logging in) were resolved before the patient entered the clinic room. Other trials have also identified IT issues as a barrier to successful implementation.[9] This may be improved by upgraded software and hardware. However, this needs consideration before recommending more widespread use of videoconferencing for interpreting. Simplicity and reliability will be crucial to any successful implementation of videoconferencing.

Implementation of videoconferencing for interpreting will require additional resources. Previous studies have shown that the additional time to access an interpreter is a barrier to the use of interpreter services.[15] An ideal system would involve a website with links to available videoconferencing interpreters and high-speed Internet access. This model is currently available in parts of the United States and appears to be cost-effective and well accepted.[10,16,17] The upcoming implementation in Australia of a widely available high-speed broadband Internet network may allow this to become a reality.

One limitation of the study was that the same interpreters who conducted the clinical consultation also undertook the patient survey (completed immediately after the consultation). The use of a second interpreter to conduct the survey, although more complicated logistically, may have provided less potential for bias. The accuracy of the interpreting was also not assessed. This was highlighted by the finding that 31% of patients indicated previous use of an interpreter via videoconference. This figure is unlikely to be accurate because, to our knowledge, this is the first use of videoconferencing for interpreting in consultations with refugees. It may be that some patients interpreted this question to include the just-completed interpreting session. Another limitation is that the numbers were too small to formally assess the acceptability of having the patient, doctor and interpreter at three different sites.

Conclusion

The present study has demonstrated that accessing an interpreter via videoconference is well accepted and preferred to telephone interpreting by both doctors and patients. In addition, the use of an interpreter accessed by videoconference for a telehealth consultation (three-way interpreting) was shown to be feasible and acceptable to doctors and patients in the small number of consultations assessed. We recommend that resources be allocated to improving the availability of interpreters that can use this technology, and ensuring that health services in Australia have access to high-speed Internet, cameras, speakers and software systems to facilitate uptake.

Competing interests

None declared.

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Discussion

This research has addressed the issue of how to provide high quality health care for Refugees and Immigrants who settle in rural Australia. The main themes include: choosing screening tests which are appropriate for refugees and immigrants from different backgrounds, providing better care to those settling in rural and regional Australia and using telehealth to safely improve access to care. These themes are examined in the context of the already existing poorer health outcomes reported for rural Australians, compared to those in large cities.

The major findings from this research are that: 1. Screening for *H.Pylori* can be a cost effective strategy to reduce gastric cancer death in high risk populations, 2. Hepatitis B genotype is varied amongst immigrants and reflects the country of origin, 3. A telehealth programme established to provide care to immigrant patients in regional Australia can provide effective care to this group, specifically for the treatment of Hepatitis C, and 4. The use of telehealth can be extended to include provision of interpreters via videoconference and this is well accepted by patients and clinicians.

These can be considered successful outcomes as clarity has been added to clinical questions that existed prior to the research being conducted. These are successful elements from the perspective of the treating clinicians. The implementation studies looking at telehealth, interpreters and Hepatitis C care provision have demonstrated success in establishing and evaluating a new service. The subsequent large expansion of this program during the covid pandemic has provided compelling evidence that this can be a broadly utilised method of care delivery.

This research has assessed success largely from the perspective of the treating clinicians and the health service. Only the surveys of patient preference conducted as part of the interpreter paper have also assessed the patient perspective of components of these care models.

Currently in Australia healthcare for refugees who settle in regional areas is largely provided by General Practitioners with support from community health care. Within the first 6 months after arrival specific settlement services are provided and this includes support with accessing housing, schooling and linked to a suitable medical practitioner. Guidelines for this care have been developed both nationally and in Victoria (58, 221). The main leadership for these has been through The Victorian Foundation for Survivors of Torture (VFST) (222). These guidelines, resources and practices are based on trauma informed principles. This has also led to the development of a Refugee Health program including programmes to improve access to Specialist services (19). The questions addressed in this research relate to this refugee support program generally, and in particular access to, and provision of specialist care.

For other immigrant groups there are not specific health services, and these immigrants will utilise General Practitioners as the access point to the health system. International students have limited pre departure screening and do not have any recommended health screening after arrival but will require health screening should they subsequently choose to immigrate (52). Health care access for undocumented migrants is less well understood. This population does not have access to universal health care and may minimise any interactions with health systems in order to maintain low exposure to government officials (223).

Paper one focuses on the cost effectiveness of screening for *H. pylori*. This paper has demonstrated that under a set of reasonable assumptions, the use of stool antigen testing represents the most cost-effective screening strategy, and that consideration should be given to utilising this amongst

populations at high risk. Clarifying high risk is more difficult, and is poorly defined in current guidelines (63). Groups of particularly high risk such as those who have a family history of gastric cancer would warrant screening (113). For people for whom the risk is simply having lived in a particular country, it is difficult to make a strong recommendation without randomised trial evidence.

The majority of studies looking at *H.pylori* eradication for reducing gastric cancer have been done in Asian populations and the recommendations for population-based screening are stronger for these populations (105, 112). Limited work has been done on *H.pylori* screening beyond these populations, or amongst immigrants from these countries (113). A randomised trial is in progress in the United Kingdom amongst older males which may partially address this question (224).

Guidelines make a weak recommendation for immigrants from specific Asian countries with a known high *H. pylori* rates (Korea, Japan, Hong Kong and the Singaporean Chinese population) (113), although this only represents a small proportion of immigration to Australia. Australian immigrants represent a very diverse group and identifying their risk of *H.pylori* colonisation and gastric cancer development remains difficult (225).

Paper one also illustrates that there is considerable uncertainty around the cost and effectiveness of any screening program. Cost estimates are very sensitive to changes in the value of various parameters, particularly the lifetime risk of gastric cancer, the cost of *H.pylori* eradication and the cost of doctor visits. Gastric cancer is a condition that generally is diagnosed in the later years of a person's life (114). Over the many years that would exist between the implementation of a screening and treatment program, and the future development of gastric cancer there is the potential for very significant improvements in the management and outcome of the disease (226, 227), and the lifetime risk of gastric cancer has been identified as the most significant cause of uncertainty within the model described.

Genotypic analysis suggests that *H.pylori* is a very longstanding part of the normal flora and accompanied humans when they migrated from Africa approximately 60 000 years ago years (228). Any program of eradication potentially has unforeseen effects on the microbiome (229). The challenge of increasing rates of antibiotic resistance forms one of the greatest challenges to human health (230) and this screening strategy would lead to significant increases in antibiotic use amongst the screened population (231). A program that involves a significant increase in antibiotic use, particularly for an organism that already has increasing rates of antibiotic resistance should be considered with caution (104, 232). Internationally gastric cancer rates overall are falling without implementation of such a program (83, 92, 233-235), although this is not occurring amongst groups who have immigrated from developing countries (114, 225).

Taking these various considerations into account it is not possible to strongly recommend the implementation of a screening program amongst immigrants in Australia at this time, and cautious consideration would seem prudent, without availability of further research to support such a program. This is in accordance with recommendations from international bodies such as the International Agency for Research on Cancer (IARC), and the WHO (104, 107, 113).

Paper two demonstrates a predominance of genotype C (subgenotype C1) infection amongst Burmese immigrants with hepatitis B. The high rates of genotype C (subgenotype C1) infection in the Burmese population have also been identified in those living in Burma with hepatitis B (236). This genotype has an association with higher rates of liver cancer and highlights the importance of ensuring that patients with hepatitis B have ongoing care and screening where it is indicated (237).

Achieving attendance at ongoing liver cancer screening is challenging and the finding that liver cancer rates are potentially elevated highlights the importance of achieving this outcome. Studies both in Australia and internationally have identified low rates of completed liver cancer screening even in situations with considerable supports to assist patients and clinicians to complete this screening (238, 239).

The African immigrant population includes arrivals from many African countries and a significant diversity of hepatitis B genotypes have been identified (240, 241). In *paper three* we demonstrated a predominance of genotypes A, D and E amongst the sampled population. One quarter of all the patients had subgenotype A1, a viral type that is associated with higher rates of liver cancer in the African community. This genotype is also associated with the onset of liver cancer at a young age and before the onset of cirrhosis (240, 242). This reinforces the current Australian recommendation that liver cancer screening should occur on a six monthly basis from the age of 20 years in African patients with hepatitis B (243).

Papers two and *three* illustrate that the genotypes of virus identified amongst immigrants are similar to those identified in studies conducted in the source country. As most chronic hepatitis B is acquired either at birth or in early childhood and has likely been acquired before departure from the home country the similar genotypes between refugees in our study in Australia, and the studies in the source country is not unexpected (99).

The evidence presented in these two papers suggests that knowledge of the genotype may be of some interest in understanding the patient's disease but will not lead to significant changes in clinical management. These two papers support the current recommendation to not include hepatitis B genotypic testing as part of routine clinical care (99, 244).

The importance of regular screening for liver cancer has been highlighted in these papers. In *paper two* it was identified that the Burmese population has higher rates of genotype C virus and in *paper three* it was demonstrated that the African population has higher rates of the A1 virus genotype, both of which are associated with higher rates of liver cancer development. Screening for liver cancer is already recommended for those with Hepatitis B who have a high risk of cancer development (243).A key challenge in managing hepatitis B in migrants is ensuring that appropriate ongoing screening for liver cancer occurs.

Immigrant screening in Australia is largely performed by general practitioners (GP's), working within significant time constraints, and effort should be directed to supporting ongoing hepatitis B care. Until this is reliably occurring, adding additional testing such as genotype is of limited relevance and has the potential to unnecessarily complicate management. The importance of ensuring guideline concordant management was also illustrated in *paper two* which showed that a significant number of patients were in a phase of hepatitis B disease where treatment should be considered and were not on treatment.

Paper four outlines the findings from the first year of the development of the telehealth program from the Royal Melbourne Hospital (RMH) for refugees and other patients with infectious diseases living in regional Victoria. It was found that a telehealth program can be successfully developed for this patient group, and that after an initial period establishing the program, the rate of technical difficulties is low. It was identified that conditions such as latent tuberculosis and hepatitis C can be successfully managed by telehealth. Utilising an internet testing facility, it was determined that a bandwidth of at least 512 kilobits/second (kbps) and latency of no more than 300 milliseconds was necessary to conduct effective telehealth consultations.

It was also demonstrated that telehealth can be utilised for non-English speaking patients and that interpreters can be successfully included in telehealth consultations. An additional benefit of the telehealth program established at the RMH was a reduction in patient travel and an associated reduction in the carbon footprint associated with the provision of health care.

The use of telehealth programs should be developed to complement existing services. This program was developed to provide access to specialist services that were not otherwise available in the local area. If telehealth programs are established in competition to existing services there is a real risk of increasing fragmentation of patient care (245). This is a particular risk for the refugee group who have complex health needs and who require coordinated patient centred care provision.

For refugees the use of telehealth can be less easy to access than for other patients (148). It has been recognised that when an interpreter is required this may make a telehealth consultation more complicated, also telehealth requires access to a reasonable quality internet connection (246). In this telehealth research patients were able to attend their local health care provider hence making adequate internet access likely. For a group of patients with significant trauma exposure it is uncertain if the telehealth mode of consultation alters patient ability to trust health providers or feel safe within the consultation (247). It is also unknown to what extent cultural beliefs effect the willingness to use technology and share health information (248). Whilst this telehealth model has been successful for those who have used the program, it is not known how many patients were unable to access the service, and what barriers prevented any access. A significant challenge for many telehealth programmes has been embedding initially successful pilot programmes into well utilised ongoing practice (249). The clinic described in this paper has now been expanded and there have been over 1000 consultations within a continuing weekly migrant health and infectious diseases telehealth clinic. After the successful implementation of this clinic the hospital has also expanded telehealth for other clinics, and by the start of January 2020 this had increased to 14 departments. The huge shift to telehealth that occurred due to the necessity of social distancing brought about by the CoVID -19 pandemic, meant that by the end of April 2020 this had increased to 40 departments (142). During 2018 over 870 telehealth consultations occurred from the Royal Melbourne Hospital. During the CoVID -19 pandemic the telehealth program had a surge in usage of over 2000% in a period of six weeks, and over 4000 consultations occurred in the month of April 2020 alone (142).

Others have also found that telehealth programs can be established for a range of health conditions and that this care can be provided safely and that the quality can be similar to onsite care (139). It is recognised that telehealth is generally well liked by patients and clinicians and that overall cost savings can occur, although these savings may not be to the health service providing the care (250, 251). Telehealth has been suggested as one of the cornerstones for improving access to care for patients in regional areas with the expectation that improving access will also improve health care outcomes (139). Currently however telehealth programs require that both end-users utilise the same software which continues to be a barrier to widespread uptake.

The six recommendations that were included in Paper 4, published in 2014, continue to be valid. Notably the expansion within the hospital has required considerable administrative support, and a freeze on the reimbursements for clinical consultations has made the financial model more challenging. The issues of lack of interconnectedness between software systems have not been resolved and the ideal that a video conference call should be as easy as a phone call is not yet a reality. Telehealth remains just one component of patient management and the need to maintain the possibility of onsite appointments continues to be important. An Australian review of the enablers and barriers to telehealth implementation has made similar findings (252).

Any program of telehealth that improves access to care but compromises quality of care is not an adequate solution. In order to be able to strongly advocate for broader access to telehealth programs, a demonstration of quality is paramount.

Paper five addresses quality of care. The important finding from this research is that the treatment outcomes for the patients who included telehealth as part of their treatment were similar to those achieved in onsite randomised clinical trials. The majority of patients were not refugees or immigrants, however the trial itself originated from the development of the telehealth program for the refugee population. The same group of clinicians who were providing care to the refugee population in regional Victoria were also involved in this study and often worked in community health centres or had an interest in the provision of health care for disadvantaged groups. The majority of those with Hepatitis C have acquired this through intravenous drug use and are often from marginalised populations (72). The telehealth program was able to expand and include this patient group that was not otherwise able to access care for their hepatitis C without significant travel. This study of hepatitis C outcomes occurred within an established telehealth program and the rates of technical difficulties during consultations were low.

This research also documented that there was a considerable saving in time and cost for the patients, and significant environmental benefit through the reduction in carbon emissions associated with travel to distant specialist health services. This accrued environmental benefit was also demonstrated in *paper four*.

In keeping with the recommendations of *paper four* the telehealth treatment program included the option of onsite review at the tertiary Hospital or at occasional regional specialist outreach visits. Further research is needed to determine if a telehealth only program would achieve similar results.

Other Australian research looking at decentralised models of care for populations living outside major centres also identified good hepatitis C cure rates with a combination of approaches (253, 254), suggesting that telehealth is one of a number of strategies that can be potentially used alone or in combination to improve healthcare access for regional Australians. Programs for hepatitis C that have included local nurse support and visiting specialists combined with telehealth have developed good clinical outcomes and may offer a model for other areas (254). The program described in *paper five* was part of a package of care to improve hepatitis C outcomes in regional Australia, and the inclusion of telehealth as part of a suite of healthcare interventions may be a better approach than stand-alone telehealth programs.

Paper five contributes to the broader telehealth literature suggesting that telehealth is ready to move beyond the trial and pilot stages, and is now appropriate to embed as a routine means of providing care (139, 249).

Paper six has outlined the establishment of a program of accessing interpreters via videoconference and demonstrated the acceptability of this. The provision of interpreters is crucial to ensuring that health care is patient centred, assists to provide a safe environment for patients and can considerably increase patient empowerment. The patient and clinician survey results have both shown a preference for the use of videoconferencing when compared to telephone interpreters, and similar satisfaction to onsite interpreter use. The establishment of this method of provision of interpreters can potentially improve both access to interpreters and quality of interpretation (167, 174). This has applicability for patients in metropolitan areas who are not able to access an onsite interpreters, as the interpreter can now be seated in another state or even another country. The demonstration of the use of video interpreters for telehealth consultations (3 point consultation

with patient, doctor and interpreter linked by videoconference) has particular relevance for patients who are based in rural areas where the use of telehealth is more common (139) and access to onsite interpreters is less commonly available (174).

This study led to a state government grant that has allowed the implementation of video interpreting into regular hospital practice. After slow initial uptake, the necessity of social distancing due to CoVID-19 has meant this has become a main method of provision of service by hospital staff interpreters during the pandemic. This was particularly beneficial as the hospital staff interpreters were a relatively elderly cohort, with a higher risk of severe CoVID-19 disease, and it was important that they were separated from other patients and staff where possible. This it is an example of a successful trial that has subsequently initiated an ongoing change in clinical practice.

Within the hospital it was recognised that non-English speaking patients who were discharged to in-home care were more likely to be readmitted within the month after discharge. Based on this finding, the findings presented in *paper six,* and then the implementation into outpatient clinics, a further health department grant has been received to expand the use of videoconferencing access to interpreters for patients who are managed through the hospital in the home (HITH) program. Research is currently being conducted to determine if this program is cost effective or reduces the rate of readmission.

Overall, the three papers describing the use of telehealth have demonstrated that telehealth programs can be considered successful as they have delivered benefits for patients in reducing travel and accessing care, for rural practitioners in improving access to specialist support, and also significant environmental benefits.

Reducing the regional health care disparity: The contribution of telehealth

In recent years the awareness and concern around the gap in healthcare outcomes in regional areas has increased (255, 256). The wide range of conditions where this is problematic are outlined in table 3 (above). The causes associated with this difference in health care outcomes whilst complex and multifactorial, can be considered in three groups;

1) Less access to high quality treatment.
2) Lifestyle and socioeconomic factors, including education attainment.
3) Much higher rates of the indigenous population living in more remote areas.

Challenges to the provision of a high quality of health care and the role for telehealth within this are discussed below.

Lifestyle and socioeconomic factors involve health services however solutions lie largely in a whole of community response that is beyond the breadth of this discussion.

Indigenous health issues include significant complexity and have attracted considerable interest in recent years. The closing the gap framework has endeavoured through a range of interventions to improve health outcomes for this group and has included annual reporting of goals by the Prime Minister (257). It is possible that some of the outcomes achieved with telehealth could also be utilised for health care in the indigenous population but as the challenges can be different separate research would need to be conducted to assess if this is the case.

Other marginalised groups may also benefit from elements of the models of care that have been developed through this research.

In Australia little research has been conducted on undocumented migrants although estimates suggest that as many as 100000 people are living in the country undocumented and in some cases have been in the country for many years (223, 258). This group has very limited access to health care as they do not have access to the universal health insurance (medicare) or access to hospital care. The majority of these however are involved in agricultural work most commonly in regional areas (258). For telehealth to be accessible to this group significant changes would need to occur to funding arrangements to provide low cost care to those without access to universal health insurance.

International students also represent a large group of temporary immigrants in Australia. Only a small amount of research has been done into health issues in this population suggesting their health issues are fairly similar to matched domestic students (259). They are required to have basic health insurance as part of their visa and will require further health screening should they choose to immigrate permanently (52). This group has high levels of technical competence and may benefit from access to telehealth care and interpreter services.

Two key determinants of access to high quality care are staffing and access to professional support.

Staffing

The challenge of ensuring appropriate medical staffing in regional Australia where the population is older, and burden of disease is higher, is ongoing (69). Many areas of regional Australia have high staff turnover and require doctors and other health professionals from overseas to sustain services (178, 192). One third of Australian doctors trained overseas, and in rural areas this is 41% (69). This is in fact a good example of the role and importance of the immigrant population in regional areas. A number of programs have been implemented to increase local staffing (135), including encouraging students to do part of their studies in rural areas. This has led to higher rates of living and working in rural areas after graduation (260). Over the last 20 years many rural clinical schools and university departments of rural health have been developed so that now over 1000 medical students, and also students of nursing and allied health are trained each year outside major metropolitan areas (261).

The use of visiting medical staff, both specialists and generalist has also been used as a solution to issues of access to care, and some 19% of Australian specialists are involved in some outreach (262). This can address immediate clinical access issues, however concerns about sustainability and the ongoing impact on the regional community have been raised (135). Financial incentives may be necessary to attract specialists to visit more remote areas (263). Models of care where a visiting specialist is also involved in education and upskilling of local staff offer a way to provide quality care but also improve capacity of onsite health staff.

The use of telehealth can provide greater access to specialist services that are not available in regional areas, and also greater access to specialists who may only make occasional onsite visits. Some areas of specialisation will be able to sustain clinicians living and working in regional areas, however less utilised specialists will always need to either visit, or be accessed remotely (264).

Lack of professional support

The lack of professional support for clinicians in regional areas continues to be cited as a barrier to quality healthcare delivery (150). Medicine is complex and becoming increasingly so, and in this

context all health professionals regularly need to seek the advice of others to manage conditions beyond their area of competency (192). This issue is of greater importance in regional areas which rely more heavily on generalists, without any reason to believe that patient complexity is less (265). Regional and overseas trained doctors may have minimal links to tertiary hospitals (192, 264), and access to mentors is limited (266).

The models of care that have been described to improve healthcare for refugees in *papers 4, 5 and 6* including developments such as the telehealth and interpreter improvements, offer successful care models that can improve support to regional patients, and health practitioners. Similar models can be encouraged to provide care for other immigrants in regional Australia, and also for the general population. The successful and effective expansion of the telehealth programme to achieve excellent clinical outcomes for those with hepatitis C, who were mostly not immigrants, is a good example of this.

These papers have outlined specific uses for telehealth in the context of outpatient clinical care however the role can be much broader than this.

One common suggestion to improve health care in regional areas has been to improve the use of technology. This can be used to improve sharing of patient clinical information, use of telehealth to provide care at a distance, and interventions such as point of care testing to provide rapid access to diagnostic results (19, 91, 267). Videoconferencing has been used successfully for education and online and remote education (150, 265). Monitoring can be done remotely and this can be uploaded to medical records and forwarding of images can be utilised to improve remote diagnosis (138).

Community involvement and coordination of care has been recognised as very important to improving rural health (19, 192, 267). Health service changes including the increased utilisation of telehealth need to be implemented in a way that is sustainable. The use of short term projects will often not lead to long term outcome changes, and has the risk of overburdening local health staff without ongoing benefit (91).

Embedding and expanding pilot projects

One of the significant challenges with many areas of research is to take the findings that have been identified in small and localised pilot projects and to implement those findings more broadly in a way that is sustainable, without requiring ongoing project or pilot funding. For telehealth sufficient pilot projects have occurred, and sufficient evidence now exists to recommended that this is expanded broadly to improve timely access to a range of specialists and other health professionals (249). For all clinical situations where either a clinician or a patient spends considerable periods of time in transit to the clinic, telehealth should be considered. Telehealth will not always be appropriate however currently many clinical situations exist where telehealth would be suitable

The settlement of immigrants and refugees in regional areas can pose significant challenges for clinicians providing health care for this group. This is in a setting when they are already faced with the problem of worse health outcomes in regional Australians. The research presented has outlined some of the challenges that exist for this population, but also some solutions such as the use of telehealth, that have the potential to improve the health care of new arrivals. These solutions can also address the broader issue of poorer health outcomes for those living outside major cities.

Key messages for the treating Clinicians

1) Consider a patient's lifetime disease exposure as this may well be different for patient's born outside Australia. This will affect screening and disease management.
2) Refugees have specific health issues which may relate to infections they have been exposed to, or trauma they have experienced during their journey.
3) Overall immigrants represent a healthy group.
4) It is essential to offer the use of a professional interpreter if a patient does not speak English.
5) Regional patients should be offered access to care of the highest level and the treating clinician may have to advocate strongly to achieve this.
6) Telehealth is now well established as a method of accessing safe, effective care for patients living in regional Australia.

Conclusion

These papers have originated from clinical questions that arose, primarily at the Royal Melbourne Hospital within the Victorian Infectious Diseases Service (VIDS) refugee, immigrant and travel clinic.

This work has successfully identified that screening for *H.Pylori* using stool antigen can a be cost effective strategy to reduce gastric cancer death in high risk groups, but further research is needed before this could be strongly recommended for all immigrants. Hepatitis B genotype amongst immigrants from Africa and Burma has been found to reflect the country of origin, and genotypes that are associated with a high risk of the development of liver cancer have been identified in both of these populations, reinforcing the importance of adherence to liver cancer screening recommendations.

A telehealth programme can be successfully established to provide care to immigrant patients in regional Australia. Using the specific example of the treatment of hepatitis C, it has been demonstrated that telehealth can be used to deliver this care effectively and with rates of cure comparable to clinical trials. The use of telehealth can also be extended to include provision of interpreters via videoconference and this is well accepted by patients and clinicians. The telehealth program has benefits for patients, clinicians and in addition environmental benefits.

The importance of having an established telehealth program has been highlighted with the CoVID-19 pandemic. The use of telehealth for outpatient consultations, and access to interpreters via videoconference that has been described in these papers, has been rapidly accelerated to become a main means of service provision within the hospital.

The findings from these papers have relevance beyond the refugee population. The use of telehealth can contribute to ensuring that the best quality of healthcare can be accessed anywhere. This is particularly relevant to the 30% of Australians who live outside the major capital cities and currently have worse health outcomes. The rural settlement of refugees and immigrants demonstrates the challenge of providing high quality health care outside major cities. The research outlined in this body of work can contribute to addressing these challenges. It is hoped this can contribute to improved health care outcomes for refugees and immigrants, but also for all those who living in regional Australia.

Appendices

Appendix 1

DEFINING REMOTENESS AREAS

Australian Statistical Geography Standard (ASGS): Volume 5 - Remoteness Structure, July 2016 (187)

The Australian Statistical Geography Standard (ASGS) defines Remoteness Areas into 5 classes of relative remoteness across Australia. These 5 classes of remoteness are:

- Major Cities of Australia
- Inner Regional Australia
- Outer Regional Australia
- Remote Australia
- Very Remote Australia

The five classes of remoteness are determined using a process that provides a consistent definition across Australia and over time. This allows statistical data to be classified in a consistent way that allows users to analyse changes in data for different remoteness categories over time.
Relative remoteness is measured in an objective way using the Accessibility and Remoteness Index of Australia (ARIA+), which is developed by the Hugo Centre for Migration and Population Research at the University of Adelaide. ARIA+ is derived by measuring the road distance from a point to the nearest Urban Centres and Localities in five separate population ranges. For more information on how ARIA+ is created see the University of Adelaide website at http://www.adelaide.edu.au/hugo-centre/spatial data/aria/

The University of Adelaide supplies ARIA+ to the ABS as a one kilometre grid which covers all of geographic Australia. Each grid point contains a value representing its relative remoteness, this value is derived using the methodology described in the link above.

The ASGS Statistical Area Level 1 (SA1) boundaries are overlayed onto the ARIA+ grid and an average score is calculated based upon the grid points that are contained within each SA1. The resulting average score determines which remoteness category is allocated to each SA1, these categories are shown in Table 1 below. This means that Remoteness Areas aggregate to States or Territories and cover the whole of Australia without gaps or overlaps.

Table 1: 2016 Remoteness Area Category Names for Australia and SA1 Average ARIA+ Value

Remoteness Area Category	Remoteness Area Name	SA1 Average ARIA+ Value Ranges
0	Major Cities of Australia	0 to 0.2
1	Inner Regional Australia	greater than 0.2 and less than or
2	Outer Regional Australia	equal to 2.4
3	Remote Australia	greater than 2.4 and less than or
4	Very Remote Australia	equal to 5.92
5	Migratory - Offshore - Shipping	greater than 5.92 and less than or
9	No usual address	equal to 10.53
		greater than 10.53
		Not Applicable
		Not Applicable

Further criteria are used by the ABS to refine Remoteness Areas. These criteria are applied to remove anomalies that the index may produce and are consistent with the methodology that was applied in the delimitation of the 2006 and 2011 Remoteness Structure. These criteria are:

- A single SA1 that is not an Urban Centre and is completely surrounded by SA1s of a different remoteness category is merged into the surrounding remoteness category.
- A cluster of SA1s that make up a Locality of less than 1,000 persons that is surrounded by SA1s of a different remoteness category is merged into the surrounding remoteness category.

Note that the above rules do not apply to coastal SA1s, where all neighbouring SA1s are classed as a different remoteness category. This is because the coastal SA1s are not considered to be completely surrounded.

The Urban Centres and Localities referenced in the above criteria are defined according to the ABS publication Australian Statistical Geography Standard (ASGS) Volume 4 - Significant Urban Areas, Urban Centres and Localities, Section of State, July 2016 (cat no. 1270.0.55.004) released in October 2017.

Within each State or Territory each Remoteness Area represents an aggregation of non-contiguous geographical areas which share the common categorisation of remoteness. While statistical data classed to this structure may be available by State or Territory, characteristics of remoteness are determined in the context of Australia as a whole;

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