Abstract:

Abstract: Viral hepatitis affects more than 320 million people globally, leading to significant morbidity and mortality due to liver failure and hepatocellular carcinoma (HCC). More than 248 million people (3.8% globally) are chronically infected with hepatitis B (HBV) and an estimated 80 million people (1.1% globally) are chronically infected with hepatitis C virus (HCV). In 2015, more than 700,000 deaths were directly attributable to HBV and nearly 500,000 deaths were attributable to HCV infection. 2-5% of HBV-infected people develop HCC per annum irrespective of the presence of cirrhosis, whereas 1-5% HCV-infected people with advanced fibrosis develop HCC per annum. The rapidly escalating global mortality related to HBV and HCV elevated viral hepatitis to be the 7th leading cause of death worldwide in 2013, from 10th leading cause in 1990.

Australia, New Zealand (NZ) and Pacific Island Countries and Territories (PICT) fall within the WHO Western Pacific Region (WPR), which has a high prevalence of viral hepatitis and related morbidity, particularly HBV. Remarkably, in this region HBV-related mortality is greater than for tuberculosis, HIV infection and malaria combined. The region provides a unique contrast in viral hepatitis prevalence, health system resources and approaches taken to achieve WHO global elimination targets for HBV and HCV infection. This review highlights the latest evidence in viral hepatitis epidemiology and explores the health resources available to combat viral hepatitis, focusing on the major challenges and critical needs to achieve elimination in Australia, NZ and PICT.

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Introduction

Hepatitis B and hepatitis C affect more than 320 million people globally and can lead to liver disease and mortality from liver failure and hepatocellular carcinoma (HCC)(1). More than 248 million people (3.2% of the world's population) are chronically infected with HBV, and over 700,000 attributable deaths occurred in 2015(2). An estimated 80 million people (globally, 1.1%) are chronically infected with hepatitis C virus (HCV), resulting in nearly 500,000 deaths in 2015(2). The five-year cumulative incidence of cirrhosis from untreated hepatitis B virus (HBV) is 10-20% and 2-5% per annum develop HCC(3), whereas 10-20% of all people with chronic hepatitis C will develop cirrhosis over 20-30 years of infection(4) and 1-5% of those with advanced liver fibrosis will develop HCC (5). The rapidly escalating global mortality related to HBV and HCV elevated viral hepatitis to be the 7th leading cause of death worldwide in 2013, from 10th leading cause in 1990(6).

Australia, New Zealand (NZ) and Pacific Island Countries and Territories (PICT) fall within the WHO Western Pacific Region (WPR) (**Figure 1**), which has a high prevalence of viral hepatitis and related morbidity, particularly HBV. Remarkably, in this region HBV-related mortality is

greater than for tuberculosis, HIV infection and malaria combined(2, 7). The region provides a unique contrast in viral hepatitis prevalence, health system resources and approaches taken to achieve WHO global elimination targets for HBV and HCV infection. This review highlights the latest evidence in viral hepatitis epidemiology and explores the health resources available to combat viral hepatitis, focusing on the major challenges and critical needs to achieve elimination in Australia, NZ and PICT.

Australia and New Zealand

Health system and demographic context in Australia and New Zealand

Australia and New Zealand (NZ) both provide universal healthcare for all citizens including heavily subsidised medications and have effective national surveillance systems for identifying the impact of notifiable infectious diseases, including viral hepatitis. Indigenous peoples (Aboriginal and Torres Strait Islander people in Australia, Māori in New Zealand) experience poorer overall health outcomes, including a greater burden of both communicable and non-communicable diseases compared with non-Indigenous peoples (8), attributed to inequitable access to resources, education and healthcare. Lower vaccination rates, increasing evidence of injecting drug use and higher prevalence of cofactors for rapid liver fibrosis progression and carcinogenesis among this population, including type 2 diabetes, metabolic syndrome, smoking and alcohol misuse(9), pose particular risks for liver

cirrhosis and HCC. Australia and NZ also have high numbers of immigrants from Asia-Pacific countries with high viral hepatitis prevalence(10, 11).

Epidemiology of hepatitis B, C and D in Australia and New Zealand

The estimated hepatitis B surface antigen (HBsAg) prevalence in Australia is 1.0%, or an estimated 239,000 people(12). Newly acquired (incident) HBV notifications have declined since 2001, reflecting broad coverage of universal infant and adolescent catch-up immunisation programs(12). In contrast, NZ has an estimated pooled age-adjusted HBsAg prevalence of 4.11% (95% CI 4.04-4.18%)(1), which is higher than in Australia. In part, this reflects larger Indigenous (NZ 14.6%, Australia 2.7%) and migrant PICT populations in NZ (13).

In Australia the majority of chronic HBV infections occur in migrants from endemic areas and their children (14). HBV prevalence and HBV-related liver cancer are higher in Indigenous (11, 31) (**Table 1**) (34). Similarly in NZ, Māori, Pacific and Asian New Zealanders have higher HBV prevalence than European New Zealanders (**Table 1**)(13). Other key risk populations include prisoners(15), people who inject drugs (PWID)(16) and men who have sex with men (MSM) (**Table 1**)(17).

Australia and NZ are both estimated to have a low prevalence of HCV infection (1.0; Genotype 1 50%, genotype 3 40%)(19)(18). In both countries, PWID account for most new infections and more than 80% of prevalent infections (1): estimated anti-HCV Ab prevalence

in PWID is 55-75%(16), > 74% of whom are HCV RNA positive (**Table 1**)(22). Other high-risk groups for hepatitis C in Australia and NZ include indigenous Australians (8-10% of HCV cases)(33), migrants from high prevalence countries (10% of HCV cases)(20, 21), prisoners(26), those with psychiatric illness(27, 28), homeless people(29), and men who have sex with men (MSM), particularly those coinfected with HIV(30); whilst a small number received contaminated blood products prior to blood screening (1992) (**Table 1**) (20, 21). New HCV notifications are declining in Australia and NZ(8)(25)(24), reflecting improved access to direct-acting antiviral treatment and harm reduction interventions (needle and syringe programs (NSP) and opiate substitution therapy (OST)(23).

Hepatitis B-D coinfection is uncommon in Australia, with most cases (71%) occurring in people born overseas in endemic areas (35). In contrast, hepatitis B-D coinfection is found in almost 20% of HBsAg-positive New Zealanders of Pacific Island ethnicity, notably those from Samoa, Kiribati and Tuvalu(36).

The burden of viral hepatitis-related liver disease, liver cirrhosis and liver cancer in Australia and New Zealand

Viral hepatitis is a significant cause of morbidity and mortality in Australia and NZ, accounting for an estimated 1.4% (Australia) and 1% (NZ) of deaths in 2015(2). HCV is the commonest cause of hepatocellular carcinoma (HCC) in Australia (41%), while HBV accounts

for 22%(37). In Australia, the proportion of people with HCV and advanced liver fibrosis and cirrhosis rose from 9% in 2004 to 19% in 2014(38). In NZ, the population-attributable risk for viral hepatitis-related liver disease mortality was estimated at 66% among Pacific Islanders, 52% among Māori and 10% among Europeans for HBV infection, and 8-14% for HCV infection (39). HCV is the commonest and HBV the third-commonest indication for liver transplantation in Australia and NZ, accounting for 23% and 6% of all adult liver transplants respectively(40). Moreover, HCV accounts for 51% and HBV 28% of all HCC-related transplants(40).

Prevention strategies for viral hepatitis in Australia and New Zealand

Vaccination remains the most cost-effective HBV prevention strategy globally and WHO recommends universal vaccination for all infants to prevent vertical (mother to child) transmission of HBV (41). Universal HBV vaccination of infants was introduced in NZ in 1988 and in Australia in 2000 and catch-up vaccination programs for adolescents and other high-risk groups were introduced by the year 2000 in both countries(40). Diversity in funded HBV vaccination for high-risk adults exist across jurisdictions in Australia, in contrast to NZ where HBV immunisation is free for all(42).

For infants born to HBsAg-positive mothers, birth dose HBV vaccination is recommended to be given within 24hrs of birth, along with hepatitis B immune globulin HBIG. In NZ, small studies in rural areas confirm the success of universal vaccination, with a decrease in HBsAg prevalence in Māori children living in the eastern Bay of Plenty from 10% in 1984 to nil in

1992(43). A study from Australia's Northern Territory also documented reducing HBsAg prevalence among Indigenous people by birth cohort, from greater than 8% prior to the 1970s to less than 2% since 2000(44). While antiviral therapy in the third trimester is recommended for women with high HBV viral loads (>log 6 IU/mL)(41); there is little data available on whether this approach is universally implemented and studies suggest significant discordance between national obstetric guidelines for management of viral hepatitis and knowledge and practice on the ground (45). Concerted efforts to obtain accurate data and improve policy are needed.

Harm reduction strategies, principally NSPs and OST, have reduced HCV transmission in Australia and NZ(24, 46, 47). In NZ, HCV antibody prevalence in PWID fell from 75% to below 55% following NSP introduction (24). Use of peers to support prevention, testing and treatment, street outreach and self-testing has improved PWIDs' health service engagement (47). However, within prisons incident HCV infections among PWID still remain high(48).

Management of viral hepatitis in Australia and New Zealand: Barriers to screening and treatment access

In Australia and NZ, despite subsidised screening, specialist management and treatment for HBV, major barriers inhibit linkage to care. In 2015, an estimated 62% of those living with HBV in Australia were diagnosed, 15.3% monitored and only 6.1% were receiving antiviral

therapy. Barriers included lack of awareness about the implications of HBV infection in patient populations (largely people from non-English speaking backgrounds), general practitioners (GPs) and other health care workers, a lack of consistent clinical guidelines referencing the role of GPs in diagnosing viral hepatitis and referring to specialist services, and underdeveloped shared care pathways for HBV management(49, 50). Since 1998, the Hepatitis Foundation of NZ has conducted national HBV screening and surveillance as part of the Treaty of Waitangi initiative to "close the gaps" in health outcomes for Māori. As of 2017, this project has identified around 30,000 people with HBsAg among adult Māori, Pacific and Asian New Zealanders, making this one of the world's largest HBV surveillance programs(51).

In stark contrast to the HBV case, the diagnosed proportion of people with HCV in Australia is among the world's highest: an estimated ~80% having being diagnosed HCV antibody positive(52). However, despite this less than half (46%) have completed confirmatory HCV RNA testing or have not received their test results. A study in Victoria estimated that 58% of individuals diagnosed as anti-HCV positive did not receive HCV RNA testing(53). Until recently, treatment uptake in Australia was low (<2%), however in March 2016, the Australian Government made an initial 5-year investment of over AUD$1 billion (approximately $720 million USD) in a risk-sharing arrangement with pharmaceutical companies, providing access to direct acting antivirals (DAAs) for all chronically infected patients, regardless of stage of liver disease, cause of infection or previous treatment

experience. This major policy decision has increased treatment uptake substantially, with over 30,000 people receiving DAA treatment in 2016 (54). Treatment is being delivered not only to people with significant liver disease, but to PWID, people serving custodial sentences, and HIV-positive MSM, groups with a high risk of incident infection. Modelling(52, 55) suggests that this approach is both cost-effective and critical for achieving WHO 2030 elimination targets (**Figure 2**). Government-supported health promotion and education programs, GP-initiated treatment and nurse-led models of care, treatment access in prisons, and treatment programs aimed at treating infected individuals' injecting and/or sexual partners are paving the way to achieving elimination in Australia(52).

New Zealand has also taken significant steps towards achieving HCV elimination. In 2012, NZ began piloting community-based targeted testing and assessment to identify the 20,000 undiagnosed New Zealanders living with HCV. In 2016, the government funded community prescribing of DAA therapy for all patients infected with HCV genotype 1 (approximately 55-70% of the infected population) with treatment rates increasing more than 20-fold since (personal communication). Funding of pan-genotypic DAA therapy in 2017, plus increasing diagnosis and linkage to care rates will further facilitate progress towards HCV elimination by 2030.

The Pacific Islands and Territories (PICT)

Health system and demographic context in PICT

The PICT include 22 countries comprising thousands of islands and atolls grouped into three distinct regions: Melanesia, Micronesia, and Polynesia (**Figure 1**). PICT are strikingly diverse in terms of population size, geography, demographics, society and culture and economy. Extensive migration occurs between neighbouring islands, south-east Asia and China, contributing to epidemiological complexity, transmission of viral hepatitis, reduced accuracy of disease surveillance and poor access to public health programs(56).

The majority of PICT are low-middle income countries (World Bank, Human Development Index), with an estimated 25% of the population living in poverty (57). Geographic isolation and small population size result in low Gross National Product and Gross Domestic Product, high transport and utility costs, dependence on imported goods and technological isolation, all factors that impede health infrastructure development(56, 57). Similar to Indigenous populations of Australia and NZ, PICT populations have high prevalence of cofactors for liver fibrosis and liver carcinogenesis (58). Smoking prevalence ranges from 22% in Fiji to 70% in Kiribati and marijuana and alcohol misuse are also common in some PICT, including Kiribati, Fiji and PNG(58). Obesity prevalence ranges from 50-80% and type 2 diabetes from 8-45%(56, 57), which are associated with liver fibrosis and liver carcinogenesis.

Epidemiology of hepatitis B, C and D in PICT

PICT have moderate-high HBV endemicity and estimates of HBsAg prevalence (based on regional studies) ranging from 3% - 23% (**Table 2, Supplementary Tables 1 and 2)** (6, 56, 57). HBsAg prevalence in adults is highest in Kiribati, New Caledonia, the Marshall Islands, Solomon Islands and Vanuatu (60, 61)(**Table 2, Supplementary Tables 1 & 2**).

Vertical, early horizontal and sexual transmission of HBV are common in PICT. HBsAg positivity is high in some PICT (**Table 2, Supplementary Table 2**) (60)(61) and younger age at first pregnancy in PICT increases risk of mother-to-child transmission, as a greater proportion of young mothers are HBV envelope antigen (HBeAg) positive with high viral load. Vertical transmission persists despite timely birth dose vaccination, with 3-5% of infants born to HBsAg mothers becoming HBsAg positive after vaccination (62).

Sexual transmission contributes to new HBV infections in unvaccinated Islanders. Other risks for transmission in PICT include traditional cultural practices (tattooing, penile injection, circumcision) and increasing rates of injecting drug use (57, 63).

While contemporary data on HCV for many countries in PICT are scarce, prevalence estimates are generally low (57, 64) (**Supplementary Table 3**). Available published data suggest HCV antibody prevalence is highest in Kiribati, Papua New Guinea (PNG) and the Solomon Islands, yet interestingly, most patients remain HCV RNA negative, suggesting either frequent spontaneous viral clearance or high false positive rates in low prevalence

settings(65). Scant literature suggests genotypes 1 and 4 dominate (63), while HBV-HCV and HIV-HCV coinfection and other sources of transmission are rarely described (63, 66).

Few published data on hepatitis D-hepatitis B coinfection in PICT exist. High prevalence of hepatitis D RNA has been found in Kiribati (37%), but none in Tonga, Fiji or Vanuatu(67).

The burden of viral hepatitis-related liver disease, liver cirrhosis and liver cancer in PICT

The prevalence of liver cirrhosis and liver cancer in PICT remain poorly characterised. A study from Palau found chronic liver disease was the fifth most common cause of death (7%)(68) and that mortality rates were twice the global average, whilst data from the Global Burden of Disease Study estimate mortality from viral hepatitis is greater than for malaria, HIV and TB combined in all PICT except Vanuatu and Solomon Islands(2).

Prevention strategies for viral hepatitis in PICT

The PICT HBV universal vaccination program has been one of the most highly effective globally among low-middle income regions. Universal hepatitis B vaccination for infants and children started between 1995-1997 in all PICT, including birth dose delivery in most countries, and WPRO HBV control initiatives have reduced HBV seroprevalence and incidence substantially in some countries in the region (59) (**Table 2, Supplementary Table 1**

and 2). In 2010, vaccination coverage was greater than 80% for all PICT except the Solomon Islands and Palau(64) (**Supplementary Table 1**). More recently, 13 countries have already achieved the 2017 WHO Regional Committee for the Western Pacific milestones of chronic HBV of <1% HBsAg among 5-year-old children, and the interim milestone of <2% prevalence by 2012(64) despite being ineligible for Global Vaccine Alliance (GAVI)-supported vaccination programs and without full government funding for national vaccination programs (**Supplementary Table 1**). Only a few countries still had HBsAg prevalence >2% among children in 2017, including PNG, Solomon Islands, Kiribati, Samoa and Vanuatu; all these countries also had the highest HBsAg prevalence prior to 2012, therefore facing greater challenge to reduce their HBsAg prevalence below targets(64). However, in some PICT – such as Samoa – 50% of births are still home/village based where administration of the birth dose is challenging (56, 57). To overcome barriers to delivery of birth dose vaccine, pilot projects delivering hepatitis B vaccine outside of the cold chain by volunteers have been successfully conducted in Kiribati and Solomon Islands(69, 70), and the Solomon Islands Government has also recently approved use of hepatitis B vaccine outside of cold chain.

Despite these achievements, significant inequities exist in birth dose vaccination delivery across PICT, ranging from 35% in PNG to >99% in Tonga (**Supplementary Table 1**) (60, 64). Multiple barriers have been identified for low birth dose uptake, including relative geographical isolation, inadequate vaccine supply/stock outs and cold chain systems,

monovalent birth dose vaccine not funded by GAVI, limited antenatal screening and HBsAg testing, births occurring outside health care facilities, lack of skilled medical staff to provide birth dose vaccination and higher obstetric complication rates(64). Use of HBIG for infants, and antiviral therapy in the third trimester is not routine in most PICT due to prohibitive cost and supply issues in the region(71). A handful of countries, including Fiji, Guam, the Cook Islands, New Caledonia, French Polynesia and Northern Mariana Island provide HBIG; in Fiji uptake is as high as 83% of infants born to HBsAg positive mothers (72). More recently, WHO-reported vaccination coverage fell in several PICT between 2010 and 2015(64) **(Supplementary Table 1)**. Reductions may reflect improved accuracy of vaccination surveillance data and transition between different vaccination regimens and products. They may also reflect loss of momentum, stock-outs and inadequate resources to deliver full schedule and birth dose vaccination. Furthermore, catch-up vaccination programs for adults have not been implemented systematically(62).

Management of viral hepatitis in PICT: Access to viral hepatitis screening and treatment

Government-subsidised HBV and HCV testing is critical to viral hepatitis elimination in the PICT. HBsAg testing is free in Fiji, Kiribati, PNG, the Solomon Islands and Tonga, but only Kiribati has an HBsAg screening and linkage-to-care policy. A key barrier to HCV screening is cost and high antibody false-positive rate due to cross-reactivity with malaria and dengue antibodies, an important diagnostic issue for low HCV prevalence tropical countries(63, 65).

Lack of treatment access is a major constraint for HBV and HCV elimination within the PICT. The WHO Global Policy on Prevention and Control of Viral Hepatitis Survey (73) was sent to Ministries of Health in all PICT, but only four of the 22 responded (Tonga, Kiribati, Solomon Islands and PNG). None of these four countries had national HBV or HCV national clinical guidelines for the management of viral hepatitis, and none provided free treatment for either virus (73). However, Fiji and Kiribati reportedly are developing HBV guidelines and PNG offers government-subsidised lamivudine and tenofovir for hepatitis B, whilst Tonga only offered standard interferon-alpha for hepatitis B monoinfection (73). There is no access to HCV DAA therapy in the PICT, outside of infrequent self-funded importation of generics (73). Furthermore, the region lacks specialists experienced in treating viral hepatitis and free routine screening for HCV occurs only in Kiribati and Fiji(57, 64, 73).

Achieving WHO elimination targets for viral hepatitis in the Western Pacific region: future solutions to current challenges

All countries in the WPRO region have agreed to achieving targets of 30% of all people living with hepatitis B and C being tested, and 50% of all eligible people receiving treatment, by 2020(64). Australia, New Zealand and the other PICT constitute a unique and important region in the global fight to achieve HBV and HCV elimination targets and considerable gains have been made in achieving these targets across the WPRO region (**Table 3**). Australia and New Zealand have made major investments in strategies to increase access to testing and

treatment for HBV and HCV, particularly with good surveillance, universal access to treatment, prescription available in primary care, treatment in prisons and harm minimisation programs. However, we now face the situation where the "easy to find" cases of hepatitis B and C have been tested and linked into care, yet barriers to accessing health services among key risk populations such as Indigenous and migrant communities, PWID and rural/ remote areas pose important ongoing challenges to achieve elimination targets. Further expansion of community-based models of care, particularly nurse-led models of care and investigation of alternative models of care such as through mental health services or OST providers, are needed. Greater engagement of at-risk populations and primary care healthworkers to provide treatment; point-of-care testing for hepatitis B and C; and streamlined management algorithms for hepatitis C such as removing the need for genotyping would further facilitate community-based models of care.

In PICT, universal access to hepatitis B and C screening and treatment are urgently needed. Across PICT, government-subsidised quality-assured HBV and HCV testing is still largely unavailable or unfunded and inaccessible, except for a few notable countries, including Fiji, Kiribati, PNG, the Solomon Islands and Tonga. Rapid point-of-care testing with WHO-prequalified assays would greatly expand diagnostic access in the region and may improve cost-effectiveness and equitable testing access compared with current laboratory-based testing. Lower cost molecular diagnostics, supporting laboratory infrastructure, providing

ongoing consumables and trained staff will continue to pose significant barriers which may require a unified regional approach.

Significant gaps in hepatitis B, C and D prevalence and incidence data availability for PICT due to resource and access limitations warrant urgent attention in order to address the hepatitis regional epidemic (**Supplementary Tables 1 - 3**).There are plans to extend the NZ HBV screening and surveillance program into neighbouring PICT, starting with Samoa and Tonga (personal communication, Prof Ed Gane). Improved surveillance to monitor progress towards elimination and provide evidence of the burden of disease to support investment in viral hepatitis are also urgently needed in PICT. The mortality estimates from viral hepatitis are far higher than for HIV, TB and malaria combined in all countries in Oceania except Vanuatu and Solomon Islands(2).

Whilst many PICT have achieved high birth dose and infant HBV vaccination coverage despite significant resource limitations, using strategies such as skilled lay healthworkers to delivery birth dose hepatitis B vaccination will improve access in geographically isolated areas, as shown in the outer islands in Kiribati. Use of vaccine outside of cold chain is also an effective strategy for resource-limit countries (74). Investment in antenatal care and birth dose vaccination also has additional flow-on benefits for maternal-child health outcomes from health system strengthening.

Currently, few PICT can afford the costs of universal access to hepatitis treatment; however, with the reducing price of generic hepatitis C DAA therapy and entecavir and tenofovir now off-patent, this situation should change. The absence of treatment for both HBV and HCV in

most PICT represents a profound inequality that demands immediate attention from the international community and major donors, in partnership with Ministries of Health, politicians and aid and civil society stakeholders. Sustainable, affordable and equitable drug access must be assured, including via mechanisms such as pooled procurement, use of generic medicines and inclusion of hepatitis medications in the universal healthcare package. Further, given the constraints of limited health care budgets and competing costs in most PICT, creative economic solutions need to be explored to provide universal treatment access, such as public-private enterprise and advocacy with major donors including the Global Fund. Australia and New Zealand are well placed in this respect and could provide support to their neighbouring PICT to secure universal antiviral treatment access through block or pooled procurement. With pan-genotypic DAAs now available, additional cost savings will be generated by removing the need for genotyping and facilitating community-based care.

The commitment of WPRO member states to support agreed HBV control goals, coupled with national policy developments, have facilitated great achievements in reducing viral hepatitis prevalence among children in the region. However, much work lies ahead to achieve targets set in the Regional Action Plan for Viral Hepatitis in the Western Pacific 2016-2020(64), and then – as agreed by all WHO members at the World Health Assembly in 2016 – to eliminate viral hepatitis as a public health threat by 2030.

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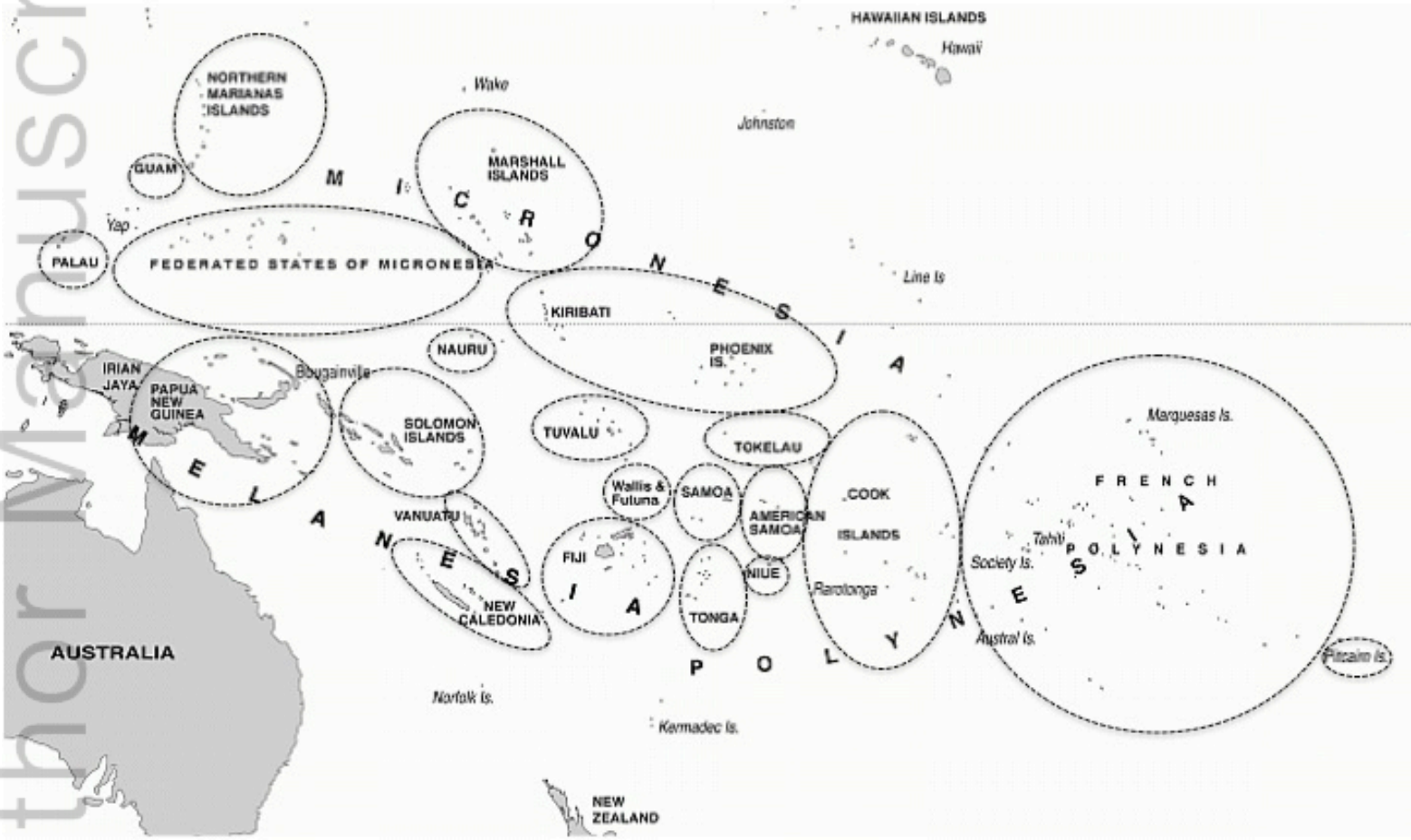
Figure Legends

Figure 1. Schematic map of the Pacific Islands and Territories

Figure 2. Modelling effectiveness of treating chronic hepatitis C virus with direct-acting antivirals in people who inject drugs and those with HCV-related liver disease in Australia.

Source: Scott, N et al. Journal of Gastroenterology and Hepatology, 2016 Apr 12. Treatment scale-up to achieve global HCV incidence and mortality elimination targets: a cost-effectiveness model.



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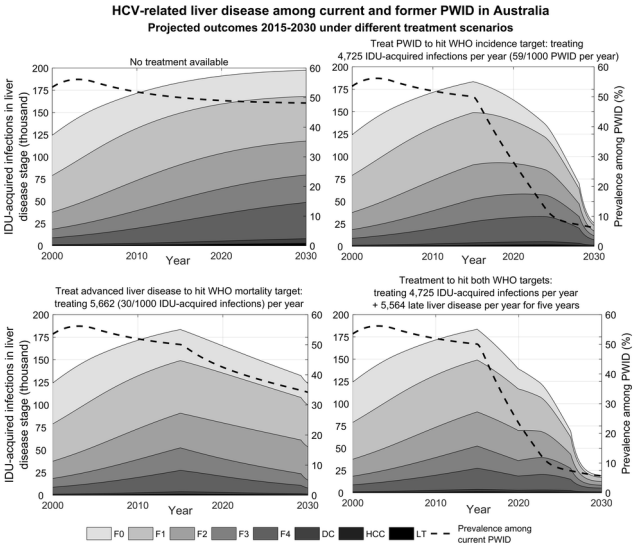

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