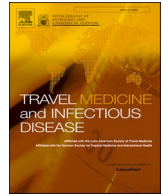




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## Travel vaccines throughout history

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### ARTICLE INFO

#### Keywords:

Pre-travel vaccination  
Travelers  
Typhoid fever  
Yellow fever  
Imported disease

### ABSTRACT

Vaccinations are an important component of travel medicine. Beyond protection of travelers, vaccines are administered to prevent the importation of vaccine-preventable diseases at home and at destination. Proof of immunization to travel dates back to the first smallpox vaccine, developed by Edward Jenner in 1796. However, it took one century to generate the next vaccines against cholera, rabies, and typhoid fever. During the 20th century the armamentarium of vaccines used in travelers largely expanded with yellow fever, poliomyelitis, tetravalent meningococcal, and hepatitis A vaccines. The International Certificate of Inoculation and Vaccination was implemented in 1933. Currently there are vaccines administered to travelers following risk assessment, but also vaccines required according to the 2005 International Health Regulations and vaccines required at certain countries. Finally, within less than one year after the declaration of the coronavirus disease 2019 (COVID-19) pandemic, the first COVID-19 vaccines were launched and approved for emergency use to control the pandemic. Despite practical and ethical challenges, COVID-19 vaccine verifications have been widely used since spring 2021 in many activities, including international travel. In this article, we review the course of development of travel vaccines focusing on those for which a proof of vaccination has been or is required.

### 1. Introduction

The wide implementation of routine vaccination programs during the second half of the 20th century has been one of the most successful public health policies throughout human history, leading to the prevention of millions of infections, deaths, and permanent complications every year [1]. Vaccinations are also pivotal in travel medicine. Beyond protection of international travelers, travel vaccines are administered in order to prevent importation of vaccine-preventable diseases at home and at travel destination [2,3]. Pre-travel vaccinations are administered following risk assessment and include routine vaccines, recommended vaccines according to travel characteristics, required vaccines according to the 2005 International Health Regulations (IHR), and vaccines required by certain countries [2–4].

Vaccine origin begins with the long history of infectious disease in humans, and in particular with the early uses of smallpox material to provide immunity. Evidence shows that Chinese used smallpox inoculation as early as 1000 AD [4–6]. Travel vaccination policies were established for people moving across borders. Vaccination policy is a central and historic responsibility of the World Health Organization (WHO), through International Health Regulations (IHR), which were

revised in close consultation and collaboration with its State Parties, international organizations, and other partners for the control of international spread of diseases [4].

Travel vaccines are not a new concept. Proof of immunization to travel dates back to 1796, when Edward Jenner developed the first vaccine to prevent smallpox in humans [5]. This procedure became known as “vaccination” derived from the Latin word “vacca” for cow [6]. In 1881 Louis Pasteur proposed the term vaccination as a generic term for preventive inoculations against any human or animal disease [7]. The International Certificate of Inoculation and Vaccination was established for the first time in 1933 by the International Sanitary Convention for Aerial Navigation to protect people traveling and to prevent the importation and dissemination of infectious diseases across borders [8]. Additional reasons for requiring vaccination may include protection of certain populations, containment of an outbreak/epidemic, reduction of mortality, and disease elimination.

Currently the WHO endorses internationally recognized certificates with proof of yellow fever vaccination for entry into certain countries, proof of meningococcal vaccination for Hajj pilgrims, and proof of poliomyelitis vaccination in certain circumstances [4]. In the event of a public health emergency of international concern which may affect

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adversely the health of human populations, additional travel requirements for proof of vaccination may be introduced [4,9].

Herein, we review the history of travel vaccines focusing on vaccines for which a proof of vaccination for travel has been or is required throughout vaccine history.

## 2. Methods

We searched PubMed, medical websites, and books through November 15, 2021 using combinations of the following words: travel, vaccine, travel vaccination requirements, vaccine history, smallpox, poliomyelitis, yellow fever, cholera, meningococcal meningitis, typhoid fever, Japanese encephalitis, tick-borne encephalitis, COVID-19, and malaria. We read the abstracts of all articles and, based on relevance to the topic, we present data from 85 references, including articles, medical or public health websites and books. Vaccines included in routine vaccination programs (e.g., measles-mumps-rubella, hepatitis B, tetanus) were not considered.

Travel vaccines are defined as vaccines recommended to travelers of any purpose of travel in the context of pre-travel preparation to an international destination. This definition concerns not only vaccines used in travel medicine today but throughout history, although some of these vaccines are also used by many countries routinely.

Proof of vaccination for traveling is defined as vaccination requirement in accordance with the IHR of the WHO [9]. Vaccination may also be required in other situations/settings sometimes e.g. work, athletic activities, and education, however the current article focuses on travelers of any purpose of travel.

## 3. Smallpox vaccine

Smallpox or variola is one of the most contagious, lethal infectious diseases caused by a poxvirus, a double-stranded virus that is unique to humans. Smallpox emerged sometime after the first agricultural settlements about 10,000 BC. The earliest written description of a disease like smallpox was documented in China in the 4th century AD. Early documentation was also found in India in the 7th century and in Asia Minor in the 10th century [10–12].

The role of travel in the global spread of smallpox during expansion of civilizations, exploration, and colonization has been traced throughout human history. Smallpox was spread by Egyptian traders to India during the first millennium BC, to China in the 1st century AD, to Japan in the 6th century as a result of increased travel and trade with China and Korea and was introduced into northern Africa, Spain, and Portugal in the 7th and 8th centuries through the Arabic expansion [11, 12]. In the 11th and 12th centuries, smallpox further spread in Europe by Crusades and in the 15th century in West Africa following Portugal occupation. Smallpox was imported by European colonists in the Caribbean, Central and South America in the 16th century resulting in the extermination of the Aztec and Inca empires, in North America in the 17th century, and by explorers in Australia in the 18th century [11,12]. Overall, smallpox epidemics had a considerable impact on the history of humankind [10,11]. It is estimated that by the beginning of the 18th century, nearly 10% of the world's population had been killed, crippled, or disfigured by smallpox [10].

“Variolation”, a procedure named after variola virus (referred then as “inoculation”), was one of the first methods for controlling smallpox [10,13]. Variolation through inoculation of material from smallpox pustules or scabs, either by nasal or cutaneous route, was firstly documented in India and China as early as 1000 AD [6,13]. During the smallpox epidemics worldwide, inoculation trials were performed in Britain and colonial Massachusetts in 1721 [6,7].

Using another poxvirus, cow poxvirus, which infected cattle, Edward Jenner, an English physician, carried out human experiments on a systemic manner over 25 years and in 1796 developed a safer practice to prevent smallpox in humans [10]. This procedure became known as

“vaccination” from the Latin word for cow “vacca” [6,7].

For many years, he observed that dairymaids were protected from smallpox naturally after having suffered from cowpox and concluded that cowpox protected against smallpox. In May 1796, Jenner used matter from a young dairymaid with fresh cowpox lesions on her hands and arms and he inoculated an 8-year-old boy, James Phipps. Subsequently, the boy developed mild symptoms which improved the next day. In July 1796, Jenner inoculated the boy again, this time with matter from a fresh smallpox lesion. No disease developed, and Jenner concluded that protection was complete [6]. Within less than three years, Jenner's vaccination practices were used in several European countries, while from 1803 to 1806 viral strains were transported to the New World by the Spanish surgeon Francisco Xavier Balmis and the first-ever mass smallpox vaccination campaign was successfully implemented [7]. In 1881 Louis Pasteur proposed that the term “vaccination” should be used for preventive inoculations against any human or animal disease and “vaccine” for the product used [5]. Vaccination became mandatory in some countries in Europe and the United States as a result of the spread of smallpox and the associated increased mortality, followed by concern about its safety, leading to opposition and then repeal of legislation in some instances [6,7]. Those supporting enforcement of mandatory vaccination argued that public good overrode personal freedom [6,7].

The concept of requiring proof of immunization to travel dates back to Edward Jenner's development of the first vaccine in 1796. As smallpox spread around the globe, eventually some leaders mandated this kind of inoculation. Mandatory vaccination began just a few years later. In 1806, Elisa Bonaparte, the ruler of Lucca and Piombino in present-day Italy (and sister to Napoleon), mandated the vaccination of newborn babies and adults [10].

However, the first International Certificate of Vaccination against Smallpox was developed by the 1944 International Sanitary Convention, which amended the 1926 International Sanitary Convention on Maritime Navigation and the 1933 International Sanitary Convention for Aerial Navigation [5]. The vaccination certificate required a vaccine reaction documented 8–14 days after primary vaccination or 48 h after revaccination for international travelers to smallpox-endemic countries. The certificate consisted of a form for each disease (smallpox, yellow fever, cholera, etc). The certificate was valid for three years [5]. The mandatory introduction of smallpox vaccination certificates significantly increased the number of vaccinated travelers, and thus contributed to preventing the importation of smallpox to non-endemic countries.

As the incidence of smallpox declined over time, some governments loosened requirements, while other mandates remained in place. A variety of court decisions have considered the validity of vaccination mandates and have attempted to address the conflict between individual rights and protection of the public's health [11,12].

Following a decade-long mass vaccination program in parallel with aggressive containment vaccinations, in 1980 the WHO declared smallpox to be the first disease to be eradicated by vaccination; this is defined as a successful goal since it is the only infectious disease to achieve this distinction. This remains among the most notable and profound public health successes in history [10,12,14].

Therefore, vaccination of travelers against smallpox was no longer required from 1981 and a stamp was used to cancel smallpox vaccination, given that the International Certificate was in use for other vaccination requirements. In 1983 the certificate was replaced by a new form lacking any provision for smallpox vaccination [5]. In addition to the vaccine used to eradicate smallpox which remained in stockpile until 2008, two safer smallpox vaccines have been approved by the United States Food and Drug Administration the past fifteen years [6,15].

## 4. Poliomyelitis vaccines

Poliiovirus, an enterovirus belonging to the Picornaviridae family, is

the etiological agent of poliomyelitis, an acute paralytic disease [16]. Documentation of poliomyelitis goes back to Egyptian civilization (1580–1350 BC). In 1789, Dr Underwood, a British physician, was the first to describe poliomyelitis as a disability of the lower extremities [17]. Large outbreaks began to occur frequently by the mid-19th century following urbanization in Europe and North America. In 1894 the first poliomyelitis outbreak of infantile paralysis was documented in the United States of America followed by a large epidemic in 1916 in New York. The wild poliovirus types 1, 2, and 3 were first identified by Sir Macfarlane Burnet and Dame Jean Macnamara [17]. In the pre-vaccine era, when poliovirus was the leading cause of permanent disability in children, almost all children became infected by polioviruses by the age of five years [16].

In 1935, Maurice Brodie, a British-born American virologist, used an inactivated poliovirus vaccine and Kollmer tested live attenuated poliovirus vaccine taken from infected monkey spinal cord, with poor results and without performing additional human studies [16]. The first poliomyelitis vaccine, however, known as inactivated poliovirus vaccine or Salk vaccine given by injection, was developed in the early 1950s by American physician Jonas Salk. In the 1960s a second type of poliomyelitis vaccine, known as oral poliovirus vaccine or Sabin vaccine, named for its inventor American physician and microbiologist Albert Sabin, was developed which contains live attenuated virus (Table 1) [18].

The number of global poliomyelitis cases has been declining dramatically over the past three decades, as a result of the Global Polio Eradication Initiative in 1988. Currently only Afghanistan and Pakistan are classified as poliomyelitis-endemic countries [17,19,20]. However, a major concern to poliomyelitis eradication has been the international spread across borders, with importation of polio cases by travelers including migrants, refugees, pilgrims or tourists into polio-free countries as well as the circulation of vaccine-derived poliovirus strains. The origin of these importations has been largely countries where poliovirus transmission was never completely interrupted [16,19]. Outbreaks also were observed in previously poliomyelitis-free countries, triggered by importation of wild poliomyelitis virus via travelers which may impose and justify an entry requirement in terms of proof of vaccination against poliomyelitis [19]. The WHO Director General declared the international spread of poliovirus in 2014 a Public Health Event of International Concern under IHR, 2005, and issued Temporary Recommendations to reduce the international spread of poliovirus [21]. Thus, travelers visiting poliomyelitis-endemic areas should be fully vaccinated against poliomyelitis and should have one booster dose if more than 10 years have elapsed since completion of the primary series. According to WHO guidelines for Pakistan there is a requirement for all outgoing international travelers and incoming long-term visitors (staying 4 weeks or more) to receive oral poliomyelitis vaccine documented on an International Certificate of Vaccination [20,21].

The Hajj pilgrimage attracts to Saudi Arabia more than 2 million pilgrims from all over the world every year. Many pilgrims are from poliomyelitis-endemic countries. Therefore, due to the concern about the potential introduction of poliomyelitis into the Hajj with subsequent international spread, the Kingdom of Saudi Arabia has introduced mandatory poliomyelitis vaccination at the point of entry for all pilgrims coming from poliomyelitis-endemic countries (Table 1) [22].

## 5. Cholera vaccines

Cholera is a severe, rapidly-dehydrating diarrheal disease caused by toxigenic serogroups of the bacterium *Vibrio cholerae*. Origins of cholera trace back to ancient times in Eurasia and the Greek physician Hippocrates described its symptoms as early as 400 BC [23]. Cholera constituted the greatest epidemic disease of the 19th century, claiming more lives than smallpox and bubonic plague in human history [23]. Starting in 1961, an ongoing cholera pandemic caused by *V. cholerae* O1 biotype El Tor started and spread to Asia, Middle East, and Africa, while after an

absence of almost 100 years, cholera reappeared in Latin America in 1991 [23]. During 2010–2017, cholera continued to be a significant problem globally with large epidemics, such as those experienced in Haiti and Yemen, and surges of endemic disease in areas of sub-Saharan Africa and Asia [24]. Massive movement of people across borders for religious, military or migration purposes in association with the improved speed of ships and railroads, highly facilitated the spread of cholera and the onset of devastating epidemics in port cities globally claiming the lives of thousands of people either en route or at destination [23]. Currently, cholera remains endemic in areas of Africa, the Indian sub-continent (where *V. cholerae* O139 Bengal emerged), Southeast Asia, where it remains a disease associated with poverty and poor sanitation, and recently cholera cases have been reported in the Caribbean (Haiti and Dominican Republic) [24]. In developed countries cholera is extremely rare, and cases are traced to travelers returning from endemic areas [23,25]. At present, areas with active cholera transmission include African countries such as Benin, Cameroon, Democratic Republic of the Congo, Ethiopia, Kenya, Mozambique, Niger, Nigeria, Somalia and Uganda, and Asian countries such as Afghanistan, Bangladesh, India, Nepal, and Yemen. In the Americas and the Pacific there is no active transmission [26].

John Snow, an English physician, was the first to trace water as source of infection while investigating the 1854 cholera outbreak in London, and the same year the Italian Filippo Pacini first saw comma-shaped bacteria that cause cholera. However, the German Robert Koch was the first to isolate the causative bacteria in 1883 connected to water supplies during the investigation of a devastating epidemic in Cairo, Egypt which was traced to Muslim pilgrims traveling from Mecca and caused the death of 13% of its population [23]. Louis Pasteur (1822–1895), a French chemist and microbiologist, was the first to develop techniques of attenuation of virulence [27]. However, Louis Pasteur was studying chicken cholera caused by *Pasteurella multocida* and he created a live attenuated bacterial vaccine for chicken cholera [27,28]. The first killed cholera vaccine for humans was developed by Jaime Ferran, a Spanish physician, in 1885 and used in mass vaccination campaigns in Spain [29]. Early work developing killed culture vaccines was reported by the Ukrainian physician Nikolay Gamaleya in 1888, while Waldemar Haffkine also described efforts with attenuated strains in 1892. The first licensed whole-cell oral cholera vaccine was developed at the University of Gothenburg, Sweden and was pre-qualified by the WHO in 2001 [25].

The WHO Requirements for cholera parenteral vaccine were adopted in 1959 and revised in 1968; however, since the vaccine has not been considered satisfactory for general use, in 1973 the 26th World Health Assembly abolished the requirement in the IHR for a certificate of vaccination against cholera [30].

Currently several cholera vaccines developed with different techniques are available (Table 1). These vaccines should be used in cholera-endemic areas, cholera outbreaks, and high-risk humanitarian crises in combination with other sanitation measures [24,25,29,30]. The oral cholera vaccines include the killed O1 whole-cell with B-subunit and the killed O1 and O139 vaccine [29–31].

## 6. Yellow fever vaccines

Yellow fever is caused by a zoonotic flavivirus which is transmitted through infected female mosquitos, primarily *Aedes aegypti*. Yellow fever has caused life-threatening epidemics throughout the last 500 years. Yellow fever virus originated from Africa. In late 17th century yellow fever virus was imported in the United States along with its vector *Aedes* mosquito, through travel during the slave trade era, since mosquitoes carrying yellow fever could survive on shipboard for weeks or months [32]. For the next two hundred years the virus continued to strike densely populated cities with favorable temperature and humidity in the Americas, mostly eastern seaports and Gulf Coast cities, killing thousands of people, including the devastating epidemics of Mississippi

Table 1

Vaccines for which proof of vaccination has been/is required throughout history.

Disease [ref]	Vaccine name	Year of circulation/ license	Vaccine type	Route of administration	Vaccination requirement
Smallpox [5–8, 12–15]	vaccine (by Jenner)	1796	cowpox virus	skin punctures	1944–1981 (International Sanitary Convention)
	Dryvax	late 19th century (withdrawn)	live-virus preparation	bifurcated needle punctures	
Poliomyelitis [16–22]	ACAM2000	2007	cell-cultured, live virus	bifurcated needle punctures	since 2013 (by Saudi Arabia for Hajj pilgrims and all visitors <15 years)
	MVA-BN	2013	recombinant	im	
	inactivated PV (Brodie)	1935	inactivated polio virus		
	live attenuated PV (Kollmer)	1935	live attenuated polio virus		
	IPV (Salk)	1955	inactivated poliovirus	im	
	OPV (Sabin)	1961	live attenuated poliovirus from WPV	oral	
Cholera [24,25, 27–31]	1) monovalent (mOPV1, mOPV2, mOPV3)				1959–1973 (WHO)
	2) bivalent (bOPV1,3)				
	3) trivalent (tOPV1,2,3)				
	1880 (Pasteur)	1884–1896	live, attenuated	injectable	
	1885 (JaumeFerraniClua)				
	killed whole-cell <i>V. cholerae</i>	1960s, 1970s	killed whole cell <i>V. cholerae</i> of the Inaba and Ogawa subtypes of <i>V. cholerae</i> serovar O1	im/sc	
Vaxchora™		2016 (FDA)	live, attenuated	oral	
		2020 (EMA)			
	Dukoral®	1991 (Sweden)	oral, inactivated, killed whole cell <i>V. cholerae</i> WC-rBS; killed whole cell monovalent (O1) vaccines with a recombinant B subunit of cholera toxin	oral	
		2001 (WHO)	WC, killed modified whole cell bivalent (O1 and O139) vaccines without the B subunit	oral	
	1) Shanchol™	2009 (India)		oral	
Yellow fever [33–38]	2) Euvichol®	2011 (WHO)			1944 (International Sanitary Convention for Aerial Navigation)
	3) mORCVAX™	2016 (WHO)			
	17D vaccine/immune serum by Max Theiler (Rockefeller Institute) live attenuated vaccine by Pasteur Institute	1938 (ceased in 1982)	live attenuated virus	injection scarification	
	1) Stamaril® (17D-204)-Pasteur		live attenuated virus	sc	
Meningococcal disease [39, 41–45]	2) YF-VAX (17D-204)-Pasteur				since 2001 (by Saudi Arabia for pilgrims)
	3) 17DD-YFV- Bio-Manguinhos (Brazil)				
	MPV4 (Menomune)	1978	polysaccharide quadrivalent (A,C,W135, Y)	im	
	MCV4	2005	conjugate quadrivalent (A,C,W135,Y)	im	
Typhoid fever [46, 47,49–55]	1) MCV4 (Menactra)	2010			early 1900s for German army and French army
	2) MenACWY-CRM (Menveo)	2012			
	3) MenACWY-TT (Nimenrix™)				
	typhoid vaccine (Almroth Wright)	1896	killed <i>Salmonella typhi</i>	–	
	typhoid and paratyphoid vaccine (David Harvey)	1916	combined killed typhoid plus paratyphoid A and B	sc	
	TCV (Typbar-TCV® and PedaTyph™)	2013 (India)	typhoid conjugate vaccine (Vi polysaccharide antigen linked to tetanus toxoid protein)	im	
COVID-19* [72–75]	ViPS	1994 (USA)	unconjugated purified capsular polysaccharide vaccine	im/sc	2021 (by countries' authorities)
	Ty21a	1983 (Europe)	live attenuated vaccine (Ty21a strain of <i>S. typhi</i> )	oral	
	Pfizer-BioNTech (Comirnaty)	December 31, 2020	mRNA vaccine	im	
	Oxford/AstraZeneca (AZD1222)	February 16, 2021	non-replicating viral vector (adenovirus) vaccine	im	
	Serum Institute of India/Covishield (Oxford/AstraZeneca formulation)	February 15, 2021	non-replicating viral vector (adenovirus) vaccine	im	
Johnson & Johnson's Janssen		March 12, 2021	non-replicating viral vector (adenovirus) vaccine	im	
	Moderna	April 30, 2021	mRNA vaccine	im	
	Sinopharm (Beijing): BBIBP-CorV (Vero Cells)	May 07, 2021	inactivated SARS-CoV-2 vaccine	im	
	Sinovac-CoronaVac	June 01, 2021	inactivated SARS-CoV-2	im	
Bharat Biotech BBV152 COVAXIN	November 03, 2021	inactivated SARS-CoV-2	im		

\*vaccines which obtained approval and Emergency Use Listing from the WHO.

COVID-19: coronavirus disease 2019; EMA: European Medicines Agency; FDA: Food and Drug Administration.

im: intramuscular; IPV: inactivated poliomyelitis vaccine; MCV4: meningococcal conjugate tetravalent vaccine; MPV4: meningococcal polysaccharide tetravalent vaccine; PV: poliomyelitis vaccine; sc: subcutaneous; TCV: typhoid conjugate vaccine; WHO: World Health Organization; WPV: wild poliovirus.

Valley in 1878, of Cuba in 1898, and of New Orleans in 1853 and 1905 [32–34]. By the end of the 19th century yellow fever, also known as “Yellow Jack” due to the yellow quarantine flag on infected ships, had spread to South America, the United States, and Europe. Yellow fever is now endemic in many areas of sub-Saharan Africa, where most cases occur, and tropical South America [33,35].

Efforts to develop a vaccine against yellow fever during the late 19th and early 20th centuries had been initially unsuccessful. The virus was first isolated in 1927 using blood from a young case in Ghana [33,35]. However, timing of documentation of the cause of the disease does not necessarily mean it is the first time that the disease occurred. During the 1930s, Max Theiler, a South African virologist and his colleagues’ research at Rockefeller Foundation in New York, led to the development of an effective yellow fever vaccine based on an attenuated strain of yellow fever virus (called 17D) [32,33]. The isolated 17D strain has lost neurotropism and viscerotropism, but kept the potential to trigger an immune response [32,35]. Meanwhile, the Pasteur Institute in France also prepared a vaccine from mouse brain cultures [33]. In 1951, Max Theiler was awarded the Nobel Prize in Physiology or Medicine for his discovery; this was the first Nobel Prize given for the development of a virus vaccine [36]. The yellow fever vaccines in use today are derived from two substrains generated from the original 17D strain, after technical developments (Table 1) [33,37]. Following successful trials in Brazil, the live yellow fever vaccine (17D) was first approved by the International Sanitary Convention for Aerial Navigation in 1944, followed by the French vaccine [27,33]. After the amendment of the International Certificate of Inoculation and Vaccination in 1944, which was established by the International Sanitary Convention for Aerial Navigation in 1933 in The Hague and came into force in 1935, the Convention included yellow fever vaccination certificate [8]. However, during the outbreak of World War II there were new and huge demands for vaccine. An epidemic of yellow fever close to the North African War zones early in the conflict made the troops vulnerable. In the United States, the vaccine was given to virtually all recruits. The vaccine was available in Europe and England too [33].

Currently, yellow fever is the most common vaccine required for international travel in order to protect travelers visiting endemic areas as well as to prevent importation of the disease to non-endemic areas. Many countries require the vaccine for all travelers or only for travelers coming from countries with risk of yellow fever transmission with some exceptions including infants younger than nine months or one year of age, depending on the country [38]. Yellow fever vaccination is required for travelers to certain areas including countries of sub-Saharan Africa and South America. Yellow fever is also recommended for all travelers to areas with endemic and epidemic disease, depending on risk factors such as long duration of travel, area of stay, and outdoor activities. It is worth mentioning the importance of reservoir hosts for yellow fever in particular non-human primates in the Americas. Vaccination against yellow fever is administered subcutaneously once in a lifetime. International certificates of vaccination against yellow fever become valid 10 days after primary vaccination and remain valid throughout life [38].

## 7. Meningococcal vaccines

Meningococcal disease is a serious illness with a case fatality rate up to 40% and causing permanent complications in up to 20% of survivors [39]. The disease is caused by a Gram-negative diplococcus called *Neisseria meningitidis* which is transmitted through oropharyngeal secretions [39]. Meningococcal septicemia was probably described by the Greek physician Hippocrates (460–375 BC) in *Corpus Hippocraticum* [40]. The Austrian bacteriologist Anton Vaykselbaum was the first to describe in 1887 meningococcal bacteria as a cause of meningitis. Epidemics of meningococcal meningitis were described in the 19th century

by Gaspard Vieusseux and Andre Matthey in Geneva, and Elisa North in Massachusetts. Several other epidemics were described later in Europe, the United States, and in Africa where the first outbreak was described in 1840. In Africa epidemics were reported more frequently in the 20<sup>th</sup> century [41]. Although meningococcal disease in travelers is relatively rare, international travel and migration may facilitate the rapid spread of meningococci, in particular in mass gatherings such as athletic events and pilgrimage [39]. The meningitis belt of sub-Saharan Africa has the highest rates of meningococcal disease globally with epidemics with serogroups A, C, W135 and to lesser extent X and Y occurring more commonly during the dry season (December through June) [39]. Travelers, who stay for long period of time with local people in the meningitis belt, especially during outbreaks of meningococcal disease as well as participants in the Hajj or Umrah pilgrimages in Saudi Arabia, are more likely to be affected [42,43]. Local and international outbreaks of meningococcal disease have been linked with the pilgrimages, including serogroup A disease outbreaks in 1987 and throughout the 1990s, and two international serogroup W135 outbreaks in 2000 and 2001 [43]. *N. meningitidis* responsible for epidemics in Nepal, China, Europe, and possibly India in the 1980s, most probably was introduced into Mecca by South Asian pilgrims attending the Hajj in 1987. Internationally, soon after the 1987 pilgrimage, group A meningococcal disease was reported from neighboring Gulf countries and among Hajjs returning to Europe and North America. In the United Kingdom, 19 cases of serogroup A disease were reported in 1987 among pilgrims returning from Mecca, and 15 subsequent cases among Muslims over the following 19 months [43]. After 1990, several outbreaks of meningococcal disease from serogroup A and to a lesser extent from serogroups W135, C, and B were documented during Umrah and Ramadan seasons and occurred among residents and Umrah visitors in Mecca and Jeddah. In response to change in the epidemiology and circulating serogroups of meningitis, the implementation of mandatory quadrivalent meningococcal vaccination (A, C, W135, Y) for pilgrims has prevented pilgrimage-associated meningococcal outbreaks since 2001 [43]. Therefore, vaccination against all meningococcal serogroups is recommended to these travelers (Table 1) [39].

Two types of meningococcal vaccines have been available. The first vaccine, a meningococcal polysaccharide quadrivalent (A, C, W135, Y) vaccine which was produced with the antigens from the outer polysaccharide capsule of the bacterium, was approved in 1978 [44]. The first meningococcal conjugate quadrivalent vaccine (A, C, W135, Y) was approved in 2005 (Table 1) [45]. Vaccines for serogroup B meningococcal disease have been licensed since 2013 in Europe, the United States and other countries [44].

## 8. Typhoid fever vaccines

Typhoid fever is a systemic illness causing considerable morbidity and mortality globally, particularly in sub-Saharan Africa, the Indian subcontinent, and southeast Asia. The causative agent *Salmonella enterica* serovar Typhi (*Salmonella typhi*) is transmitted via the fecal-oral route via contaminated water and food, with humans acting as the sole reservoir [46].

Typhoid fever goes back to ancient times. Based on DNA examination of dental pulp collected from a mass burial pit, typhoid fever was implicated as a probable cause of the Plague of Athens in 430 BC, which ended killing one fourth of the population, including the Athenian politician Pericles, but also the Golden Age of Greece [47]. The disease most probably was brought in Piraeus port by ship and spread across Athens. At that time Athens had a population density comparable to modern-day New York City, since populations from the surrounding countryside were entering the city because of the Peloponnese War [48]. According to historians, a similar epidemic in Jamestown, an English

colony in Virginia between 1607 and 1624, was responsible for eliminating the entire colony. Other large typhoid epidemics were reported in the army during the American Civil War and the Spanish-American War [49]. Mary Mallon (also known as “typhoid Mary”), a healthy chronic carrier of *Salmonella typhi* who immigrated to the United States in 1884, has become synonymous with the history of investigation of typhoid fever outbreaks. Mary Mallon, through her work as a cook, contaminated the food while preparing meals for families and spread the infection to many persons [50].

The discovery in 1880 by Karl Joseph Eberth of the bacillus responsible for typhoid fever was a landmark in enteric fever history, as it was called at that time [51]. By the early 1900s, an important innovation was inoculation against typhoid fever with heat-killed *S. typhi* strains. Almroth Wright, Professor of Pathology at the Royal Army Medical College, pioneered inoculation in Britain in 1896, although his claims of priority were challenged in 1907 in favor of Richard Pfeiffer, a German bacteriologist and a student of Robert Koch [51,52]. Inoculation failed to continue due to the opposition from anti-vaccinationists army officers who preferred to rely on sanitary measures. However, a large number of British soldiers were inoculated before going to India and during World War I before proceeding overseas. They were also inoculated against smallpox [51,52]. Germany implemented compulsory vaccination in the army, and in France, typhoid vaccination was permitted by the Académie Nationale de Médecine from 1911 and was made compulsory by the French army in 1914 using a combined typhoid and paratyphoid A and B vaccine [51].

Currently, international travelers to endemic areas are at risk of infection if they travel to areas with low sanitation standards. The majority of typhoid fever cases in industrialized countries, including the United States and Europe, are imported from India, Pakistan or Bangladesh and concern mostly travelers who visited friends or relatives (VFRs) residing under poor sanitation conditions [53]. Vaccination against typhoid fever is recommended primarily for travelers to countries with a very high endemicity of typhoid fever and in particular to those traveling to the Indian subcontinent, Africa, Southeast Asia, and South America, as well as for those at high-risk because of special circumstances e.g., travelers VFRs or travelers who will be in close contact with the local population. Increasing multidrug resistant and extensively drug resistant typhoid may change the calculus for administering typhoid vaccine before travel. Some isolates are now virtually untreatable because of extreme resistance [53–55].

There are three typhoid fever vaccines available which vary by geographic region of the world and over time: (1) typhoid conjugate vaccine (not currently licensed in many countries although they have excellent record in terms of safety, immunogenicity and efficacy); (2) oral live-attenuated Ty21a vaccine; and (3) unconjugated Vi capsular polysaccharide parenteral vaccine Vi [54]. The parenteral Vi-polysaccharide (Vi-PS) or oral attenuated Ty21a vaccines are recommended for travelers to endemic countries e.g. the Indian subcontinent, Africa, Central and South America, and Southeast Asia. The protective efficacy against typhoid fever has been estimated to be 50–80% [46,53].

## 9. Other travel vaccines

### 9.1. Rabies vaccine

Rabies is an almost uniformly fatal encephalitis caused by Lyssaviruses after exposure to infected animal bite. Rabies is present in mammals in most parts of the world. Lyssaviruses, present in bats and skunks of the Western Hemisphere, likely co-existed with domestic dogs of Native Americans for centuries. Dog-maintained rabies began 200 years ago with the first importation of dogs in the New World in the late 16th and early to mid-17th centuries [56].

Rabies is probably first mentioned in the Babylonian code (23rd century BC), however the first detailed description of animal rabies was

provided by the Greek philosopher Democritus in 500 BC [57]. Louis Pasteur was the first to develop an effective vaccine against rabies administered through inoculation. The vaccine was used to treat a human bite victim in 1885. The recipient received a subcutaneous injection of fully inactivated homogenate, followed by injection of material derived from infections of spinal cord desiccated for shorter periods that contained progressively more virulent preparations of virus [58]. Pasteur’s approach proved highly effective, and the methodology spread widely with further improvement regarding inactivation. A new paradigm for rabies vaccines followed the development of cell culture for virus propagation [58]. Currently there are two types of rabies vaccines, human diploid cell vaccine and purified chick embryo cell vaccine. However, other vaccines are used in some parts of the world (e.g., purified Vero cell) [38].

The risk for travelers depends on factors that increase the risk of exposure to rabies, including remoteness of the destination, rabies epidemiology, and duration of stay in endemic areas [38]. Pre-exposure rabies vaccination therefore is recommended for high-risk travelers such as those engaged in outdoor activities, working with animals or laboratory workers handling animal specimens, long-term travelers and expatriates [38].

### 9.2. Hepatitis A vaccine

The hepatitis A virus, a positive-stranded RNA virus, is an ancient hepatotropic virus, belonging to the Picornaviridae family that has been infecting humans for millennia [59]. The disease was first described by the Greek physician Hippocrates (460–375 BC) [60]. Outbreaks of hepatitis A were described in Europe in the 17th and 18th centuries. Infection is transmitted through fecal-oral route, particularly in settings with poor food and drinking-water control and poor sanitation. A causative yet unidentified infectious agent leading to liver injury was already suspected in 1908, however hepatitis A (“infectious hepatitis”) and hepatitis B (“serum hepatitis”) were differentiated in 1942, following epidemiological studies during World War II [20,61]. The hepatitis A virus was isolated for the first time in 1979 [61,62]. In 1986 Provost and colleagues successfully prepared a killed, safe and highly effective hepatitis A vaccine. The first inactivated hepatitis A vaccine was licensed in 1995 [62].

Hepatitis A infection is one of the most common vaccine-preventable diseases in travelers, with an incidence of 6.0–30.0 cases per 100,000 person-months in non-immune travelers at risk destinations. Hepatitis A vaccination is recommended for travelers aged  $\geq 1$  year visiting destinations of intermediate or high endemicity, such as Africa, Asia, Middle East, Central and South America, and Eastern Europe, and particularly for travelers at increased risk for infection and/or severe illness (e.g., immunosuppressed patients, patients with chronic liver disease, and men who have sex with men) [38,63]. Before the development of the highly effective hepatitis A vaccine, immune globulin im was given to protect travelers and was highly protective. The number of imported cases in developed countries decreased substantially over the last two decades, which is mainly attributed to vaccination of travelers against hepatitis A as well as to other factors such as integration of hepatitis A vaccine into childhood immunization programs in some countries, and improvement of sanitation and access to clean water in many areas [63].

### 9.3. Japanese encephalitis vaccine

Japanese encephalitis (JE) is an arboviral disease caused by JE virus (JEV), a single-stranded RNA virus that belongs to the genus *Flavivirus* and transmitted mainly by the vector *Culex tritaeniorhynchus*. Humans do not have high enough viremia to be important as source of infection for mosquitoes. Some human activities may influence JE epidemiology e.g., pig farming and change of land use. JE emerged in Japan in the 1870s and JEV was first isolated in 1935 [64]. Currently, JE is established in rural areas in eastern and southern Asia and the Pacific islands,

and is the most important cause of epidemic encephalitis worldwide with several thousand clinical cases and deaths every year.

For most travelers to endemic areas the risk for JE infection is extremely low, particularly for short-term visitors to urban areas. However, the risk varies according to season, destination, duration of travel, and activities. Vaccination is recommended for travelers (proof of JE vaccine is not required for entry in any country), including military personnel, to endemic countries or areas where farming involves irrigation by flooding such as rice grown, who plan to engage extensively in outdoor activities during the transmission season [65]. Some countries routinely give JE vaccine to all/most of population in certain areas.

Currently available JE vaccines include inactivated Vero cell-derived vaccines, live attenuated vaccines and live recombinant (chimeric) vaccines for individuals  $\geq 6$ ,  $\geq 9$ , and  $\geq 8$  months of age, respectively [38].

#### 9.4. Tick-borne encephalitis vaccine

Tick-borne encephalitis (TBE) is caused by a single-stranded RNA virus that belongs to the genus *Flavivirus* which has 3 subtypes: European, Siberian, and Far Eastern. TBE virus is transmitted to humans through the bite of an infected tick of the *Ixodes* species which act as both vector and virus reservoir [66]. The virus is maintained in discrete areas of deciduous forests. Infection can also be acquired through unpasteurized dairy products, rarely through laboratory exposure and slaughtering of viremic animals and very rarely from person-to-person, through blood transfusion, solid organ transplantation, or breastfeeding [66,67].

TBE is endemic to focal areas of Western/Central Europe, Russia and Asia including China, Japan, Kazakhstan, Kyrgyzstan, Mongolia, and South Korea with an increasing health risk also for travelers [66–68]. Most cases occur from April through November, in particular during summer when ticks are active. The overall risk of acquiring TBE for an unvaccinated traveler to a high-risk area during the TBE virus transmission season has been estimated at 1 case per 10,000 person-months of exposure [66–69].

Two inactivated cell culture-derived TBE vaccines are available in Europe, in adult and pediatric formulations: FSME-IMMUN (Pfizer, France) and Encepur (GSK, Germany). TBE-Moscow (Chumakov Institute) and EnceVir (Microgen) inactivated TBE vaccines are available in Russia and SenTaiBao (Changchun Institute of Biological Products) inactivated TBE vaccine is manufactured in China. Routine primary vaccination series requires  $\geq 6$  months for completion [66,70,71]. Although, a rapid vaccination schedule has been evaluated for both European vaccines, most travelers visiting TBE-endemic areas will use tick bite protection rather than preventive vaccination [67,70,71]. Pre-travel vaccination is recommended for travelers exposed outdoors in rural endemic areas during the transmission period [38].

##### 9.4.1. COVID-19 vaccines

From late 2019, the coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has significantly affected the lives of billions of people with considerable health, societal, economic, and travel consequences worldwide. Travel and tourism had had a profound impact on the evolution of the pandemic the first months, but also to the spread of variants across borders [72,73]. However, within less than one year after the declaration of the COVID-19 pandemic by the WHO in March 2020, there has been a rapid expansion in vaccine research, including new vaccine platforms, as a key measure to control the pandemic and rapid return to normality [9]. With the deployment of COVID-19 vaccines, “COVID-19 vaccine verification” has been widely implemented in order to regulate access to social and recreational gatherings, workplaces, or schools as well as to resume safe travel [9]. Currently, most countries require a COVID-19 vaccine verification or certificate to allow fully vaccinated persons to move unhindered across borders. Although COVID-19

certificates are not exempt from practical and ethical challenges, they most probably constitute a routine requirement for the next years [74]. A very important issue is the significant variability in the acceptance of vaccines as proof of vaccination against COVID-19 for arriving travelers even among European Union member states [75]. Currently there are 28 COVID-19 vaccines approved globally, yet only eight of them obtained approval and Emergency Use Listing from the WHO (Table 1). Other issues that may arise include time-limitation of certification, and number of doses that will be required as a result of the rapidly evolving epidemiologic situation. Some countries also modify requirements for testing among travelers depending on vaccine status [76,77]. However, countries have the autonomy to issue emergency use authorizations for any health product in line with their national legislation and regulations [77]. It is highly likely that the COVID-19 pandemic will influence practices and perceptions of vaccination policies for travelers the coming years.

#### 9.5. Malaria vaccine

Malaria is a common and life-threatening disease in many tropical and subtropical areas caused by the protozoan parasites *Plasmodium falciparum*, *vivax*, *malariae*, and *ovale* which are transmitted to humans by female *Anopheles* mosquitoes. Malaria co-evolved over millennia alongside humans and is documented in ancient Egypt as shown by the surviving evidence of the enlarged spleens from Egyptian mummies [78, 79]. A disease characterized by intermittent fevers was described in *Corpus Hippocraticum* and classified as tertian fever and quartan fever [79]. Malaria was imported from the African rain forests through the Nile to the Mediterranean in Greece and eventually in Rome in the 1<sup>st</sup> century AD, and then spread across Europe over the centuries and to the New World by European colonists and slave trade [78,79]. In 1878 Alphonse Laveran, a French army physician, first identified *Plasmodium* gametocytes while examining under microscope blood from a young soldier with malaria in Algeria [79]. Evidence that malaria was transmitted by *Anopheles* mosquitoes came less than 20 years later from the work of Robert Ross, a British army physician, and the Italian malariologists Giovanni Battista Grassi, Amico Bignami and Giuseppe Bastianelli, which also elucidated the life cycle of *Plasmodium* parasites in humans [79].

Currently, malaria is the most frequently imported infectious disease by travelers to non-endemic countries. It is estimated that more than 10,000 international travelers annually visiting malaria-endemic countries become ill with malaria after returning home. Currently malaria prophylaxis recommendations for travelers include mosquito bite protection and malaria chemoprophylaxis [80].

Several malaria vaccine candidates have been under development in various preclinical or clinical phases [81–83]. More than half of these vaccines consist of a single antigen and most of them are based on recombinant proteins. The causative agent of malaria *Plasmodium falciparum* has a complex life cycle, and although many antigens could feasibly be targets of protective responses at distinct phases during the cycle, these antigens are often polymorphic [84].

## 10. Conclusion

Vaccination is a major public health achievement of the past two centuries. Since the development of the first smallpox vaccine by Edward Jenner in 1796, many vaccines have been developed and several are currently used in travel medicine or are under development or in clinical trials. Disease burden and severity were early drivers of vaccine development, followed by scientific advances in microbiology and vaccine technology. Vaccine requirement policies have been developed by public health authorities and various institutions and organizations, for people crossing borders in order to prevent the spread of diseases. Vaccination policies may differ among countries, according to their impetus, design, target population, and reinforcement. Factors that may



influence vaccination policies and requirements for travelers include the emergence or elimination of epidemics, significant associated morbidity and mortality, lack of treatment, impact on tourism, and development of new vaccines [85]. Political and cultural issues and vaccine policy history are centrally important factors for vaccine mandate policymakers to consider [85].

The on-going COVID-19 pandemic triggered the implementation of new vaccine platforms. The global use of COVID-19 vaccine verification most probably will influence practices and perceptions of vaccination policies for travelers the coming years.

## Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Declaration of competing interest

All authors: nothing to declare.

## Acknowledgement

The opinions presented in this article are those of the authors, and do not necessarily represent those of their institutions.

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