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A latent trajectory analysis of young sexual and gender minorities adherence to three rectal microbicide placebo formulations MTN035 a randomized crossover trial

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Review

Review

Travel vaccines—priorities determined by incidence and impact

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Abstract

Background: Infectious disease epidemiology is continuously shifting. While travel has been disrupted by the COVID-19 pandemic and travel-related epidemiological research experienced a pause, further shifts in vaccine-preventable diseases (VPDs) relevant for travellers have occurred.

Methods: We conducted a literature search on the epidemiology of travel-related VPD and synthesized data for each disease with a focus on symptomatic cases and on the impact of the respective infection among travellers, considering the hospitalization rate, disease sequela and case fatality rate. We present new data and revised best estimates on the burden of VPD relevant for decisions on priorities in travel vaccines.

Results: COVID-19 has emerged to be a top travel-related risk and influenza remains high in the ranking with an estimated incidence at 1% per month of travel. Dengue is another commonly encountered infection among international travellers with estimated monthly incidence of 0.5–0.8% among non-immune exposed travellers; the hospitalized proportion was 10 and 22%, respectively, according to two recent publications. With recent yellow fever outbreaks particularly in Brazil, its estimated monthly incidence has risen to >0.1%. Meanwhile, improvements in hygiene and sanitation have led to some decrease in foodborne illnesses; however, hepatitis A monthly incidence remains substantial in most developing regions (0.001–0.01%) and typhoid remains particularly high in South Asia (>0.01%). Mpox, a newly emerged disease that demonstrated worldwide spread through mass gathering and travel, cannot be quantified regarding its travel-related risk.

Conclusion: The data summarized may provide a tool for travel health professionals to prioritize preventive strategies for their clients against VPD. Updated assessments on incidence and impact are ever more important since new vaccines with travel indications (e.g. dengue) have been licensed or are undergoing regulatory review.

Key words: Prevention, epidemiology, dengue, COVID-19, hepatitis, rabies

Introduction

Much has happened since the publication of the last logarithmic scale on travel vaccine priorities, even more since the last article that associated disease incidence and impact have been related.[1–3]

With respect to epidemiology, the COVID-19 pandemic interrupted most travel mainly 2020 to 2022 and additional public health emergencies of international concern were declared by the World Health Organization (WHO) on Ebola in the Democratic Republic of Congo (2018) and on monkeypox [now mpox] (2022). The number of dengue cases reported to WHO from over 100 countries increased over 8-fold over the last two decades to 5.2 million in 2019.[4] Influenza had virtually disappeared in the Northern and Southern Hemisphere for two seasons each during the pandemic,[5] but rebounded early and for a prolonged duration in the Northern Hemisphere winter 2022/23.[6] While in

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Western Europe and other high-income regions vaccine coverage for measles has never been optimal,[7] large measles outbreaks have been recorded in Africa and on the Indian subcontinent subsequent to the lapses of immunization during the COVID-19 pandemic.[8–9] Wild poliomyelitis virus (WPV1) has resurfaced in Mozambique and the list of countries with circulating vaccine-derived polioviruses (cVDPV 1, 2, 3) is long, now including even the USA, Israel and the UK.[10] Japanese encephalitis endemicity has broadly expanded in Australia and even potential endemicity on other continents is considered.[11,12]

New vaccines relevant for travellers have been marketed since 2018, first and foremost a whole range of COVID-19, novel influenza and hepatitis B vaccines not to be discussed in detail in this review. The first dengue vaccine, Dengvaxia, is available in the USA, but not in Europe and it is only exceptionally recommended for travellers. In contrast, Qdenga (formerly TAK-003) is more relevant for travellers.[13,14] Vaccines in phase III studies against *Escherichia coli* associated with travellers' diarrhoea, chikungunya, Zika and Lyme disease may soon become relevant to travel health professionals. None of these infections related to vaccines on the horizon will be discussed here.

Although travel health professionals had to focus on other priorities than to conduct travel-related epidemiological research during the COVID-19 pandemic, recent publications provide insights relevant for decisions on priorities in travel-related vaccine-preventable diseases (VPDs). For each travel-related vaccine, we provide a one-paragraph summary on travel-related incidence with a focus on symptomatic cases and a second one on the impact of the respective infection on travellers. For the latter, we consider hospitalization, sequelae and the case fatality rate (CFR). Since the properties of vaccines [except for Bacillus Calmette Guérin (BCG)] and recommendations for them are formulated by national expert bodies, these will not be discussed here. Similar to previous publications, the goal is to provide a tool for travel health professionals to prioritize preventive strategies for their clients based on best estimates in incidence and impact.

Methodology

Essentially the same methods were used as previously published; however, this review did not reassess the GRADE conclusions.[2]

Data sources

Using Medical Subject Headings in PubMed, we checked the respective VPD AND travel AND imported OR epidemiology. All types of publications in English, French, German, Italian and Spanish were included; the search extended from 2001 to May 2023. Some additional sources were detected by reviewing the references. As this is not a systematic review, we did not keep track of the numbers of titles screened.

Data analysis

While we were unable to estimate incidence rates when just attack-rates per trip of undetermined duration were published or when there was no denominator, we converted from million days of travel or other durations to cases per person-months (pm) assuming a linear distribution. Whenever several studies had differing results, we included an average in the figure; as the differences were small in the logarithmic scale the difference would usually have been <1 mm. While in the previous publication we had included the source in the figure,[1] they are now just in the text.

Definitions

We define 'non-immunes' to include those not vaccinated or immune by natural infection. Among those vaccinated, we have been unable to determine whether they are still immune, as the publications hardly ever include data on timely booster application.

In the text, GeoSentinel and EuroTravNet will be mentioned. Both are clinic-based global surveillance systems that track diseases among travellers in their destination country and upon return. Currently GeoSentinel comprises 71 clinics worldwide. Clinical information is collected by physicians and entered into a database which is maintained by the U.S. CDC. By nature, GeoSentinel is unable to provide denominator data; thus, no incidence rates are generated, but it offers valuable data on proportionate morbidity.[15]

Incidence and impact of travel-related vaccine-preventable diseases

The past 5 years have informed several lessons. COVID-19 is a new risk; other infections have become more relevant for travellers, such as yellow fever, while the incidence of some 'traditional' travel infections, such as hepatitis A, has further decreased and the logarithmic scale (Figure 1) has been adapted accordingly. Dengue frequently affects travellers and the position of the new vaccine (whose pros and cons are not discussed here) in the incidence priority figure must be determined.

Past publications regarding prioritization focused on incidence and impact of infectious health risks among non-immunes with destinations in tropical or subtropical or also in low-and-middle-income countries (LMICs). As shown below particularly with respect to COVID-19 and influenza, this is no longer the sole targeted risk group.

Frequent travel-related VPD risk, exceeding 1 per 1000 pm

COVID-19. COVID-19 vaccines have been required for entry to or transit through some countries, to board cruise ships or to enter some venues. Most studies on airports and on cruise ship travel reported on outbreaks before COVID-19 vaccines were available and the quality of evidence was rated as 'low to very low'.[16–19] Data are scarce on broad epidemiological surveys documenting the incidence of COVID-19 in travellers since the introduction of vaccines. A recent EuroTravNet report, which included travellers until September 2021, shows a drastic increase of COVID-19 diagnosis to a peak of 12.7%, and often malaria had primarily been considered.[20] Contrary to the VPD described below, it must be assumed that the vast majority of travellers had some immunity against SARS-CoV-2 by vaccine or previous infection, but that breakthroughs resulted in symptomatic infections. Recent anecdotal reports on 200-passenger

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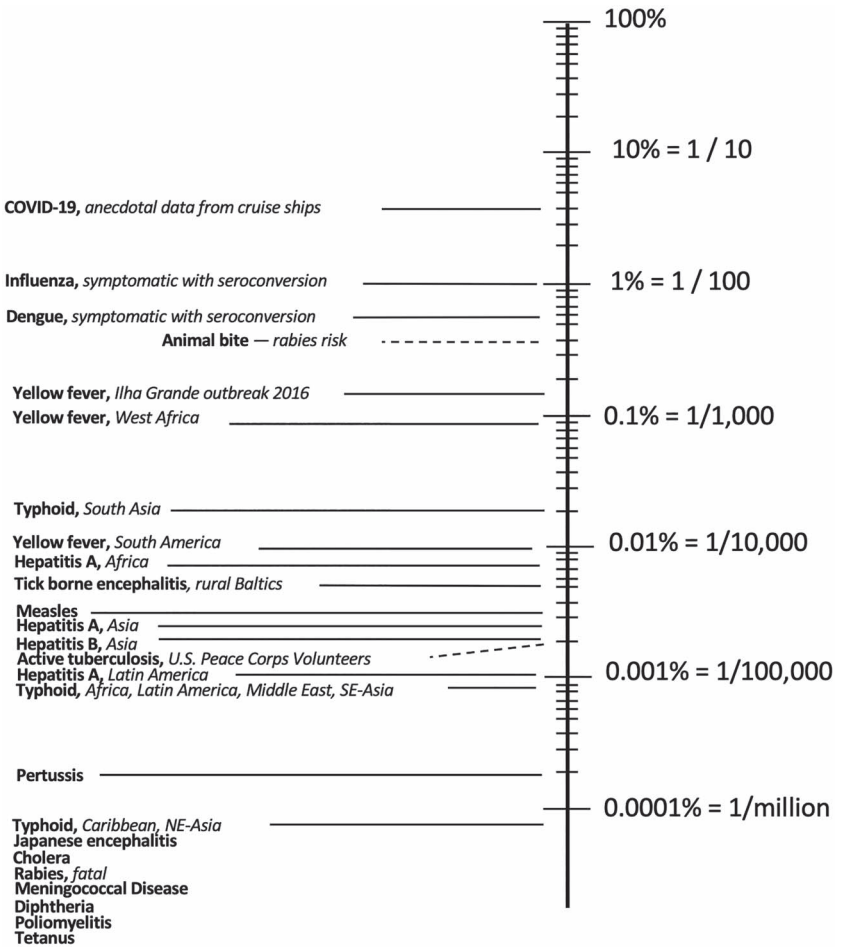


Figure 1. Incidence rate per month of VPDs in travellers; best estimate for non-immunes

ships in the Arctic and Antarctic lasting 17 and 22 days, respectively, indicate that despite vaccination requirement and pre-departure PCR testing, outbreaks occurred with 4% of the passengers on several expedition cruises leading to quarantine on board (R.S., personal observation). A far higher proportion showed symptoms, but many did not visit the infirmary and thus were not tested by the staff. Currently the risk of COVID-19 infection is clearly the highest risk of any infection even in a vaccinated population—this is illustrated by the fact that at the CDC Epidemic Intelligence Conference in April 2023 among 1,443 respondents 181 (13%) tested positive for SARS-CoV-2 despite the fact that >99% had received ≥1 vaccine dose and about half of the total population had COVID-19 previously (www.cdc.gov/media/releases/2023/s0526-eis.html).

Also lacking are data on the impact or specifically the CFR of COVID-19 in travellers. Prior to the availability of vaccines, fatalities on board occurred.[18] The EuroTravNet study had 3 fatalities among 649 patients diagnosed with COVID-19, but there are no data as to whether those had been immunized.[20] Among vaccinated passengers, the CFR of persons infected with Omicron variants is estimated to be <1%,[21] and with gradual increase of the background immunity, a progressive decrease of this health risk in travellers can hopefully be expected.

Influenza. Non-pharmaceutical interventions (NPIs) have contributed to a sharp decrease in influenza virus circulation particularly during the first pandemic year, but NPI requirements have been lifted and possibly the community immunity decreased.[8] Seasonal influenza has returned to Australia in 2022 with an early peak in June; the number of laboratory-confirmed influenza cases was almost twice the 5-year average.[22] Similarly, early peaks and prolonged seasonality were registered in North America and Europe in the 2022/23 winter season.[6] Several pre-pandemic surveys have shown that unimmunized travellers to any destination anytime in the year have an incidence rate (IR) of about 10 per 1000 pm in non-immunes.[23–25] In closed communities of cruise ships, prolonged outbreaks have been recorded even in summer in cool climate zones, possibly triggered by an index case originating during winter in the other hemisphere.[26] In over 30 publications that described influenza outbreaks on cruise ships over the past two decades, most were seasonal influenza outbreaks that occurred outside the 'traditional' influenza seasons.[27] In addition, a 2016 systematic review of 41 studies of respiratory virus propagation during transportation and in transportation hubs found that cruise ship influenza outbreaks typically affect 2–7% of the passengers present on the ship.[28]

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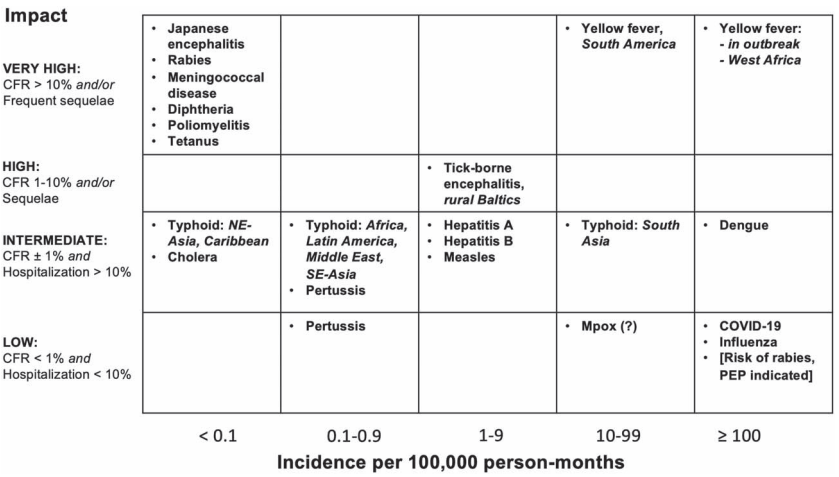


Figure 2. Impact of symptomatic VPDs in travellers (CFR = case fatality rate; PEP = post-exposure prophylaxis after potential exposure to rabies)

Influenza infection may be asymptomatic or may have a serious impact resulting in severe illness or death. A prospective study in long-term (3–12 months) travellers to the tropics 2008–2011 found a 15% attack-rate of serologically confirmed influenza, but only 6.3% had fever and only 2% had influenza-like illness.[29] In the general population, overall 0.04% are hospitalized, which increased to 0.07% for patients aged >65 years.[30] Fatalities among travellers have been recorded during cruises, although rare.[31] In the port of Barbados, none of the 21 deaths among passengers during a 5-year period were attributed to influenza or other infectious diseases.[32]

Dengue. The burden of dengue has become heavier in the past 30 years; it is the leading vector-borne disease globally and continues to spread.[33] According to GeoSentinel data, dengue virus (DENV) is the leading cause of fever in returning travellers from many parts of the world.[34] Among returned Israeli travellers, DENV attack-rates have quadrupled during the period 2008 to 2019 with the highest incidence in those returning from Thailand and India.[35] Studies limited to symptomatic patients post-travel neglect those travellers who were ill abroad. Prospective studies are more relevant and reported IRs of 11 and 47 per 1000 pm in Dutch long- and short-term travellers to Suriname, respectively, and of 6.7 to 58.7 per 1000 pm among other short-term travellers.[36,37] A study in US travellers found an IR of 28.7 per 1000 pm.[38] The IR were similar for all continents with endemicity and no seasonal pattern was recorded.[36,39] In contrast to older studies, the latest study found that DENV infections 'was five times higher in tourist [median travel duration 19 days] than in those visiting friends and relatives (VFR), although the 95% CI overlapped'.[37] Potentially false-positives due to cross-reactivity with yellow fever, Japanese encephalitis or tick-borne encephalitis vaccinations have been excluded in the recent studies.[37,38] Dengue is not only a health risk to the traveller, but returned travellers may become the origin of an autochthonous outbreak as repeatedly shown in Mediterranean countries.[40]

Our rating focused on symptomatic cases, not on seroconversions including also asymptomatic cases. The three prospective studies reported presence of fever in 18–49%, even less had dengue-like illness defined as fever plus at least one additional symptom: myalgia, arthralgia, headache, retro-orbital pain or skin rash.[36–38] Thus, the IR limited to symptomatic DENV infection is about 6 per 1000 pm in the endemic areas of Asia, Africa and America. While two thirds of VFR had serological evidence of previous DENV infection, the rate among tourists was 5%.[37] It is known that the relative risk of severe dengue in secondary infection is increased by a factor of 2 to 7 as compared with primary infection.[41] Travellers with DENV infection were hospitalized in 10%[36] to 39%[42] (Figure 2) of the majority upon return. Dengue haemorrhagic fever and dengue shock syndrome are rare in this population; few travellers died of dengue, most of them after a primary infection.[41,43,44] According to a recent study among 51 cases with dengue, the out-of-pocket costs were about USD 3700 and the loss of income USD 570.[42]

Rabies—potential travel-related rabies exposures

Some may disagree to find rabies in the 'frequent' category; however, it would be a mistake to report only rabies diagnosis and fatality. A meta-analysis derived an estimated IR of potential travel-related rabies exposures of 4 per 1000 pm.[45] A more recent German airport study reported an attack-rate of 2% per trip, 1.5% during the initial 4 weeks.[46] Predictors of exposure to rabies risk, such as VFR, young age and male sex, have been identified, but anyone is at risk, even business travellers.[47–49] Risk awareness about rabies is 'relatively low'.[50] Post-exposure prophylaxis (PEP) is indicated for all Category II and III exposures and consists of 'extensive and thorough wound washing (often neglected[46]) … together with rabies immune globulin (RIG) administration, if indicated, and the administration of a course of several doses of rabies vaccine'.[51] No prospective study has documented the proportion of travellers with PEP indication following possible rabies exposure that actually obtained PEP, but recent retrospective surveys indicate that only 14% of those with potential rabies virus infection seek professional healthcare,[46] and among those who did, only 3.8 to 24.7% for whom RIG was indicated received RIG in the country of exposure.[47] In GeoSentinel clinics 2007 to 2018, the indication for rabies PEP was 22.7 times greater than the diagnosis of hepatitis A.[52]

Between 1990 and 2019, 83 cases of rabies have been recorded among travellers, 3.5 cases annually in the 2004 to 2019 period.[53] However, it would be inappropriate to neglect

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the problem just because the number of fatalities is low. Also important is the lack of vaccines and RIG in many parts of LMICs[54] that necessitates the exposed travellers to change their travel plans, which is costly when an entire family has to purchase new airline tickets, i.e. because children are those who have been bitten. In addition, the lack of awareness for the need to seek medical evaluation upon exposure and the inadequate PEP both in the country of exposure[47] and upon return home to Europe or North America hinder timely and appropriate response.[55,56] Hence, it is justifiable—particularly as a 'life-time investment' with no more boosters needed—to broadly recommend rabies pre-exposure prophylaxis (PrEP) to travellers with destinations in the 116 countries, territories and jurisdictions identified as moderate to high risk.[54,57] PEP without PrEP does not exclude rare fatal breakthrough infections even in the USA, but no PEP failure following PrEP has been reported.[58,59]

Yellow fever. In the last travel vaccines priority list, yellow fever (YF) ranged as very low risk. For more than a decade, just a single international case (Spain ex Ghana) had been reported (Poumerol G, personal communication at APTHC Singapore 2012).[1,60] In addition, three YF infections have been observed in a family returning from an endemic to a non-endemic area within Brazil.[61] Earlier, between 1979 and 2002, ten anecdotal cases in travellers were published and at the time the risk of YF in unvaccinated travellers was estimated to be 1 to 8/1000 pm depending on the epidemic activity.[62] Outbreaks in South America and Africa from the end of 2016 to 2018 resulted in many exported cases to non-endemic countries: from Angola to China ($n = 11$),[63] the Democratic Republic of the Congo (>50), Kenya (2), Mauritania (1) and Morocco (1),[64,65] from Suriname and from Gambia/Senegal to the Netherlands,[66,67] from Peru to the USA,[68] from Brazil to various European (6) and other South American (6) countries,[69–71] and in a Danish citizen who was travelling in Bolivia.[72] Four among the six Europeans with YF acquired in Brazil January to March 2018 had stayed on Ilha Grande, which had 1.4 million visitors in 2018, many just on a day trip. Assuming that 10% of the visitors are Europeans, 35 000 would have visited in a 3-month period; if these visitors on average stay for 6 days and were not vaccinated, the 4 cases would correspond to an IR of 1.7/1000 pm in this high-risk situation. Similarly, the risk for unvaccinated travellers to West Africa had been estimated at 1/1000 and for destinations in endemic regions of South America to 0.5/1000 pm, respectively.[73]

Among 10 travellers associated with the recent outbreak in Brazil, the CFR was 40%.[74]

Intermediate travel-related VPD risk: <1 per 1000 to 1 per million pm

Monkeypox. In the early phase of the 2022 global outbreak, a substantial proportion of MSM were infected through mass gatherings in Antwerp, Gran Canaria and elsewhere.[75] One Romanian with HIV returned from Spain not only with monkeypox (mpox), but also acquired hepatitis A and syphilis.[76] Meanwhile, the risk population has developed risk awareness and to some extent adopted countermeasures.[77] Travel-related IR is unavailable (therefore mpox is not included in Figure 1), but surely was high when the international spread erupted initially.

Most cases of mpox have mild symptoms, with hospitalization rate of 2 to 17%.[77–79] In the USA, six (6) deaths were reported (CFR 0.02%).[77]

Typhoid. The IR for typhoid is highest in South Asia, particularly for visitors to Afghanistan, Bangladesh, India, Nepal and Pakistan. The first Committee to Advise on Tropical Medicine and Travel (CATMAT) statement, which was based on GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology, concluded that the risk of acquiring typhoid in travellers to South Asia was about 1/3000 as compared with about 1/50 000 to 1/100 000 for destinations in North and Sub-Saharan Africa, the Middle East and South America and less than 1/300 000 among visitors to the Caribbean, Central America and the Eastern Mediterranean.[80,81] More recent publications essentially confirm the gradient and offer more details: In Australia, 887 cases of typhoid fever acquired abroad 2010 to 2017 were notified. When denominator data were applied, the IR was highest with 28.5 and 21.0/100 000 pm for Samoa ($n = 34$) and South Asia ($n = 667$), respectively.[82] Although Oceania had data gaps in most previous travel surveys, recent records showed rates of 3.3/100 000 pm for Papua New Guinea and 1.0 to 5.4/100 000 pm for other Pacific Islands.[82] The rate was <1/100 000 pm for Southeast Asia [including Myanmar with 8.4 ($n = 7$) and Indonesia with 1.6 ($n = 55$)], Africa, the Middle East and <1/million for North-East Asia including China, the Americas (limited numbers) and Europe.[82] Similarly, among 54 cases imported to Sweden, 50 originated in Asia (no details on region), 4 in Africa corresponding to 0.5 per 100 000 pm, and none in Latin America or Europe.[83] While it is difficult to compare these IR with attack-rates per trip, a gradual decline in the risk of typhoid with time seemed to be occurring.[84] This is confirmed by a Dutch study, which—despite a restrictive vaccination policy—recorded a reduction particularly in popular tourist destinations, such as Morocco, Turkey and Indonesia.[85] Similarly, the importation of typhoid from the Caribbean (except from Haiti) has decreased among US travellers to 1 case/year from Jamaica (2016) and Barbados (2015), respectively, and this corresponds to <1/million.[86] The proportion of VFR among typhoid cases was 85% and 82% according to a US and London surveys, respectively,[87,88] but only 53% in a recent GeoSentinel study.[89] Also, backpackers or foreign aid volunteers are traditionally referred to as risk groups. Since the typhoid vaccines focus on protection against *S. Typhi*, only this infection among all enteric fevers is discussed here. As protection of a typhoid vaccine against *Salmonella enterica* serotype Paratyphi A is questionable, the epidemiological features of this infection are not subject of this paper.[84,90,91]

Typhoid fever ranks second, after malaria, among the most common severe and potentially life-threatening travel-related infections and the concern about multidrug resistance is continuously increasing.[84,92,93] According to GeoSentinel experience, 61% of the patients with *Salmonella typhi* infection were hospitalized.[89] In Canada, the cost per travel-related (including immigrants) case of enteric fever was CAD 8071 (0–33 563) in the years 2012 to 2014.[94] Mortality with appropriate

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treatment is 0 to 2%[92,95,96]; one fatality has been documented in a traveller.[97]

Hepatitis A. The hepatitis A vaccine has long been considered the primary travel vaccine. However, the IR over the decades has gradually decreased from 1/300 to 1/16 000 (6.2/100 000) pm among European travellers in the 2009 to 2015 period for the highest risk continent, Africa.[98,99] Similarly, the IR among Swedes in Africa 2009 to 2013 was 9.9/100 000 pm.[83] The rates for Asia were 2.5 and 2.9, for Latin America 0.9 and 1.1, and overall (including Europe, North America, Oceania as well) 0.6 and 1.1/100 000 pm, respectively, in the two surveys.[83,98] A Dutch study illustrated that the attack-rate declined from 7.5 to 3.5/100 000 travellers, respectively, when the 2003 to 2005 period was compared with 2009 to 2011.[100] Several outbreaks have recently been recorded mainly among European travellers upon return from North Africa and Turkey.[98,101,102] One survey showed a particularly high risk for travellers in Hungary.[103] Occasionally not only travellers import hepatitis A, but consumption of food imported by them may lead to outbreaks among friends and family back home[101]; outbreaks associated with commercially imported food items are not subject of this review. The overall reduction in IR is explained primarily by improvement in hygiene and sanitation and access to clean water in many countries and specifically in major tourist destinations.[104] UK experts downgraded 36 countries with respect to hepatitis A vaccine recommendations for short-term travellers (recommendation for vaccine maintained for VFR) and this resulted in no increase in notification of imported cases.[105] Universal hepatitis vaccination programs in some countries and widespread recommendations (with some exceptions in Northern Europe) to immunize international travellers with destinations in high or intermediate endemicity countries against hepatitis A may also have contributed to this reduction. However, according to a Dutch survey conducted 2016 to 2018, only 41% of at-risk travellers had a valid hepatitis A vaccination in their vaccination records and 68% had anti-HAV antibodies.[106] Similarly, an older study showed that HAV protection among US high-risk travellers and also in residents was only 12–22%, and recent data on various risk groups show a persistent low vaccine coverage.[107,108] Many future travellers do not have pre-travel consultations and miss an opportunity to be protected by hepatitis A vaccine,[104] and many are unaware of their vaccination status.[109] Data from various countries demonstrate that hepatitis no longer is mainly an infection imported by returning travellers, but that to a substantial extent it is related to outbreaks among migrants or to men who have sex with men (MSM).[110,111] This is also supported by the fact that even during the COVID-19 lockdown period in Switzerland, the incidence of hepatitis A decreased only by 5%, whereas other 'usual imported infections' were reduced by 50 to almost 90%.[112]

Among GeoSentinel patients with hepatitis A, 59% were hospitalized.[104] Among all hepatitis A cases (including non-travellers) in 11 European countries, the most recent hospitalization rates varied between 23 and 93%.[113] In various countries, the proportion of hospitalized patients increased; some associated this with a shift to older adults or in younger MSM.[114,115] Complications were fulminant hepatitis A, liver failure, various haemorrhagic problems and coma; occasionally a liver transplantation was performed.[113] In Canada, the cost per travel-related (including immigrants) case of hepatitis A was CAD 5576 (0–59 358) in the years 2012 to 2014.[94] Two hepatitis A fatalities in travellers have been published.[116,117]

Tick-borne encephalitis. On the basis of only four tick-borne encephalitis (TBE) cases among Israeli travellers, an average IR of 11/100 000 pm (range 0.6 to 26.7 depending on destination) has been extrapolated.[118] As this rate is in the same order of magnitude as the annual IR of the local population in Baltic States, the regions with the highest incidence in Europe, this most likely is an overestimate. In 2012, the European Centre for Disease Prevention and Control (ECDC) and other sources included 38 TBE cases that were internationally acquired, which corresponded to an attack-rate of 0.5 to 1.3/100 000 per trip abroad.[119] Assuming that the average period of exposure among travellers is <1 month, the IR of TBE in the Baltic States can very roughly be estimated to be about 5/100 000 pm in those with exposure in the countryside.

The impact of TBE infections depends on the virus subtypes, with the European (TBEV-Eu) resulting in milder illness as compared with the Siberian (TBEV-Sib) and Far Eastern subtypes (TBEV-FE). Nevertheless, TBEV-Eu may result in sequelae including persistent cognitive impairment both in children and adults.[120–122] Meningitis is observed less often in older patients, though meningoencephalitis and encephalomyelitis with resulting permanent sequelae are seen more frequently. Overall, the case fatality rate is less than 2%.[123]

Measles. According to the publication on infections acquired abroad 2009 to 2013 by Swedish residents, the IR for measles was 3.2 per 100 000 pm, based on 95% vaccine coverage.[1,83] Among 113 confirmed cases of measles reported in Canada 2019, 90% were imported or import related, but the proportion of residents, visitors, immigrants or VFRs was unclear.[124] In the USA during 2001 to 2016, 553 of 2098 (26%) confirmed measles cases were imported and among them 62% were US residents.[125,126] In both North American countries, most cases were either unvaccinated or the vaccination status was unknown. Some adult travellers were not vaccinated against measles even though they presented for pre-travel consultation.[127] Transmission has been documented in short- and long-haul flights[128,129]; a 68-year-old Swiss female was most likely infected by another Swiss passenger seated a few rows away on a flight from Singapore to Zurich and developed severe pneumonia (R.S., personal observation). Although concern about transmission at the Hajj 2019 was expressed, measles cases had not been recorded that year or earlier,[130–132] which stands in contrast to other mass gatherings.[133] As routine vaccinations have been suboptimal particularly in VFR destination countries, a higher incidence has been observed there and thus the risk of infection may increase for those without adequate immunization.[134]

Importation of a single case resulted in an outbreak with 40 patients, including 19 hospitalizations[135]; such risk is compounded when diagnosis and isolation are delayed.[136] Serious complications are more common in the very young and in adults >30 years and depending to which age group is affected in an outbreak, hospitalization rates vary. In the USA, 10% were hospitalized 2019 and there were no deaths among 1249 cases.[137]

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The ECDC estimates the case fatality to 1–3 per 1000; this rate is higher in LMICs.[138,139]

Hepatitis B. According to the abovementioned Swedish report, the IR of acute hepatitis B in the year 2012 was 1.8 among travellers to Asia and 0.6/100 000 pm among any international travellers, respectively.[83] Since Northern Europe introduced universal hepatitis B vaccination late (shortly after 2000), most adult travellers have not been vaccinated and most travel-associated cases were linked to sexual transmission.[83,140] Reports from other European countries highlight that high proportions, up to two-thirds, of acute hepatitis B affected VFR.[141] A substantial proportion of acute hepatitis B cases are now diagnosed in immigrants who hardly get pre-departure health advice.[142] In contrast, countries with universal hepatitis B vaccination have demonstrated a decrease in all age groups and also in travellers.[143] In migrants recently arrived in Europe who are likely to become VFRs, vaccination overall and specifically for hepatitis B catch-up doses are overlooked.[144] The proportion of VFRs immunized against hepatitis B is smaller as compared with other adult Dutch travellers.[145,146] Vaccination coverage (≥3 doses) among US travellers to countries with high or intermediate endemicity in 2015 was 31.7%.[147]

In the USA, acute hepatitis B is associated with 63% hospitalization rate and 0.45 deaths per 100 000 population[148]; to our knowledge, there are no such data on travellers.

Tuberculosis. According to the GeoSentinel surveillance network, 201 patients with tuberculosis (TB) were registered 2008 to 2020, among them 136 (67.7%) with multidrug resistance and 25 (12.4%) with extensive drug resistance.[149] Foreign-born immigrants were the vast majority ($n = 196$, 97.5%); among five low-incidence country residents, three were exposed during long-term business travel and one each had been studying abroad or a VFR. Similarly, professionally exposed risk groups, such as U.S. Peace Corps Volunteers, acquired acute TB in 2/100 000 pm.[150] More than half of the TB cases in migrants occurred five or more years after immigration. Not a single tourist had TB.[149]

The impact of TB is highly variable, which will not be elaborated in detail. Also, it is questionable whether the BCG vaccine plays a role in travel health as it is uncertain to what extent it protects adults and particularly travellers.[151] WHO states that 'there is paucity of evidence on the potential preventive efficacy of pre-travel BCG immunization'.[152]

Pertussis. Pertussis vaccines and natural infection with *Bordetella pertussis* confer some immune protection, the duration of which is not lifelong and poorly understood.[153] A report on infections acquired by Swedes abroad 2009 to 2013 shows evidence for an IR of 0.2 per 100 000 pm for pertussis assuming a 20% vaccine protection rate.[83] A GeoSentinel survey on 1999–2015 showed a median age of 44 years for such patients; often the infection had been acquired in India or China.[154]

There are no published data on the impact of pertussis in different age groups of travellers.

Rare travel-related VPD risk, <1/million pm

This group lacks evidence-based data on IR; the assessment essentially relies on anecdotal reports. Some of these infections are rarely observed overall in travellers, while others are associated with risk behaviour or with outbreaks at the destination. With respect to the impact, there are insufficient data on travellers and we must base on general experience.

Japanese encephalitis. A recent report cites an estimated risk of Japanese encephalitis (JE) due to travel to Asia of less than one case per 1 million travellers from non-endemic areas, but this and another recent paper also highlight risk groups: long-term travellers, visits during the JEV transmission season, spending time in rural areas, extensive outdoor activities, and accommodations without air conditioning, screens or bed nets.[155,156] Among Scandinavian travellers, the attack-rate had been 0.2 to 0.4/100 000,[157] while a Swedish survey reported only a single case 2009 to 2013 and an IR of 0.02/100 000 pm in all travellers to Asia.[83] Expatriates staying in Korea had an attack-rate of 0.1/100 000 in the 2007 to 2016 period.[158] Data gaps preclude more precise IR estimate despite recent anecdotal reports of additional cases.[159–164] Hence, the current estimated IR is about 1/million pm, but probably higher in specific risk groups. Additional studies on the risk particularly in Bali are needed in view of the many anecdotal reports and of the fact that the annual incidence in local children is 7.1/100 000 and 92% that have antibodies against JEV.[165] Notably, JE in 2022 has expanded to Australia with 45 cases notified in five states and territories, where it has not been reported previously.[166]

Symptomatic infection is rare (<1%) but can be devastating if it occurs, with one-third of symptomatic patients recovering completely but two-thirds having long-term neurologic and/or psychologic sequelae.[159]

Cholera. The WHO annually reports about cholera in the Weekly Epidemiological Record. The data for 2020 and 2021 were not representative because of restricted travel opportunities: besides cases imported within Asia and Africa (for instance to Singapore, the United Arab Emirates, Oman, Bahrain), there was one case diagnosed in Australia 2021 and two each in Canada and the Netherlands. Also, in 2019 only five cases in Japan and two in Australia were recorded, while in 2018 there were eight cases imported to the USA from Haiti, and one each to Japan and New Zealand. As of early December 2022, CDC reported that 8 travellers with cholera had returned to the USA from Pakistan, Iraq and Bangladesh, among 25 countries with active transmission. This illustrates that the risk of cholera varies depending on the worldwide transmission status and is increased during outbreak situations with humanitarian activities. The risk of reported cholera is below 1/million pm, with substantial underreporting; higher IR base on a study published 20 years ago.[167,168]

Although no fatal cholera among Western travellers has been published in recent years, apparently one death occurred among 64 patients diagnosed in the USA between 2012 and 2018.[169] Another patient developed acute renal failure after a business trip but recovered.[170] Some cases of cholera with limited clinical importance remain unnoticed, as experienced on Phuket Island in a British student with moderate travellers' diarrhoea, where *Vibrio cholerae* 01 was detected during a scientific study (R.S., personal observation).

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Invasive meningococcal disease. Except for outbreaks related to mass gatherings, very few cases of invasive meningococcal disease (IMD) have been published in travellers. A recent review on IMD in travellers did not mention any travel-related case.[171] But more recently imported serogroup B IMD has been reported in Italy in a traveller from Georgia and a case of serogroup W was detected in Japan in an Argentinian traveller.[172,173] The detection of two serogroup C isolates resistant to ciprofloxacin in Canada and Japan suggested importation from China as clone (ST)-4821 is mainly found there.[174,175] Possibly chronic carriers can import pathogens.[176] In the African meningitis belt, the use of MenAfriVac, a monovalent meningococcal conjugate vaccine, drastically reduced IMD caused by serogroup A, while the proportion of serogroups C and W increased, but overall, the incidence of IMD decreased.[177] Previous analysis estimated an IMD attack-rate of <1/million, with no increase as compared with staying home, and there is no indication that this has increased.[178] As a result of required tetravalent meningococcal vaccination, no major IMD outbreaks were recorded at the Hajj or Umrah despite the fact that in 2017 only 77% of pilgrims were vaccinated.[179,180] During mass gatherings in the past decade, 5 scouts and 1 parent were affected by serogroup W IMD after the World Scout Jamboree in Japan 2015.[179] Earlier, one case of serogroup B IMD was detected at the European Youth Olympic Sports Festival in Spain and outbreaks of IMD have repeatedly been recorded in refugee camps.[181,182] But IMD even following mass gatherings in recent years is an exceptional consequence.[133]

The CFR in IMD is 22% and another 20% have sequelae.[171]

Diphtheria. Respiratory diphtheria is rare but has been associated with travel. Recently, two UK-born adult tourists imported the infection from Tunisia; both were fully vaccinated with a last dose given 15 or more years earlier.[183] A case of laryngeal diphtheria imported from West Africa has been recorded in a Swedish tourist.[184] Recently, migrants imported diphtheria to various European countries, and this resulted in outbreaks in asylum centres.[185–187] In the past, the cutaneous form of diphtheria has been imported by travellers more often.[188] Vaccination with diphtheria toxoid vaccines might not prevent cutaneous colonization with *Corynebacterium diphtheria*.[189] The incidence is <1/million but cannot be quantified more precisely.

In the UK, 11 of 33 diphtheria cases (19 cutaneous, 10 respiratory, 4 mixed or other presentations) were hospitalized and 6% were fatal among all cases, 15% among those with respiratory symptoms.[190]

Poliomyelitis. The Global Polio Eradication Initiative regularly publishes global maps and lists the number and location of recent WPV and cVDPV cases.[191] Besides wide circulation of cVDPV in Africa and Asia, a case of paralytic cVDPV has been detected in New York State in an unvaccinated person in July 2022 and cVDPV has also been detected in Israel and in London wastewater[10]; WPV3 was detected in sewage in the Netherlands.[192] From 2003 to 2014, there were 191 new importation events into previously polio-free countries, resulting in 3763 reported cases of paralytic polio in 43 countries.[193] The incidence of polio is <1/million in Western travellers.

The majority of those infected remain asymptomatic, but in about 1% the central nervous system is affected, resulting in paralysis.[194]

Mumps. In the USA, mumps outbreaks have occurred via imported cases in university campuses, summer camps including spread to Canada, and some cases required hospitalization.[195–197]

Tetanus. A single case of tetanus has been documented in a traveller,[198] which reflects the fact that most travellers have been vaccinated and that protection is long lasting.[199] However, additional cases may be hidden in national surveillance data.

Pneumococcal disease. A recent publication explored the risk of pneumococcal infections in UK travellers. However, no data on that risk in travellers were presented, just risk scores per country were assessed.[200] This is a neglected topic so far, but there are reports on transmission in an individual traveller and in mass gathering events.[201–202]

We are unaware about travel-related cases or even outbreaks of rubella or varicella.

Limitations

There are multiple limitations to such an assessment. First, underestimation of cases associated with the fact that travellers may have been treated abroad and because many cases remain unpublished even when diagnosed back home. With respect to animal bites, there is an overestimation of the risk of rabies, as not all are rabid; but since no one wants to play Russian roulette, PEP is always indicated in potential risk. Second, the proportion of travellers protected by vaccination or by prior infection is often only vaguely known. Third, denominator data are often rough estimates. For many IR, this results in low or very low confidence in the data as per GRADE.[2] Additional limitations inherent particularly to large retrospective studies have been previously listed as well as the need for future research.[91]

Further research needs

The decision on priorities with respect to VPD in travellers should be based on the burden of disease and disability-adjusted life years. The lack of published data on the years lived with a disability, and scarce data on years of life lost, constrain such decision-generation and call for further research. A particular focus is needed on what happens while the traveller is abroad. Cohort studies with TRAVEL (Tracking Risks Abroad on Vacation with Electronic Locators) on the smartphone[203] may fill the gap on incidence and impact of VPD. Also, we desperately need more details on the outcome of VPD in travellers who returned home.

Conclusions

Despite limitations, this review allows for determination on priorities of travel vaccines based on available incidence data and consideration of the severity of VPD among travellers. Conclusions on recommendations are drawn by national expert groups, and these often differ. As shown for typhoid, the risk

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broadly differs according to the destination. While the U.S. CDC recommend immunization to those travelling to typhoid-endemic regions (e.g. U.S. CDC for 'most travellers' to Tanzania, Thailand, Barbados), the Australian Immunization Handbook in contrast recommends vaccination to those exposed to suboptimal food hygiene and VFR only,[204,205] and Canadian and German bodies limit this indication for travellers with destinations in South Asia or for travel under simple conditions (backpackers, trekkers, foreign aid volunteers or long-term stays) in other endemic regions.[81,206] In pre-travel consultations, it must be determined how much and what type of risk the future traveller is willing to take, how much he or she is willing to pay. To reduce costs, some recommend vaccination in the destination country.[207] Besides costs, limited effectiveness of some vaccines may also play a role in the discussion and decision. There is a broad range between maximum coverage against all VPD to 'only the necessary', or required. This is an arbitrary decision to be taken by the future traveller upon discussion with the travel health professional. Between Europe and North America, a difference in practice is reflected by the fact that typhoid vaccine is the most commonly administered travel vaccine in a US health care system[208] as compared with its 5th rank in various Swiss travel clinics.[209] Overall, the presented data on the burden of disease offer awareness on the orders of magnitude and can be used as strategic guidance for the 'typical' traveller. In a consultation, it is essential not only to consider the imminent voyage, but potential cumulative exposure of the person. Finally, let us remember and not neglect the fact that death associated with VPD in travellers is rare as compared with those associated with accidents and non-communicable diseases.[210,211]

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