REVIEW

Vaccine-Preventable Travel Health Risks: What Is the Evidence—What Are the Gaps?

Robert Steffen, MD,* Ron H. Behrens, MD,† David R. Hill, MD, DTM&H,‡ Christina Greenaway, MD, MSc,§ and Karin Leder, MBBS, PhD¶

*Department of Public Health, Epidemiology, Biostatistics and Prevention Institute, University of Zurich, WHO Collaborating Centre for Traveller’s Health, Zurich, Switzerland; †Hospital for Tropical Diseases and Department of Clinical Research, London School of Hygiene and Tropical Medicine, London, UK; ‡Global Public Health, Frank H. Netter MD School of Medicine, Quinnipiac University, Hamden, CT, USA; §Division of Infectious Diseases, Jewish General Hospital, and the Center for Clinical Epidemiology, Lady Davis Institute for Medical Research, McGill University, Montreal, Canada; ¶Infectious Disease Epidemiology Unit, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia; §Victorian Infectious Disease Service, Melbourne Health, Parkville, Melbourne, Australia

DOI: 10.1111/jtm.12171

Background. Existing travel health guidelines are based on a variety of data with underpinning evidence ranging from high-quality randomized controlled trials to best estimates from expert opinion. For strategic guidance and to set overall priorities, data about average risk are useful. The World Health Organization (WHO) plans to base future editions of “International Travel and Health” on its new “Handbook for Guideline Development.”

Methods. Based on a systematic search in PubMed, the existing evidence and quality of data on vaccine-preventable disease (VPD) risks in travelers was examined and essentials of vaccine efficacy were briefly reviewed. The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework was used to evaluate the quality of the data.

Results. Moderate-quality data to determine the risk of VPD exist on those that are frequently imported, whereas in most others the level of confidence with existing data is low or very low.

Conclusions. In order for the WHO to produce graded risk statements in the updated version of “International Travel and Health,” major investment of time plus additional high-quality, generalizable risk data are needed.

The World Health Organization (WHO) has annually published International Travel and Health from 1989 until 2012 (previously known as Vaccination Certificate Requirements and Health Advice for International Travel). However, in 2013 the book was not published and in 2014 only certain sections were updated on-line. WHO plans to revise this publication based on the new Handbook for Guideline Development, which emphasizes a rigorous evidence-based approach to making recommendations and screening of contributors to minimize conflicts of interest. The process of reviewing the literature and properly grading each recommendation in this book will require a major investment of time to reach an acceptable consensus. The objective of this narrative review is not to embark on such a major endeavor, but to provide an updated account on the state of the existing evidence and quality of data of travel-related risks due to vaccine preventable diseases (VPDs). This will not replace the work WHO proposed, but will provide travel medicine practitioners with a framework by which to counsel travelers, while understanding the quality of the best data on which the recommendations in VPD estimates are based.

Existing travel health guidelines are based on a variety of sources of varying quality of evidence that includes data from randomized controlled trials, controlled trials, epidemiological and observational studies, expert consensus, nonexpert opinion, and best estimates. Some guidelines quantify the magnitude of travel risk inferred by the incidence of disease at the destination country, while others differentiate the risk of disease exposure to travelers from the disease incidence rate in the native population. The differential risk between these groups
Figure 1 Current estimates on vaccine-preventable disease incidence among Western travelers to tropical and subtropical destinations—absolute risk of disease/month of travel. Insufficient data on non-immune travelers to include yellow fever, measles, mumps, rubella, varicella, pertussis, tetanus, diphtheria, pneumococcal infection, etc. LT = heat-labile enterotoxin; ST = heat-stable enterotoxin; ETEC = enterotoxigenic Escherichia coli; TD = travelers’ diarrhea; PPD = purified protein derivative used in tuberculin sensitivity testing.

may be substantial. For individual counseling, ideally there would be data on different types of travelers to the same destination; unfortunately, this type of detailed information is generally not readily available.

For strategic guidance and to set overall priorities, data about the average risk in a typical traveler—those on a usual tourist itinerary or businesspersons, in contrast to travelers who visit friends and relatives (VFRs) or members of extreme travel—are transparent and useful (Figure 1). In this perspective, we will review the existing evidence and quality of data on VPD risks in travelers who originate from industrialized countries.

The type of infection, “epidemiology,” and “travel” were searched using Medical Subject Headings in PubMed from database inception to the end of December 2013; critically reviewed recent and relevant publications that defined the risk of these infections in international travelers were also included. Publications that reported denominator data and those published after 2000 were prioritized. Symptomatic infections were emphasized rather than seroconversions, as symptomatic disease may be more relevant to individual travelers. This implies that there may be many additional, unrecognized, subclinical infections, a potentially large reservoir of asymptomatic infections that is often of public health interest. The essentials of impact of the respective VPD and efficacy of the vaccine will also be very briefly summarized. The limitations associated with quantifying the magnitude of travel-associated risk from the different types of study designs and risk measurements will be discussed in an accompanying review.

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) is an evidence-based method that is increasingly being adopted to systematically assess the quality of data (or confidence in estimates from a body of literature) and to produce recommendations and guidelines. The key factors that are considered when developing recommendations with GRADE are assessment of the quality of the evidence base, balancing the harms and benefits of the intervention—the gold standard being the randomized clinical trial—and the values and preferences. However, the GRADE approach to assess the confidence in estimates of baseline risk from observational, nonintervention studies, which is the type of data used most often when assessing travel-related risks, is still under development. Nevertheless, a table that provides a simplified summary of the quality of the body of evidence for each VPD using the suggested GRADE categories has been included; the column on the right indicates that the database is far from optimal for several of the VPDs (Table 1).

The Canadian Committee to Advise on Tropical Medicine and Travel (CATMAT) has recently produced recommendations and a guideline on preventing typhoid in travelers. They used the GRADE framework to assess the quality of the data, the harms and benefits of typhoid vaccine, and the quality of the observational data quantifying travel-associated typhoid risk to produce their recommendations. GRADE is labor-intensive but may be a useful investment in the long term to make evidence-based recommendations.
### Table 1  
Methods by which data on vaccine-preventable diseases (VPD) in travelers resident in industrialized countries were generated (for references see text)

<table>
<thead>
<tr>
<th>VPD</th>
<th>Design</th>
<th>Risk of bias</th>
<th>Consistency*, †</th>
<th>Recentness‡</th>
<th>Confidence as per GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travelers' diarrhea</td>
<td>Cohorts (n = 3)</td>
<td>Selection by recruitment in travel clinics</td>
<td>Yes for incidence rate</td>
<td>After 2000</td>
<td>From moderate to high</td>
</tr>
<tr>
<td>LT-ETEC</td>
<td>By-product of intervention studies</td>
<td>Few destinations only</td>
<td>Variations depending on destinations</td>
<td>After 2000</td>
<td>Moderate; older data unreliable for time frame after 2000</td>
</tr>
<tr>
<td>WC/rBS vaccine efficacy against TD</td>
<td>Nonrandomized, nonblinded studies, and expert opinions</td>
<td>Multiple, often inappropriate study design, lack of diagnostic tests, etc.</td>
<td>Broad variation</td>
<td>After 2000</td>
<td>Very low</td>
</tr>
<tr>
<td>Influenza</td>
<td>Cohorts (n = 3)</td>
<td>Selection by recruitment in travel clinics</td>
<td>Yes</td>
<td>After 2000</td>
<td>From moderate to high</td>
</tr>
<tr>
<td>Typhoid</td>
<td>Notification</td>
<td>Incomplete; missing cases§</td>
<td>On order of magnitude</td>
<td>Some after 2000</td>
<td>Moderate</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Notification</td>
<td>Incomplete; missing cases§</td>
<td>On order of magnitude</td>
<td>Some after 2000</td>
<td>Moderate</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>Notification</td>
<td>Incomplete; missing cases§</td>
<td>On order of magnitude</td>
<td>Some after 2000</td>
<td>Moderate</td>
</tr>
<tr>
<td>Rabies</td>
<td>Anecdotal collection</td>
<td>Incomplete; missing cases; benefit PEP?</td>
<td>Only one review</td>
<td>After 2000</td>
<td>Very low for rabies infection</td>
</tr>
<tr>
<td>Tick-borne encephalitis</td>
<td>Expert opinion</td>
<td>Extrapolation from exposed locals</td>
<td>Only one statement</td>
<td>After 2000</td>
<td>Very low</td>
</tr>
<tr>
<td>Meningococcal disease</td>
<td>Notification</td>
<td>Incomplete; missing cases§</td>
<td>Only one review</td>
<td>Data 1986–1989</td>
<td>Very low</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Anecdotal collection</td>
<td>Incomplete; missing cases§</td>
<td>Overlapping reviews</td>
<td>After 2000</td>
<td>Low</td>
</tr>
<tr>
<td>Poliomyelitis</td>
<td>Notification (WHO)</td>
<td>Migrants neglected</td>
<td>Probably reliable</td>
<td>After 2000</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cholera</td>
<td>Notification (WHO)</td>
<td>Incomplete; missing cases§</td>
<td>Questionable</td>
<td>After 2000</td>
<td>Very low</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Expert opinion</td>
<td>Extrapolation from exposed locals</td>
<td>Repeated one statement</td>
<td>After 2000</td>
<td>Very low</td>
</tr>
</tbody>
</table>

GRADE = Grading of Recommendations, Assessment, Development and Evaluation; LT-ETEC = *enterotoxigenic Escherichia coli* producing heat-labile enterotoxin, WC/rBS = whole cell/B-subunit of cholera toxin, TD = travelers’ diarrhea; WHO = World Health Organization; PEP = postexposure prophylaxis.

*Also considering imprecision, for example, because of lack of data on confidence intervals.

†Indirectness not listed, as no extrapolations from native populations were included.

‡Year of data collection.

§Missing cases by lack of compliance with required notification, illness abroad, case not diagnosed, etc.
for travel-related risks. The ultimate goal of this review is not to provide recommendations for each individual vaccine but rather to review what data exist on the baseline travel risk of these diseases and describe the overall quality of these data and identify gaps in the data for which better information is needed.

**VPDs With High Risk (1–10 per 10,000 Travelers per Month of Travel)**

Three infectious diseases including travelers’ diarrhea (TD), influenza, and hepatitis A have been ranked as the most common VPDs in travelers over the past several years.

**TD Associated With Heat-Labile Toxin-Producing Enterotoxigenic Escherichia coli**

Incidence Estimates

TD continues to be the most frequent infection acquired during travel to most destinations in the tropics and subtropics. Three recent cohort studies conducted in travel clinics in Zurich (n = 2,800), Amsterdam (n = 1,202), and Leiden (n = 390) documented a crude incidence rate of 0.58 (SE, 0.22) to 3.95 (SE, 1.47) per 100 travel-days depending on the destination. All three studies noted that the rates were highest during or after travel to Northern/Western/Middle Africa and in South-Central Asia or South Asia. At some destinations, there were considerable variations between the data sets: for example, in South America, the rates were 0.58 (SE, 0.22) and 1.96 (95% confidence interval [CI]: 1.59–2.42) in the two Dutch studies, respectively, and 1.48 in the Swiss study (extrapolated from classic TD with a 2-week incidence of 20.7%; 95% CI, 16.9–24.5). Overall, this corresponds at most to a small decrease from traditionally reported 20% to 60% attack rates for a 2-week stay. In view of an overall consistency of these results, confidence in estimates of the baseline risk was rated as moderate to high (Table 1). Larger cohorts would be needed to increase the confidence at destinations on a country level.

**Clinical Impact**

TD is typically a self-limited illness with an average duration of 4 days even if untreated, but it often interferes with planned activities, and thus is frustrating for travelers. Effective therapy of TD reduces the duration of illness. While TD fatalities are rare, there can be associated morbidity and potentially disabling enteric and extra-intestinal long-term complications, as recently reviewed. Of long-term complications, post-infectious irritable bowel syndrome, investigated in several traveler studies, was the most frequent. When the Rome III criteria were used, 3.0% of patients with TD developed irritable bowel syndrome within 6 months of travel, compared with 0.7% of travelers without TD. These rates have been higher when Rome II, other less stringent criteria, and different methodology and populations have been used.

**Vaccine**

In many countries, an oral cholera vaccine containing killed *Vibrio cholerae* O1 and the B-subunit of cholera toxin [WC/rBS (whole cell/B-subunit of cholera toxin), Dukoral, Crucell (a Johnson & Johnson Company), Leiden, The Netherlands] is available; in some countries (eg, Canada), it is additionally licensed for “protection against TD,” or (eg, Switzerland) for prevention of “TD caused by heat-labile enterotoxin producing enterotoxigenic Escherichia coli (LT-ETEC).” LT-ETEC is similar to the B-subunit of cholera toxin. According to a systematic review of 51 studies providing data on the etiology of TD in 30,984 patients from 1973 to 2004, the proportion obtained owing to ETEC was 30.6, 31.2, and 33.6% in South Asia, Africa, and Latin America/Caribbean, respectively, but only 7.2% in Southeast Asia. A decreasing ETEC rate over the years was noted particularly in travelers to Latin America (negative correlation coefficient of 0.41; p = 0.036), while such changes were not significant in other parts of the world. Analysis of 20 *E. coli* colonies per TD stools collected in Mexico, Guatemala, and India resulted in a higher yield of ETEC (75.6%), but only 32.9% were heat-labile enterotoxin (LT), heat-stable enterotoxin (ST)/LT, or mixed ETEC. Thus, estimates on the effectiveness of this vaccine against the syndrome of TD vary from 1% to 7% (expert opinion) to 28% and more in various nonrandomized studies using a biased analysis. A recent Cochrane review concluded that there is currently insufficient evidence from randomized controlled trials to support the use of the oral cholera vaccine Dukoral for protecting travelers against ETEC diarrhea.

**Influenza**

Incidence Estimates

Three prospective studies have assessed the incidence of influenza among travelers to tropical and subtropical countries. On the basis of the cohorts with 1,450, 1,190, and 387 travelers, the rate of serologically confirmed cases was 8.9 per 100 person-months, whereas in symptomatic—essentially febrile—cases, the rates were 1.0 and 0.9 respectively. Despite varying study methods and cohorts, these studies reflect the same order of risk magnitude. Visitors to destinations in East and Southeast Asia had a sevenfold higher risk of influenza as compared with those to other destinations.

**Clinical Impact**

For most persons, influenza is self-limited; however, it has the capacity to cause serious complications, predominantly pneumonia. Fatalities secondary to influenza typically occur in those with underlying chronic medical conditions, although they can occur in previously
Healthy individuals, including those who are pregnant. While anti-viral treatment can slightly shorten the duration of illness when initiated promptly after development of symptoms, it has not been routinely adopted for travelers.

Vaccines

Every 6 months the WHO issues recommendations on the composition of influenza viral vaccines for the Northern and Southern hemisphere influenza seasons. While protection is not ideal, efficacy of influenza vaccine is documented even against mismatched strains and in older subjects.6 Although the incidence of influenza was higher in unvaccinated travelers in one study, the protective effect of immunization failed to achieve significance (p = 0.883).12 While 65% of Australian Hajjees have been reported to receive influenza vaccine for their pilgrimage,13 from personal experience, convincing other travelers is difficult.

Hepatitis A

Incidence Estimates
Numerous retrospective studies indicate that monthly incidence rates for hepatitis A per 100,000 nonimmune travelers to nonindustrialized countries have decreased over the past 40 years. In the 1970s, rates were estimated to be 300 per 100,000 travelers (n = 221 cases),16 falling from 30 between 1996 and 2001 (extrapolation from 295 annual travel-related cases),37 to 6 to 28 between 1988 and 2004 (n = 2,784),38 and most recently to 12.8 between 2000 and 2010 (n = 60).39 In Canada, almost two thirds of patients with hepatitis A, and in Sweden half of the cases were associated with VFR travelers.40,41

Clinical Impact
Hepatitis A is an important disease because it incapacitates most adult patients for several weeks. Management is limited to general supportive care. The case fatality rate is 1.8% in those older than 50 years.42

Vaccines
Hepatitis A vaccines are highly efficacious,43 and boosters are not currently recommended as the period of protection following a primary series of two doses exceeds 25 years1 or is even lifelong.1,44

VPDs With Intermediate Risk (1–10 per 100,000 Travelers per Month)

Hepatitis B

Incidence Estimates
Since the implementation of infant or adolescent hepatitis B vaccination in a majority of countries, imported infections have decreased. Three studies conducted in the past 22 years have reported rates of travel-associated hepatitis B acquisition. In a study of Danish travelers, the monthly incidence was 10.2 per 100,000 nonimmune travelers (n = 14, 39), and 6.6 (converted from incidence density of 22 per 100,000 travel-days; n = 1 in a cohort of 361).45,46 In the third study from the Netherlands, 25 of the 52 cases of hepatitis B had a source most likely not associated with travel.47 The rate was 4.5 per 100,000, and VFR and long-term travelers were at particularly high risk.47 In contrast, the Danish report highlighted that 62% of cases occurred in travelers who spent less than 4 weeks abroad.48 Older surveys with larger number of cases48 indicated that high-risk destinations did not correlate with the destination country’s prevalence of hepatitis B surface antigen49; individual behavior abroad is likely to be more relevant. Only few cases associated with nosocomial infection abroad, particularly with medical tourism, have been documented,49 and close contact with locals, especially casual sex, are more relevant.

Clinical Impact
While most cases of hepatitis B in adults are asymptomatic, 30% to 50% will experience symptoms that can be more severe than hepatitis A and result in incapacitation and hospitalization. Management is limited to general supportive care; occasionally liver transplantation is needed. The case fatality ratio of acute hepatitis B is 1%; chronic infection, which occurs in about 5% of those infected as adults, may result in the long-term complications of cirrhosis and liver cancer.44

Vaccines
Hepatitis B vaccines are highly effective, and a complete series in those who seroconvert probably provides protection for life.1,44

Typhoid Fever

Incidence Estimates
A decrease in travel-related enteric fever transmission rate has been associated with improved hygienic conditions at many frequently visited destinations in emerging market nations. The highest rates in travelers occur in those who have visited South Asia (Pakistan, India, Nepal, Sri Lanka, and Bangladesh), at a stable attack rate of 33 cases per 100,000,10 followed by West and Central Africa.49–54 CATMAT now summarizes the risk to be 1 to 2 cases per 100,000 for Africa (except southern Africa with usually negligible risk rate), the Middle East and South America, and <1 per 300,000 for the Caribbean and Central America.10 Surveillance in the UK determined somewhat lower rates: in travelers to South Asia, the risk was 17 cases per 100,000, and outside the Indian subcontinent, the rate may be as low as 0.05 per 100,000 travelers.55 High-risk groups include children, VFR travelers, those with prolonged duration of stay, and possibly those with no gastric acidity.10 Importantly, the endemic incidence rate for typhoid fever is often an unreliable surrogate of risk in travelers, given the risk in endemic populations is much greater.
as compared with travelers having an adjusted incidence ratio of 4:205.56

Clinical Impact

Typhoid and paratyphoid fevers are systemic diseases of varying severity; in industrialized countries, patients are commonly hospitalized for antibiotic treatment. Complications such as relapse, intestinal hemorrhage or perforation, endocarditis, or splenic abscess can occur. The case fatality rate in travelers is less than 1%.10,13,56

Vaccines

Two vaccines against Salmonella enterica serovar Typhi, a live-attenuated oral vaccine, Ty21a, and a parenteral product containing the Vi polysaccharide antigen, are marketed in industrialized countries. Both protect about 50%10 to a maximum of 80%44 of recipients for 1 to a few years, depending on the vaccine, and in the case of the Ty21a vaccine, the number of doses administered (three vs four doses). Both vaccines have a very low risk of serious adverse events,10 but the live oral vaccine should not be given to people who are immunocompromised.

Rabies

Incidence Estimates

This rare infection is included in the intermediate-risk group in view of the frequent potential exposures and the unknown number of cases prevented by postexposure prophylaxis (PEP). Forty-two human deaths because of imported rabies in Europe, the United States, and Japan were recorded from 1990 to 2010.57 According to a Thai report, 1.1 per 100 travelers per month had been bitten by animals, mostly dog, during travel in Southeast Asia and 3.1 per 100 had been licked.58 Among those who were bitten, only 37% went to a hospital for postexposure treatment. In Europe and in North America, thousands are given PEP each year for potential rabies risk.59,60 PEP was indicated in 3.6 per 1,000 Peace Corps Volunteers per month.61 Despite the many potential exposures in travelers, fortunately few cases progress to rabies, as indicated by the number of imported cases57—but overall the confidence in estimates on the risk of rabies is very low.

Clinical Impact

Rabies has a virtually 100% case fatality rate once symptoms appear.

Vaccines

Several tissue-culture-derived vaccines are very effective and well-tolerated.62 Access to postexposure treatment with immunoglobulin is very limited and unpredictable globally.63–65; members of the International Society of Travel Medicine have access to a web-based resource (http://www.is tm.org/WebForms/Members/Member Resources/Publications/Handouts/globalavail.aspx).

Tick-Borne Encephalitis

Incidence Estimates

Anecdotal reports of tick-borne encephalitis (TBE) acquired by travelers to Europe and Northern Asia have been published.66–68 Even though it is not known how many visitors to areas such as Central Europe have been exposed, based on extrapolations, an estimate of 10 clinical cases of TBE per 100,000 person-months has been published.69 Among 194 American service members who trained extensively in endemic areas of Central Europe in the 1980s (3,297 person-months of potential exposure), 3 were seroconverted, corresponding to an infection rate of 0.9 per 1,000 person-months; none developed clinical symptoms.70

Clinical Impact

In endemic areas, a minority of the Ixodes sp. ticks are inflected with the TBE virus.71 Among those bitten by an infected tick, the rate of asymptomatic to symptomatic infection is about 250:1. Of those who are symptomatic, two thirds will have a self-limited febrile illness that resolves after a few days. After a symptom-free interval, a second phase of illness with meningitis, encephalitis, or myelitis may occur in one third of these patients, of whom up to 40% will have permanent sequelae; the older the infected person the higher the proportion.71,72 Only supportive therapeutic options exist. The case fatality rate among the small proportion of patients who develop neurological symptoms in Europe is 3.5% (H. Zeller, personal communication). In the Far East, it can exceed 20%, with this difference likely secondary to the difference in virulence between Western and Siberian viral subtypes.73

Vaccines

Two inactivated vaccines are available in Europe and a few additional countries. They have a good tolerance profile and their protection rates exceed 95%.73,74

Tuberculosis

Incidence Estimates

There are several reports of tuberculosis (TB) transmission en route75 or abroad as measured using tuberculin skin test or interferon-gamma release assay (IGRA) conversion following foreign travel.76 The risk increases with longer duration of travel and higher TB incidence in the destination country, and is also affected by the type of travel and the work done (if any) in these countries. Long-term travelers with extensive contact with the local population in countries having higher TB incidence have a similar risk of acquiring infection as the indigenous population. On the basis of over 25 million volunteer-years, the US Peace Corps incidence rates for purified protein derivative (PPD) conversions and active TB cases were 1.28 and 0.06 per 1,000 volunteer-months, respectively.77 In a Dutch cohort of 1,072 long-term travelers, higher rates of 2.8 per 1,000 person-months of travel were recorded; the rate was
0.6 if healthcare workers were excluded. Immigrants who return to their home countries to visit friends and relatives (e.g., VFR travelers) are at particularly increased risk of exposure to TB infection and development of disease. Studies on immigrants from the Indian subcontinent estimated that 22% of patients with TB in the midland region of the UK were because of travel to their countries of origin. Also 56% of TB cases in the Moroccan immigrant population in the Netherlands were associated with recent travel to Morocco. There are no data on risks for short-term holiday travelers. As there is an absence even of anecdotal reports, infection is presumably unlikely in this population.

### Clinical Impact
The clinical severity of infection is highly variable and depends on site(s) of infection, timing of diagnosis, microbial sensitivity, and host co-morbidities.

### Vaccine
As per recommendations of WHO, Bacillus Calmette–Guérin (BCG) vaccine is of very limited use for travelers. It may offer protection against severe forms, particularly pulmonary TB and possibly against miliary and meningeal TB in the first year of life, and to a lesser degree also in children.

### VPDs With Low (<1 per 100,000) or Very Low Risk (<1 per 1,000,000 Travelers per Month)
For defining risk with very low incidence, it is not possible to use case numbers in travelers as there are too few cases to be meaningfully divided by a large dominator of travelers. Thus, the definition of geographic risk is important. Most would agree that the incidence rate per month for several neurological infections—meningococcal meningitis, Japanese encephalitis (JE), and poliomyelitis—as well as for yellow fever (YF) and diagnosed cholera is less than 1 patient per 100,000, thus indicating very rare risks in the "usual" traveler.

### Cholera
Incidence Estimates
Annually imported cases of cholera in travelers and migrants are reported, some in clusters from areas with epidemics. In 2012, 129 imported cases were recorded, including 88 in Malaysia. As demonstrated in Singapore, increasing standards of environmental hygiene—already discussed for hepatitis A and typhoid—have resulted in a declining incidence of cholera in many regions of the world. However, others, such as Hispaniola and some countries in Africa and South Asia, continue to report large numbers of cases. Currently, there is a lower incidence rate of diagnosed cholera among travelers from industrialized countries compared with a retrospective study conducted three decades ago, where an attack rate of 1 in 500,000 was reported. Gastric acidity is a known protective factor, and doxycycline when used for malaria prophylaxis may play a protective role.

### Clinical Impact
Moreover, in most cases, *V. cholerae* infection is asymptomatic or so mild that cases clinically appear as "travelers' diarrhea" (Steffen, personal communication). In contrast to an approximately 1% case fatality rate in populations where cholera is endemic, we are unaware of any death associated with cholera in a traveler in this century.

### Vaccine
The WC/rBS oral cholera vaccine (Dukoral) marketed in many Western countries confers 85% to 90% protection for up to 6 months in all age groups and efficacy remains at about 60% after 2 years in older children and adults. Various other oral vaccines are available mainly in Asia; all these cholera vaccines are safe. No country requires proof of cholera vaccination as a condition for entry, and the International Certificate of Vaccination or Prophylaxis no longer includes a specific page for cholera vaccination.

### Meningococcal Disease
Incidence Estimates
Acquisition of meningococcal disease during travel has recently been reviewed. In this single retrospective survey, risk during travel was not higher when compared with that at living in industrialized countries. An increased environmental risk has been documented with crowding, and historically associated with religious pilgrimage during the Hajj. After quadrivalent immunization became a requirement by the Saudi authorities in order to obtain a visa to the Hajj, the incidence of meningococcal disease in Hajj pilgrims has become negligible. Anecdotal reports among travelers were described in cases or small outbreaks with no obvious risk factors. We are unaware of reports documenting an excessive risk for travelers during the November to June seasonal epidemic of meningococcal infection in the African Meningitis Belt, but this may be because a substantial proportion of visitors have been immunized.

### Clinical Impact
Infection with *Neisseria meningitidis* can progress rapidly despite antibiotic therapy. Up to 20% of patients will have permanent debilitating sequelae, and symptomatic disease is fatal in up to 15% of patients.

### Vaccines
For travelers, quadrivalent ACW135Y polysaccharide and conjugate vaccines are available; mono- and bivalent vaccines are less commonly used. Vaccines against serogroup B are now available in some countries, although their recent introduction means that there is no documented experience of use specifically for travel.
All available vaccines have an excellent safety record, with efficacy rates exceeding 85%. Conjugate vaccines are immunogenic at younger ages and generally have protective efficacy that lasts longer than unconjugated polysaccharide vaccines. Japanese Encephalitis

Incidence Estimates

There are anecdotal reports on travel-associated JE every year. In a review of 55 cases reported in travelers from 1973 to 2008, the purpose of travel for 60% was tourism. While the majority of cases fit known risks (travel to rural areas of endemic regions for a month or more), one third had stayed in endemic areas for less than a month. On the basis of 7 cases in Sweden, an attack rate of 1 case per 300,000 travelers was extrapolated; among the 21 patients in that review, 13 had stayed only in “typical” tourist destinations for at most 5 weeks. According to 55 cases in a global assessment, the rate was less than one per 1 million travelers.

Clinical Impact

Most cases of infection with JE virus are asymptomatic. Of those 1:200 individuals who develop clinical disease, approximately one third will die and another third with have permanent neurologic sequelae.

Vaccines

In Western and endemic countries, several inactivated and attenuated-live vaccines are used. All show seroconversion rates after a primary series of at least 95% and are well tolerated. Booster recommendations vary according to the preparation administered.

Polio

Incidence Estimates

Importation of poliomyelitis to industrialized countries is rare, with the last published case reported from Australia in 2007, when a student returned from a visit to Pakistan. However, polio remains endemic in three countries: Nigeria, Pakistan, and Afghanistan. In 2013 and 2014, international spread has occurred into Cameroon, Ethiopia, Kenya, Somalia, and other African countries from Syria and Iraq. Only a few years ago, China reported importation of polio from Pakistan. In June 2014, WHO reported that wild poliovirus type 1 had been detected in sewage water near Sao Paolo, Brazil, international airport with a close match to a strain recently isolated in Equatorial Guinea.

Clinical Impact

More than 95% of persons infected by poliomyelitis virus remain asymptomatic. However, a small number will die because of polio, and those who develop flaccid paralysis will have life-long disability.

Yellow Fever

Incidence Estimates

The geographic areas at risk of YF have been recently defined using human and nonhuman case reports, clusters and outbreaks, seroprevalence data where vaccination is not universal, and ecologic factors such as vegetation and altitude. Recent modeling estimates 130,000 cases of YF in endemic countries. The current expert-estimated risk of acquiring YF in unvaccinated travelers to West Africa is 10 to 50 cases per 100,000 visits over a 2-week exposure. This risk was extrapolated from the local population at risk in West Africa during historical YF outbreaks in the 1970s; the risk could be as high as 73 per 100,000 per month in unvaccinated travelers. Risks are estimated to be lower for travel to the Amazon Basin of South America, although during outbreak periods the risk could be as high as 18 cases per 100,000. These risk estimates do not match case reports of YF in travelers (10 reports from 1970–2012, with the last one in 2002; G. Poumerol, personal communication), but a proportion (possibly only 30%) of exposed persons is likely to have been immunized and many holiday destinations have vector control.

Clinical Impact

YF will be asymptomatic or mild in about 50% to 85% of infections and therefore escape diagnosis. Commonly the case fatality rate varies between 5% and 50%, but among the 10 travelers diagnosed with this infection, only 2 survived.

Vaccines

Vaccines for YF are highly effective, but the first dose may rarely be associated with potentially fatal viscerotropic and neurologic disease. These severe adverse events occur at a rate of about 0.3 to 0.8 cases per 100,000 doses, more frequent than severe adverse events with other travel vaccines, and persons 60 years and older may be at an increased risk. Thus, travel healthcare providers should carefully consider vaccination only in people who are truly at risk of YF infection, especially in primary vaccine recipients; potential vaccine recipients appreciate to be involved in the decision making.

VPDs With Insufficient Data on Travel-Associated Risk for Classification

Measles, Mumps, Rubella, and Varicella

For several infections, data on incidence rates in travelers have not been published. Measles has been
transmitted en route onboard planes or ships,\textsuperscript{111,112} while abroad or imported into the traveler’s country of origin following return and resulting in outbreaks.\textsuperscript{33,113–115} Importation of measles following travel is the most common epidemiologic factor for measles cases in countries that have eliminated indigenous measles, such as the United States.\textsuperscript{114,115} There have also been anecdotal reports of cases of mumps,\textsuperscript{116} rubella,\textsuperscript{111} and varicella\textsuperscript{76,111} in travelers.

Others
Only very few cases of travel-associated tetanus,\textsuperscript{117} diphtheria,\textsuperscript{118} pertussis,\textsuperscript{119} and pneumococcal infections\textsuperscript{75} have been published. We are not aware of any reports on human papillomavirus infections clearly attributed to travel.

Conclusions
There are moderate quality data to determine the risk of VPDs that are frequently imported, such as that of influenza or typhoid. Decreasing rates of hepatitis A over the past four decades illustrate how rates may change over time and highlight the need for regular literature updates. In many countries, following universal vaccination programs in the countries of origin of the travelers, and improvements in sanitary conditions at the destination, measuring exposure to such infections in travelers will become increasingly difficult. Understanding the high-risk destinations and traveler activities helps inform policy for pre-travel immunization. For diseases such as measles, rubella, and pertussis that remain endemic in most parts of the world, it is important to ensure that travelers are up-to-date with their routinely recommended immunizations. Many countries have also expanded their routine vaccination against influenza. This will protect not only those who are immunized for travel, but also their country of origin from the reintroduction of disease. For uncommonly imported diseases such as rabies, YF, and TBE the quality of the data on the estimate of baseline risk is very low. The baseline risk estimate that varies in different geographic regions and by season needs to be balanced with the disease severity and characteristics of currently available preventive measures in order to decide on an optimal strategy to protect individual travelers. This emphasizes the ongoing importance of non-vaccine measures for avoidance, such as thorough washing of any bite wound with copious water and soap to avoid rabies infection. Populations living in areas where “traditional travel infections” are widespread may be immune by previous infection or national immunization programs—thus extrapolation from endemic country data may be inappropriate. It is also essential to assess the excessive travel health risks as compared with staying home.\textsuperscript{120}

To assist WHO in developing guidelines, additional research is needed to improve the quality of data. The ideal data on which to estimate travel-associated risk are population-based studies of disease confirmed based on laboratory diagnosis (numerator) with denominators that are representative of all travelers at risk. The large data bases such as GeoSentinel, EuroTravNet, and TropNetEurop identify sentinel cases, and provide insight into the relative magnitude and geographic distribution of risks but are limited by the fact that they are not able to measure denominators and thus absolute travel risk cannot be estimated. Additional data on special risk groups, such as VFR travelers, children, and the elderly, are needed to determine the incremental travel-associated disease-specific risks in these individuals. Future cohort studies should attempt to include a wider sample of travelers and not be limited to those who attend travel clinics, as this creates a selection bias. We must develop means to systematically obtain as complete information as possible on rare travel-related infections even from countries where these diseases are not notifiable. Serosurveys would give us a better idea of subclinical infections, which would help define risk destinations. To be able to compare studies and to conduct meta-analyses, standardized case definitions and the same regional classification should be used.\textsuperscript{18}

Acknowledgments
S. L. Norris, MD, MPH, MSc, Guidelines Review Committee Secretariat, World Health Organization, Geneva, Switzerland and G. Poumerol, MD, MSc, World Health Organization, Health Security and Environment Cluster, Geneva, Switzerland offered guidance and helpful comments on drafting the manuscript.

Declaration of Interests
R. S. has accepted fees for contributing to education or serving on advisory boards, reimbursement for attending meetings, and/or funds for research from Baxter, GlaxoSmithKline, Intercell (now ValNeva), Novartis Vaccines & Diagnostics, Sanofi Pasteur MSD, and Takeda. R. B. has received funding from Intercell (now ValNeva) for research. K. L. has received research and travel support from GlaxoSmithKline and Sanofi. C. G. has received research support from GlaxoSmithKline, Merck Frost, and Sanofi Pasteur. D. R. H. has no interest to declare.

References
Evidence on Travel Vaccine-Preventable Health Risks


