Research Review
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Hepatitis B Vaccination for Travellers

About the Expert

Dr Jenny Visser
BSc, MBChB, FRNZCGP, MTravMed.

Jenny is Senior Lecturer in Travel Medicine in the Department of Primary Health Care and General Practice, University of Otago, Wellington. She convenes and teaches the University's postgraduate qualifications in Travel Medicine enjoying the stimulation that teaching brings. She also works part time in clinical travel medicine at The Travel Doctor in Wellington. Jenny's background is in general practice having then specialised in travel medicine. She has worked in many roles and places, including being a full time general practitioner in Wellington for 12 years, medical advisor to New Zealand Land Search and Rescue, medical officer on the research vessel Tangaroa (spending five summers in Antarctica), a season as a volunteer doctor at a high altitude rescue post in Machermo, Nepal and two months on set in a remote village in Bougainville, Papua New Guinea as film crew doctor.

More people are travelling overseas than ever before, whether it be for social, recreational, or business purposes. International travellers are exposed to a variety of health risks, including vaccine-preventable diseases. The purpose of this review is to present evidence-based information and guidance on hepatitis B vaccination for travellers. The review is primarily intended for healthcare professionals who provide pre-travel health advice, including GPs, travel doctors, practice nurses, pharmacists, and those specialising in travel medicine. It may also be of interest to infectious disease physicians.

Hepatitis B

Hepatitis B, which is a liver infection caused by the hepatitis B virus (HBV), continues to be considered a major health problem worldwide.

In some individuals, hepatitis B manifests as an acute illness but in others it results in chronic infection that carries a high risk of death from cirrhosis and liver cancer.[1,2] An estimated 248 million people have chronic HBV infection globally.[3] The Global Burden of Disease study determined that there were 636,400 deaths due to liver carcinoma and cirrhosis and other chronic liver diseases caused by HBV infection in 2015.[4]

Hepatitis B is transmitted via contact with blood, semen, or another body fluid from a person infected with the HBV.[1,2] It cannot be cured and vaccination is the best way to prevent infection.[1,2] The vaccine is 90–95% effective in preventing HBV infection and the development of chronic disease and liver cancer due to hepatitis B.[5,6]

New Zealand (NZ) was one of the first countries to introduce universal infant immunisation against hepatitis B in 1988 (after first introducing it for HBV infected-mothers in 1985).[7] Introduction into the programme was accompanied by a catch-up programme for pre-schoolers implemented during 1988. A further catch-up programme for all school children was implemented in 1990. By 2013, NZ had attained 92% coverage of completed HBV vaccination in those eligible for funded vaccine.[8] However, it has been estimated that people with chronic HBV infection will continue to provide a source of infection to non-immune people until the end of the century.[9]

Why travellers may be at risk of HBV infection

Globally, the number of international inbound tourists increased from 435 million in 1990 to 1.19 billion in 2015.[10] Between 1990 and 2010, the number of people with chronic HBV infection increased from 223 million to 248 million.[3,11]

The 2.5-fold increase in the number of international travellers over the past two-and-a-half decades combined with the high, and increasing, number of people chronically infected with HBV suggests that many travellers are at risk of HBV infection. According to an analysis of GeoSentinel Surveillance Network data in 2010, HBV infection was the fourth most common vaccine-preventable disease, after enteric fever, acute hepatitis A, and influenza, among North American travellers returning home unwell.[12]

For travellers, the risk of HBV infection depends primarily on three factors:[13]

1. Prevalence of HBV infection in the country or area of destination.
2. Extent of direct contact with blood or body fluids from potentially infected individuals, i.e. engagement in high-risk behaviours, having to seek medical or dental care, those at increased occupational risk.
3. Duration of travel.

Travellers who acquire HBV infection when abroad are at risk of hepatitis-related morbidity and mortality and are a potential source of infection to the community upon their return.[13]

1. Prevalence of hepatitis B

Hepatitis B is found world-wide, with the prevalence of chronic HBV infection varying widely between countries (**Figure 1**).[3] Destination, therefore, is a major factor in determining the risk of HBV infection.[13]

Areas of low HBV prevalence (<2% HBsAg seropositivity) include Australia, the UK, Western Europe, and the Americas.[3] NZ is a lower-intermediate prevalence (2–4%) country that contains sub-populations with high rates of HBV carriage (i.e. people of Maori, Pacific Island, and Asian ethnicity).[15,16] Higher-intermediate prevalence (5–7%) areas include Asia and the Pacific.[3] High prevalence (≥8%) countries are most common in Africa, but also exist in the Asia and Pacific regions.

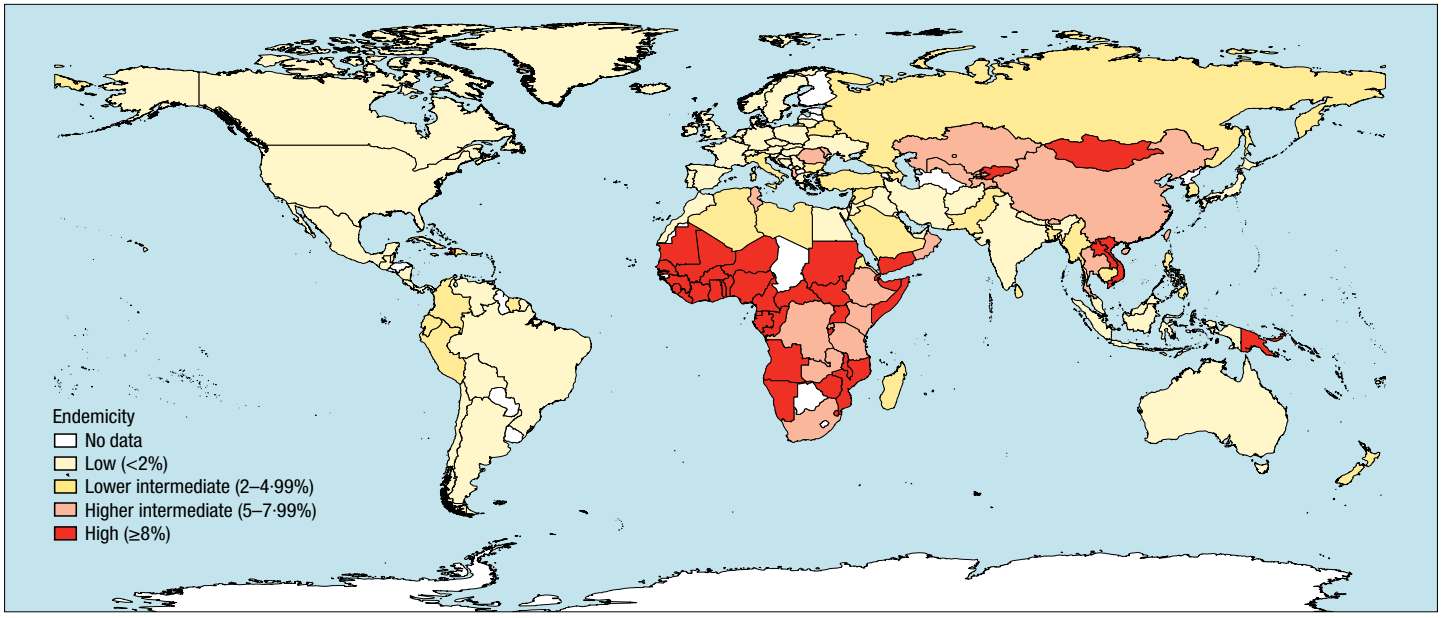

Figure 1. HBV infection prevalence by country.[3]

2. High-risk behaviours

Behaviours that carry a high-risk of HBV infection include: sexual contact with a new partner; medical procedures that necessitate direct exposure to human blood or body fluids (e.g. surgery, dental, laboratory tests); transfusion of blood or blood product that has not been tested for HBV; and activities involving exposure to needles (e.g. acupuncture, body piercing, tattooing, injecting drug use) that have not been appropriately sterilized.[13]

Travellers could be exposed to any or all of these risks. There is some evidence that participation in risk-taking behaviours is more common during travel.[13]

Studies have shown that travellers have a poor knowledge of travel-related infections and vaccine-preventable diseases and place themselves at risk of infection through their behaviours while abroad.[13] For example, a 2004 survey found that only 28% of Australian travellers who spent ≥3 nights in East or Southeast Asia had received HBV vaccination prior to travel and 49% participated in at least one activity with a risk of acquiring hepatitis B.[17] In a 2003 survey of Australians who had visited a country of medium to high HBV prevalence, fewer than half (46%) had been vaccinated against hepatitis B and approximately one-third engaged in at least one activity associated with increased risk of exposure to HBV.[18]

3. Duration of travel

There is epidemiological evidence that travellers with a longer duration of travel, particularly those in close contact with the local population (e.g. expatriates, aid workers, missionaries), are at higher risk of infection than short-term travellers and therefore they should always be offered vaccination.[13,19] Although there is evidence of a low risk of contracting HBV for short-term travellers to countries with high HBV endemnicity,[20] there is also evidence that many high-risk situations are not predictable prior to travel, which supports an all-inclusive approach to discussing hepatitis B risk in travellers.[21]

General pre-travel vaccination advice

All travellers should be encouraged to consider vaccination requirements well in advance of overseas travel.[7] A pre-travel visit is an opportunity to evaluate a traveller's vaccination status and update routine vaccines. Travellers should also receive advice regarding the modes of HBV transmission and activities that increase their risk of HBV infection.

As part of its official health and travel advice, the NZ Ministry of Foreign Affairs and Trade (MFAT) recommends that New Zealanders travelling overseas should consult their doctor or a travel health specialist approximately six to eight weeks before travel regarding specific health concerns in the country of travel and any vaccinations required for the areas being travelled to before travelling.[22,23] MFAT recommends that, at the very least, travellers should ensure that all their routine immunisations are up-to-date. It also specifies HBV infection via unsterile medical equipment as being a risk of medical, cosmetic, or dental treatment overseas.

In general, vaccines for travellers include:[24]

1. Routine vaccines, i.e. those used in national vaccination schedules (e.g. HBV, MMR, diphtheria).
2. Recommended vaccines, i.e. selected vaccinations advised prior to travel to countries at risk of certain diseases (e.g. HBV, hepatitis A, rabies, Japanese encephalitis).
3. Required vaccines, i.e. those that are mandated by International Health Regulations or for entry into specific countries (e.g. yellow fever, meningococcal disease).

Guidelines for pre-travel HBV vaccination

The US Centers of Disease Control and Prevention (CDC) recommends that HBV vaccination should be administered to all unvaccinated people travelling to areas with intermediate to high prevalence of chronic hepatitis B (i.e. HBsAg ≥2%).[25] However, the CDC also states that vaccination to prevent hepatitis B may be considered for all international travellers, irrespective of destination, based on the traveller's risk exposure profile.

The Australian Department of Health recommends HBV vaccination for long-term or frequent travellers to areas of intermediate or high HBV endemicity, including Asia and the Pacific, due to the potential for unintended exposure to HBV.[26]

In NZ, HBV vaccination is recommended, but not funded, for migrants from HBV endemic countries and travellers to HBV-endemic regions.[7]

Regions of high HBV endemicity frequently also have high hepatitis A virus (HAV) prevalence, and combined vaccination against hepatitis A and B provides a convenient means of ensuring that travellers are adequately protected against both infections.[27] The safety and immunogenicity of combination hepatitis vaccination is comparable to HBV and HAV monovalent vaccination.[28-30] It should be noted that maximum protection against both infections requires the administration of a minimum of three doses of the combined vaccine pre-travel.

Expert comment:

The pre-travel consultation revolves around personalised risk assessments of all travel-related hazards.

The risk of contracting hepatitis B virus, including potential modes of transmission, should be discussed with all travellers. Vaccination can be offered to those who have not been previously vaccinated who are seeking maximum protection (note that many other diseases, including hepatitis C and HIV, share these modes of transmission. These activities should still be avoided irrespective of hepatitis B vaccination status).

All those eligible for funded hepatitis B vaccine should have their vaccination status evaluated and missed doses administered.

It is important that those advising travellers are familiar with when hepatitis B vaccination was incorporated into the New Zealand National Immunisation Programme. Immunocompetent persons who have been fully vaccinated at any time in the past do not require further vaccination. New Zealanders born since 1988 (aged 29 years and younger in 2017) are likely to have been vaccinated as babies. An older cohort (up to age 45 years of age in 2017) may have been vaccinated, but given evidence that catch-up programme coverage and vaccine uptake was patchy, for those aged between 29 and 45 years of age, in the absence of a clearly documented completed primary series vaccination cannot necessarily be assumed.

Having discussed risk factors with all travellers, some may opt for vaccination to cover both travel and non-travel-related risk.

Travellers at increased risk of HBV exposure who should be targeted for pre-travel vaccination include:

- All those travelling to countries with intermediate to high prevalence of hepatitis B (HBsAg ≥2%), especially if likely to be at increased risk of exposure including:
  - Those travelling for elective medical procedures.
  - Those at occupational risk (including all healthcare professionals).
  - Those more likely to engage in activities that would increase their risk of exposure to contaminated equipment, blood, and body fluids (unprotected sexual contacts, intravenous drug use, tattoos, body piercings).
  - Those visiting friends and relatives.
  - Long-term and frequent travellers (the cumulative risk is less in those undertaking infrequent short term trips; however, short-term travellers have been infected).

It should be noted that exposures are not always predictable, hence the recommendation from some authorities that hepatitis B vaccination be advised for all travellers to countries with prevalence of HBsAg ≥2%. However, strict adherence to this guideline would include all travellers to New Zealand.

Travel (especially if short term) to countries with low hepatitis B prevalence is unlikely to expose most travellers to a significant risk of HBV infection and pre-travel vaccination is not routinely recommended.

Healthcare Professional Resources

Pre-travel health and vaccination information:

Immunisation Advisory Centre
http://www.immune.org.nz/

NZ Immunisation Handbook
http://www.health.govt.nz/publication/immunisation-handbook-2014-3rd-edn

NZ Ministry of Foreign Affairs and Trade (MFAT)
https://safetravel.govt.nz/health-and-travel

Centers for Disease Control and Prevention's Travelers' Health
https://wwwnc.cdc.gov/travel

WHO's International Travel and Health
http://www.who.int/ith/en/

Surveillance and disease outbreak information:

Morbidity and Mortality Weekly Report (MMWR)
https://www.cdc.gov/mmwr/index.html

EuroSurveillance Journal
http://eurosurveillance.org/

Pacific Public Health Surveillance Network
http://www.pphsn.net/index.htm

Weekly Epidemiological Record (WER)
http://www.who.int/wer/en/

Special groups for pre-travel HBV vaccination

Categories of travellers requiring special consideration for HBV vaccination prior to departure include:

1. Older unvaccinated travellers.
2. Travellers to Asia and the Pacific.
3. Medical tourism travellers.
4. Travellers visiting friends and relatives (VFR).

1. Older unvaccinated travellers

Although the global prevalence of HBV infection, and hence the risk to travellers, is likely to decline as a result of the widespread introduction of universal infant vaccination programmes, adult travellers born before the implementation of childhood vaccination programmes (mainly pre-2000 in most Western countries) have probably not been vaccinated against hepatitis B.[13]

Accordingly, some older travellers are likely to be susceptible to HBV infection and should be considered for HBV vaccination. In NZ, this will be individuals born prior to 1972, i.e. adults aged >45 years (as of 2017; and taking into account that many people born before 1988 could also have been vaccinated via catch-up programmes, including the 1990 school-based catch-up programme).

2. Travellers to Asia and the Pacific

Asia and Pacific countries are major destinations for travellers. In 2015, 279 million international tourist arrivals were received by Asia and the Pacific, accounting for nearly one quarter of the world's arrivals, and the number is projected to reach 535 million by 2030.[10] Of the record high 2.58 million overseas trips made by NZ residents in 2016,[14] 17% (or 442 million) were to Asia and 14.5% (or 376,000) were to the South Pacific (excluding Australia) making these regions among the top travel destinations for New Zealanders. Many countries in Asia (e.g. China, Laos, Thailand, Vietnam) and the South Pacific (e.g. Papua New Guinea, Tonga, Samoa, Vanuatu) are of upper-intermediate to high HBV prevalence.[3,31]

Moreover, HBV vaccine coverage and dose completion (i.e. all three doses) has been suboptimal in some Asian and Pacific countries (e.g. India [67%], Indonesia [85%], Myanmar [72%], Nauru [79%], Pakistan [72%], Papua New Guinea [68%], Solomon Islands [83%], Vanuatu [59%], Vietnam [59%]).[8] Even in Asian and Pacific countries that have achieved >90% coverage of completed HBV vaccination through universal infant immunisation (i.e. almost all counties since the 1997 WHO recommendation), the local cohort most likely to interact with travellers is unvaccinated adults for whom the prevalence of HBV is high intermediate (5–7%).[8,31]

Recommendation of HBV vaccination for travellers to countries of intermediate to high HBV prevalence, such as Asia and the Pacific, should be based on likelihood of infection during travel and evidence of previous immunisation, either from vaccination or recovery from prior infection.[31] A suggested decision tree for HBV vaccination for international travellers to Asia and Pacific countries of intermediate to high HBV prevalence is presented in **Figure 2**.

For travellers without evidence of previous HBV immunity (i.e. fully completed, and preferably documented, primary vaccination or known naturally-acquired immunity), HBV vaccination is recommended in those with HBV exposure risks and travelling to a country of higher HBV endemicity.[31] The likelihood of HBV immunity in travellers from low endemic countries who were born before universal infant vaccination is low as is the likelihood of having developed immunity from previous infection. Immunisation should, therefore, be considered in travellers from countries of low HBV endemicity, especially for those planning long-term travel to Asia and Pacific countries with intermediate to high HBV prevalence (**Figure 2**).

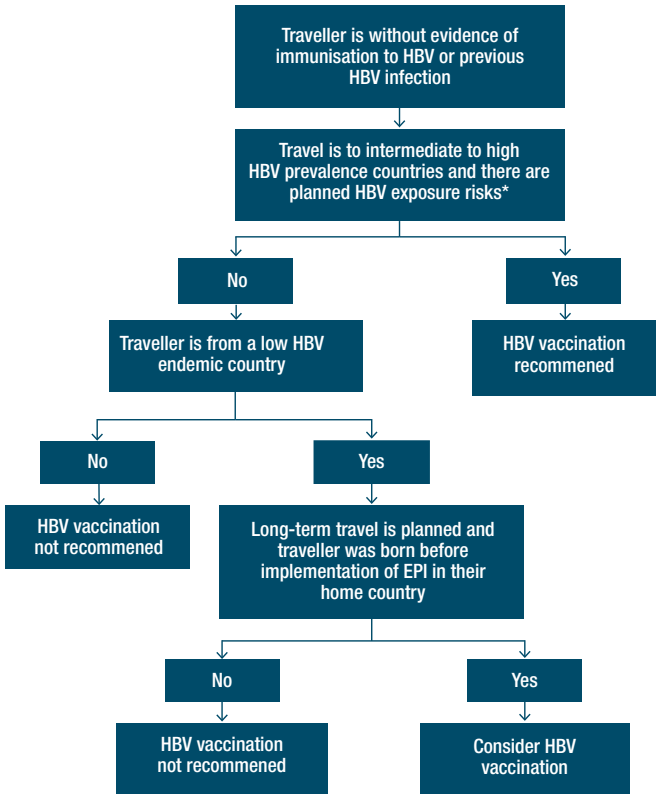

Figure 2. Proposed decision tree for HBV vaccination for travellers to high-risk countries in Asia and the Pacific.[31] *HBV exposure risks include sex with a new partner, getting a tattoo or piercing, or having any medical procedure. EPI = expanded programme of immunisation

3. Medical tourism travellers

Medical tourism refers to people travelling abroad for the specific purpose of accessing medical treatment, commonly heart surgery, cosmetic surgery, and dentistry.[23,32] Some people travel overseas for medical care because a specific treatment is not available in their country of residence or it is cheaper or immediately available in another country. Other medical tourism travellers may be immigrants who prefer to return to their country of origin for healthcare.

However, medical tourism can come with risks. Medical services in some destination countries may not screen blood or blood products for blood-borne infections, such as hepatitis B, and, because infection control standards may vary, blood-borne diseases can be transmitted via the use of non-sterile medical equipment.[23,25] Organ transplant tourism, for example, is associated with high rates of blood-borne viral infections.[33] According to a meta-analysis that assessed the risks of transplant tourism, people who receive a kidney abroad are significantly more likely to contract blood-borne diseases, including hepatitis B.[34]

4. Travellers visiting friends and relatives

One definition of a VFR traveller is any traveller whose intended purpose of travel is to visit friends and family in a country where the health risk is different from their current country.[35] Typically, they are immigrants, migrant workers, and migrant students.

VFR travellers have a higher risk of acquiring infections during travel than other travellers.[36-38] The main reasons for their higher risk are that, compared with those travelling for other purposes, VFR travellers are more likely to:[24,35]

1. Lack awareness of the travel-related health risks and preventive measures.
2. Believe they are immune to diseases in their country of origin.
3. Not seek a pre-travel health consultation or do so closer to departure.
4. Make last-minute travel plans to visit sick relatives or attend a funeral.
5. Not accept a recommended vaccination.
6. Stay for extended periods of time, which increases exposure time to viral diseases.
7. Use public transportation or drive themselves, which increases their risk of injury and hence need for local medical treatment.
8. Have unprotected intercourse.

In addition, cost may be a barrier to seeking pre-travel health advice and accepting a vaccine recommendation.[24,35] The cost of pre-travel consultation and vaccination, which are unfunded and unlikely to be covered by health insurance, may be a substantial financial burden for some VFR travellers, in particular those with large families.

Given their higher risk of infection, it is important to identify VFR travellers and provide advice and appropriate information and education about travel health and vaccines. VFR travellers can be identified by:[35]

- Noting the foreign-born status of patients at time of practice enrolment.
- Using ethnicity data in practice management software to identify foreign-born patients.
- Asking foreign-born patients, presenting for any reason, if any future travel is planned.
- Using opportunistic enquiry to determine the currency of routine and travel vaccination.
- Asking about health issues during recent travel.
- Asking about recent travel in patients with atypical medical presentations or when considering antibiotic therapy for infections.

Summary

Travellers that should be considered for HBV vaccination are:

1. VFR travellers.
2. New Zealanders born before 1972 (i.e. NZ adults aged >45 years of age as of 2017). Also it cannot be assumed that those aged between 29 and 45 years of age have been vaccinated without clear documentation.
3. Travellers visiting Asia, the Pacific, or other regions having an intermediate to high prevalence of HBV infection.
4. Travellers participating in medical tourism, including immigrants returning to their home country for medical treatment.
5. Long-term travellers.

Pre-travel HBV serological screening

Travellers from low endemic countries and who were born before universal infant HBV vaccination are unlikely to have HBV immunity and only a small number will have serological evidence of prior infection.[31] Therefore, pre-HBV vaccination serological screening in this group would seem unnecessary. In the US, routine pre-vaccination screening for susceptibility to HBV infection is not recommended because it has not been found to be cost effective.[39]

In individuals who have been vaccinated, although antibody titres decline in the years following HBV vaccination, there is strong evidence that an immune memory (i.e. anamnestic response) is retained after primary vaccination.[40-43] The WHO states that complete HBV vaccination ". . . provides protection for at least 15 years and, according to current scientific evidence, probably for life".[24] Hence, pre-vaccination screening of travellers who have been previously vaccinated would also seem unnecessary, especially if there is clear documentation of a completed primary series.

Situations in which serological screening might be useful include confirming hepatitis B status in VFR travellers born in countries with intermediate to high HBV prevalence, in those whose vaccination status is unclear, and in those at on-going high-risk exposure (e.g. healthcare workers).

Expert comment:

Pre-vaccination serological screening for hepatitis B is rarely indicated. A completed primary series of hepatitis B vaccination (including childhood vaccination) is accepted by most authorities to provide long-term, likely lifelong, immunity. Serological screening years after vaccination will not necessarily reflect immune status: measurable antibody titres fall with time, but most will retain immune memory and produce a booster response if exposed. A high titre many years after vaccination does confirm immunity; however, a low one does not necessarily mean the traveller is not immune.

Travellers born after the introduction of hepatitis B vaccination into the childhood immunisation schedule and who have either documentation of a full primary series or reasonable grounds to believe they received all the routine childhood vaccinations do not require hepatitis B serology pre-travel.

If there is uncertainty regarding previous hepatitis B vaccination and the traveller is perceived to be at higher risk of exposure or desires maximum protection; then serology can be considered. However, a clear plan of what to do if the serology indicates low titres needs to be in place before serology is ordered. Because many travellers present with limited time, in such cases it might be simplest to assume they have not been vaccinated previously and give a full primary series pre-travel.

Serology to establish hepatitis B status would also be justified in those who may have been at risk of exposure to the virus and who have not already been screened. Those born and raised in countries with low endemicity who do not have a high-risk profile do not require serology pre-vaccination.

Accelerated HBV vaccination schedules

Complete HBV vaccination requires three doses of vaccine, with the standard schedule being to administer the second and third doses at one and six months after the first.[7] However, many travellers usually do not present with a six-month lead time. For example, a European survey showed that 40% of international travellers waited until 4 weeks prior to departure before seeking pre-travel health advice.[44] In this situation, an accelerated HBV vaccination schedule pre-travel is necessary.

An accelerated schedule administered on days 0, 7, and 21 (with a booster at 12 months) is recommended for rapid protection.[13] Immunogenicity studies have shown that the 3-week HBV vaccination schedule elicits high rates of seroprotection lasting up to 1 year.[45,46] The combined hepatitis A and B vaccine administered using an accelerated schedule (either 3-week or 4-week) has also been demonstrated to induce early immunogenicity against both hepatitis B and hepatitis A.[30,47]

In addition to providing last-minute pre-travel protection against hepatitis B, other benefits of using accelerated schedules versus standard schedules include:[48]

- Enhanced adherence to and subsequent completion of the vaccine course.
- Greater convenience for the vaccine recipient.

EXPERT'S CONCLUDING COMMENTS

Infection with HBV can have significant health impacts. Vaccination has been shown to be an effective way of reducing the burden of HBV, hence the inclusion of hepatitis B in the World Health Organization's Expanded Programme of Immunisation. Even in travellers who may not be at increased risk of contracting hepatitis B while travelling, the pre-travel consultation provides an opportunity to discuss hepatitis B risk factors and to vaccinate those who desire maximum protection. Because vaccination is likely to induce long-term immunity, this is an opportunity to vaccinate not only for this trip but also for future travel and for life. Travel to destinations with intermediate to high prevalence of hepatitis B carriers is a risk factor for contracting hepatitis B, especially in those at higher risk of exposure. The benefits of hepatitis B vaccination should be discussed with all such travellers. A primary series requiring multiple doses can be a barrier to completion pre-travel; however, an accelerated schedule is licenced for both hepatitis B monovalent and combination hepatitis B and hepatitis A vaccines.

TAKE-HOME MESSAGES:

- With increased rates of international travel and tourism, HBV infection has the potential to occur in people lacking HBV immunity travelling in a country of intermediate to high HBV prevalence.
- The risk of HBV infection depends primarily on the prevalence of disease in the destination country, duration of travel, and activities undertaken while abroad.
- HBV is still highly prevalent in many countries in the Asia and Pacific regions, which are major destinations for NZ travellers.
- VFR travellers are at higher risk for vaccine-preventable diseases than other travellers and less likely to present for travel advice.
- HBV vaccination is recommended for all travellers to countries with an intermediate or high HBV prevalence.
- For convenience, a combined hepatitis A and hepatitis B vaccine can be considered for travellers who may be exposed to both HBV and HAV.
- Accelerated HBV vaccination is immunogenic and convenient for travellers who require last-minute protection against hepatitis B.

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