Overview

Burden of typhoid fever and cholera: similarities and differences. Prevention strategies for European travelers to endemic/epidemic areas

D. AMICIZIA, R.T. MICALE, B.M. PENNATI, F. ZANGRILLO, M. IOVINE, E. LECINI, F. MARCHINI, P.L. LAI, D. PANATTO
Department of Health Sciences, University of Genoa, Italy

Keywords

Salmonella Typhi • Cholera • Typhoid fever vaccines • Cholera vaccines • Travel medicine • International travel

Summary

The burden of diarrheal diseases is very high, accounting for 1.7 to 5 billion cases per year worldwide. Typhoid fever (TF) and cholera are potentially life-threatening infectious diseases, and are mainly transmitted through the consumption of food, drink or water that have been contaminated by the feces or urine of subjects excreting the pathogen. TF is mainly caused by Salmonella typhi, whereas cholera is caused by intestinal infection by the toxin-producing bacterium Vibrio cholerae. These diseases typically affect low- and middle-income countries where housing is overcrowded and water and sanitation are poor, or where conflicts or natural disasters have led to the collapse of the water, sanitation and healthcare systems. Mortality is higher in children under 5 years of age. Regarding their geographical distribution, TF has a high incidence in sub-Saharan Africa, India and south-east Asia, while cholera has a high incidence in a few African countries, particularly in the Horn of Africa and the Arabian Peninsula.

In the fight against these diseases, preventive measures are fundamental.

With modern air travel, transmissible diseases can spread across continents and oceans in a few days, constituting a threat to global public health. Nowadays, people travel for many reasons, such as tourism and business. Several surveys have shown that a high proportion of travelers lack adequate information on safety issues, such as timely vaccination and prophylactic medications. The main objective of this overview is to provide information to help European travelers to stay healthy while abroad, and thus also to reduce the potential importation of these diseases and their consequent implications for public health and society.

The preventive measures to be implemented in the case of travel to countries where these diseases are still endemic are well known: the adoption of safe practices and vaccinations. It is important to stress that an effective preventive strategy should be based both on vaccinations and on hygiene travel guidelines.

Furthermore, the emergence of multidrug-resistant strains is becoming a serious problem in the clinical treatment of these diseases. For this reason, vaccination is the main solution.

Introduction

The burden of diarrheal disease is very high, accounting for 1.7 to 5 billion cases per year worldwide. Specifically, diarrheal diseases are associated with an estimated 1.3 million deaths ann-ually, with most occurring in resource-limited countries. Very young children are the most vulnerable, the incidence of severe gastroenteritis being highest in the first 2 years of life. Indeed, up to 25% of deaths in young children in Africa and south-east Asia are attributable to acute gastroenteritis. In these geographical areas, total mortality has declined in recent decades, owing to the increased use of oral rehydration therapy, improved nutrition, increased breastfeeding, better supplemental feeding, female education, immunization and improvements in hygiene and sanitation. Nevertheless, morbidity due to diarrhea has not declined in the same manner. Indeed, in low-income countries, children under three years old experience, on average, three episodes of diarrhea every year. Although the burden is greatest in low-income populations with poor access to safe water, sanitation and urgent medical care, acute infectious diarrhea is also a common cause of outpatient visits and hospital admissions in high-income regions, and is a major health problem globally [1].

Diarrhea is caused by a wide range of etiological agents, including viruses, bacteria and parasites. Among the etiological agents responsible for diarrheal diseases are *Salmonella Typhi* (*S. typhi)*, *Salmonella Paratyphi* (*S. paratyphi*) and *Vibrio Cholerae*. In this overview, the burden of typhoid and paratyphoid fever and cholera is described in order to provide updated information for European travelers to endemic areas and to identify the best preventive strategies.

Typhoid and paratyphoid fever

Typhoid fever (TF), also known as enteric fever, is a potentially life-threatening multi-systemic illness. It is mainly caused by Salmonella enterica, subspecies enterica serovar *typhi*, and to a lesser extent by serovars *paratyphi* A, B, and C, which are members of the family of *Enterobacteriaceae* [2]. The genus Salmonella is divided into serovars on the basis of surface antigens: O antigen, based on the lipopolysaccharide (LPS) compo-

nent; and H antigen, based on flagellar proteins. Moreover, pathogenic strains of *S. typhi* and *S. paratyphi* C present a Vi antigen polysaccharide component [3].

Clinical features

S. typhi is restricted to human hosts, and chronic carriers constitute the reservoir of infection.

The disease is mainly transmitted through the consumption of food, drink or water that have been contaminated by the feces or urine of subjects excreting bacteria (sick or convalescent people or chronic asymptomatic carriers). After *S. typhi* has been ingested, it reaches the intestinal epithelium, where it colonizes macrophages and dendritic cells in the lamina propria; however, these fail to destroy the bacterium [4]. Subsequently, bacteria invade the bloodstream, multiply and spread to the lymph nodes, spleen and liver, causing multi-systemic disease [5]. The main manifestations of the disease are fever, which can reach 38°-40°C, and abdominal symptoms (such as diarrhea or constipation). Nonspecific symptoms, such as weakness, anorexia, headache and dizziness, may precede the fever. Moreover, rose-colored spots may appear on the trunk, and patients may also experience neuropsychiatric manifestations, hepatomegaly and splenomegaly. The most severe complications are gastrointestinal bleeding, intestinal perforation and typhoid encephalopathy, which occur in 10-15% of patients, generally in the third and fourth weeks of infection [6, 7]. The duration of infection is a major determinant of the risk of severe complications, and a delay in administering appropriate antibiotic treatment may have serious consequences. Isolation of *S. typhi* from blood is the most common method of diagnosis, though the bacterium can also be isolated from bone marrow, feces and duodenal fluid. Blood culture displays suboptimal sensitivity, generally being positive in only about 50% of cases. It also has several limitations, including the volume of blood needed, the need for prompt transport to the laboratory, interference due to prior antibiotic use, limited laboratory expertise and equipment, and expense [8]. Bone marrow culture increases the diagnostic yield to approximately 80% of cases. Stool culture is not usually positive during the earliest phase of the disease [9]. Multiple cultures increase sensitivity and may be required in order to reach a diagnosis. Although the Widal test (based on the detection of agglutinating antibodies to 'O' and 'H' antigens) is unreliable (may give false-positive or false-negative results), it is widely used in developing countries because of its low cost. Newer serologic assays for *S. typhi* infection are occasionally used in outbreak situations, and are somewhat more sensitive and specific than the Widal test [2]. Early diagnosis and the prompt institution of appropriate antibiotic treatment are essential for the optimal management of TF, especially in children. *S. paratyphi* causes paratyphoid fever. *S. paratyphi* is thought to cause milder disease than *S. typhi*, with symptoms being predominantly gastrointestinal [10]. While this is probably true of *S. paratyphi B* infection, there are insufficient data to draw conclusions regarding *S. paratyphi A* [11].

Ciprofloxacin is commonly used as an empiric treatment, as fluoroquinolones are recommended. However, as fluoroquinolone-resistant or multidrug-resistant strains are spreading, third-generation cephalosporins are used when the possibility of resistance is high [6, 12].

Epidemiology

TF is one of the main causes of enteric disease worldwide [13]. The incidence of TF (overall population) is reported in Figure 1. Recent estimates of the global incidence of typhoid and paratyphoid fevers in 2017 indicate 14.3 million people affected (76.3% caused by S. typhi) [14], a 44.6% decline from the 25.9 million in 1990 [5, 8, 15, 16].

The distribution of the disease differs widely throughout the world (Fig. 1). In geographical areas with a high incidence, the main risk factors are inadequate drinking water and inadequate sanitation; indeed, low- and middle-income countries are mainly affected, owing to the lack of clean water and of proper sanitation. Moreover, other risk factors are: high population density, unsanitary living conditions, poor hygiene, low socio-economic status, and recent contact with a patient affected by TF [17]. In 2014, the World Health Organization (WHO) attributed 502,000 deaths to inadequate drinking water and 280,000 to inadequate sanitation [18]. TF has a heavy burden in Asia, with an overall incidence of 170.8 cases per 100,000 people per year, though this estimate varies across the continent [14]. Specifically, Buckle et al. estimated an annual incidence rate of 394.2 per 100,000 in southern Asia. With regard to Africa, the incidence is estimated to be 724.6 cases per 100,000 people per year; however, it is probably underestimated, owing to the lack of information and surveillance systems in the continent [14]. Moreover, Africa suffers many cases of invasive non-typhoid salmonellosis, which are additional confounding factors in estimating the TF burden [17]. TF also affects countries in Latin America, the Caribbean and Oceania, although to a lesser extent, with a median incidence rate of 22.3 cases per 100,000 people per year [5].

In 2014, Mogasale V et al. studied the incidence of TF in various parts of the world, showing that it was considerably higher in low- and middle-income countries (risk-adjusted and corrected for blood culture sensitivity) (Fig. 1) [19].

A 2017 study by Antillón et al. found that the age-group most commonly affected by the disease is in the range between 2 and 14 years. Specifically, incidence peaks in the 2-4 years age-group, while it is lower in children < 2 years of age and adults. It must be stressed that children, even when properly treated, have a high mortality rate. These authors estimated that the expected number of TF cases per year is 17.8 million across all low-income and middle-income countries. According to their analysis, almost 40% of all cases occur in sub-Saharan Africa (7.2 million), although the uncertainty of their estimates is considerable. Figure 2 reports the incidence (per 100,000 person-years) in the Global Burden of Disease

Fig. 1. Typhoid incidence in low- and middle-income countries (risk-adjusted and corrected for blood culture sensitivity), adapted from Mogasale et al. [19]. Colors indicate different incidence values, with darker shades corresponding to higher incidence.

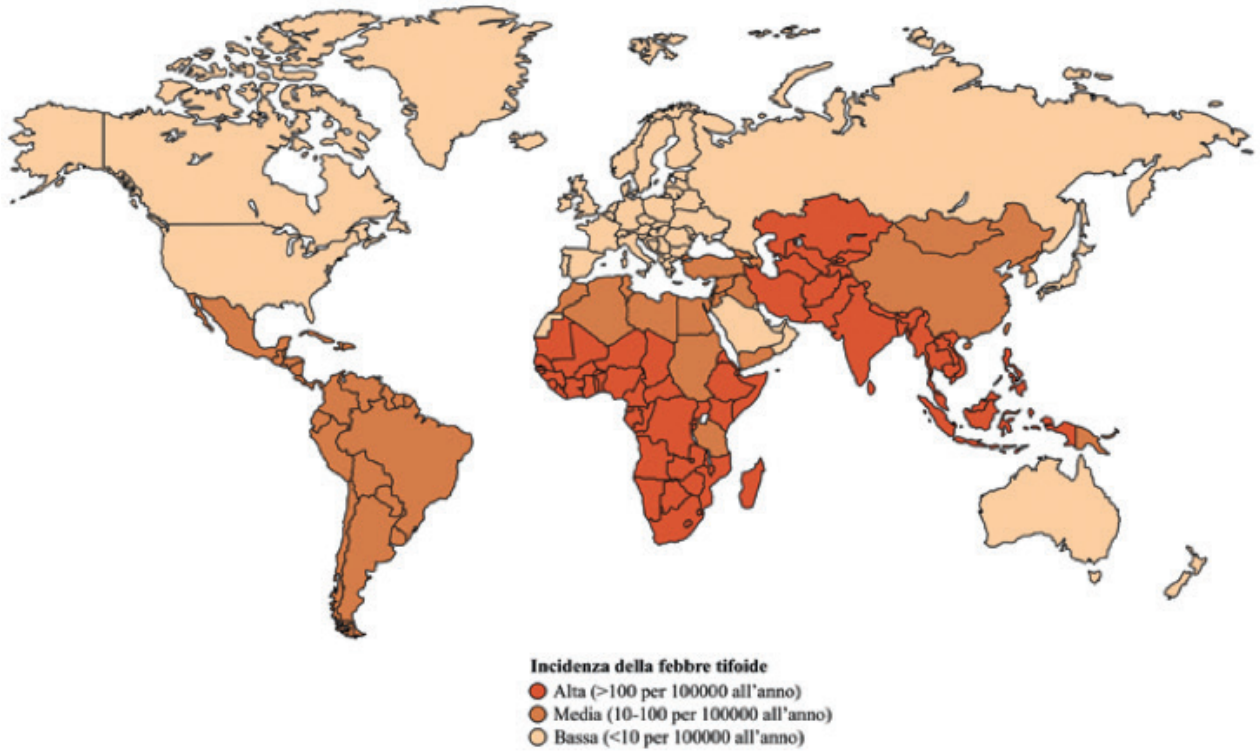
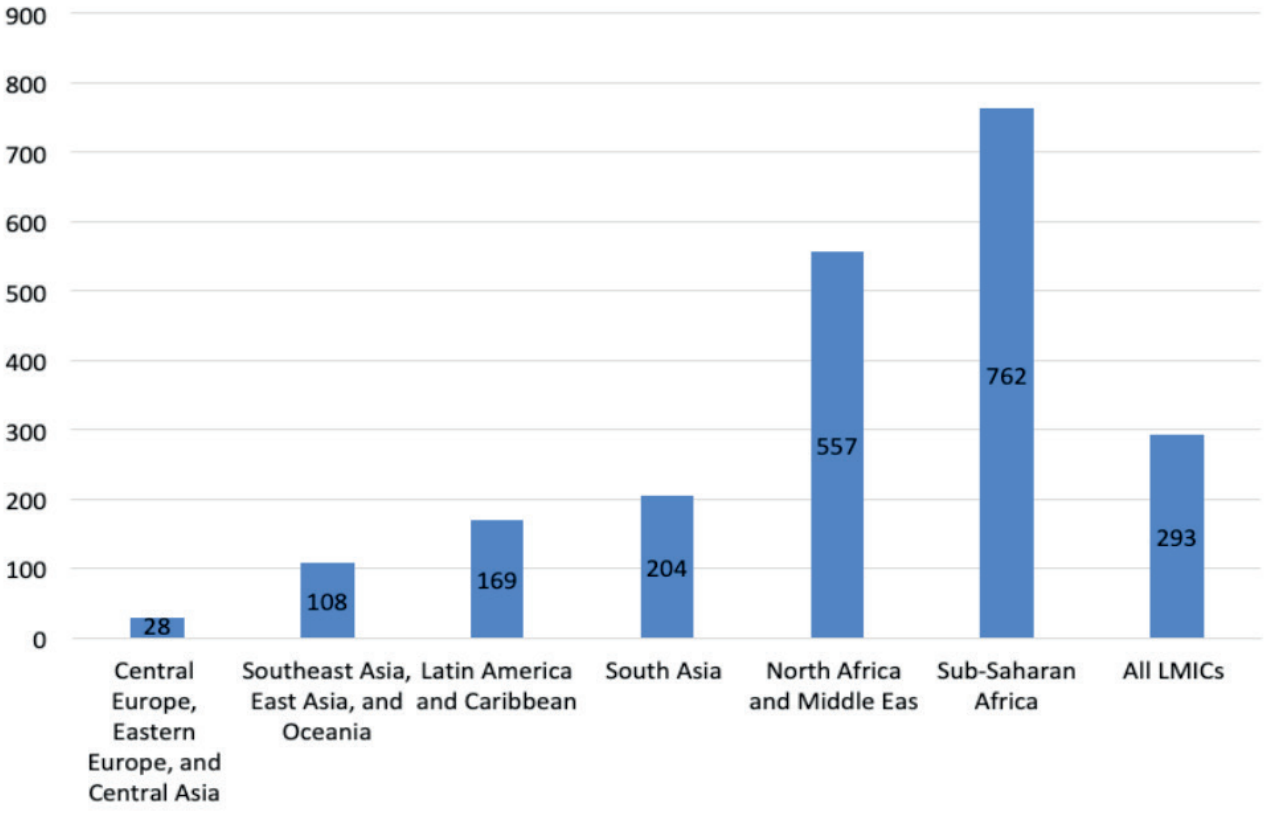


Fig. 2. Incidence in the Global Burden of Disease regions and sub-regions made up of low- and middle-income countries. The incidence is per 100,000 person-years. Adapted from Antillón et al. [20].



regions and sub-regions made up of low- and middle-income countries [20].
In developed countries, the incidence rate per 100,000 per year varies from < 0.1 to 0.3, and the disease mainly affects people who travel to endemic areas located in low- and middle-income countries [15].
The median TF mortality rate varies from region to region: high-income countries such as North America, Europe, Australia and New Zealand register less than 0.1 deaths per 100,000 people per year, while the mortality rate is higher in Sub-Saharan Africa (7.2) and Southern Asia (3.9) [15].
S. paratyphi A has been found to be responsible for a considerable, and increasing, proportion of cases of enteric fever in some Asian regions [8].
A very recent systematic review by Marchello et al. reports the incidence of blood culture-confirmed TF without restrictions on age, country, language or time. The authors identified Africa and Asia as regions with high TF incidence, with a peak in children younger than 15 years old (particularly between 2 and 4 years old). These results confirm the global incidence trend of new cases of TF [21].
The impact of *S. typhi* and *S. paratyphi* disease is probably underestimated, owing to inadequate surveillance systems in the most severely affected areas, the low sensitivity of diagnostic tools, and healthcare inequalities resulting in scant health-seeking behavior among populations at the highest risk [22].

Vaccination

Despite major efforts to prevent and treat cases of enteric fever, millions of new infections of typhoid fever occur in many areas where sanitation is poor and food and water supplies are unsafe, frequently involving travelers to endemic areas [22].
In the fight against this plague, preventive measures are fundamental. Vaccination against typhoid is an effective preventive intervention, especially when coupled with hand-washing, the treatment of household water, and the provision of adequate sanitation [4].
Well-tolerated and effective vaccines are currently available. One of these is based on the use of live attenuated bacteria and is administered orally; the other is based on Vi capsular polysaccharide (Vi-PS), and is administered intramuscularly or subcutaneously [4].

Ty21a vaccine (Vivotif®)

A mutated strain of *Salmonella* (Ty21a) that reproduces the natural infection is contained in Ty21a vaccine (Vivotif®).
The Ty21a strain is a Ty2 mutant, with deficiency of the uridyl diphosphate-galactose enzyme (UDP-Gal) -4-epimerase. The deficiency of this enzyme prevents the conversion of UDP glucose to UDP galactose, one of the components of the lipopolysaccharide membrane of *Salmonella*. The absence of galactose UDP determines the formation of an LPS that does not contain O antigen, which is the most important surface antigen. In this phase, the mutant strain is not immunogenic; however, since the Ty21a strain is fed by galactose, the bacterium becomes capable of generating UDP galactose by means of an alternative route, managing to express a complete and immunogenic LPS. Despite its immunogenic capacity, the mutant strain is not virulent, as the galactose is partially accumulated as galactose-1-phosphate and UDP-galactose, which induce bacterial lysis. *S. typhi* Ty21a is a stable mutant with no possibility of reversion either *in vitro* or *in vivo*. This particular strain causes an abortive infection, stimulating an immune response at the intestinal level and inducing both a humoral, cell-mediated and antibody reaction [23, 24].

Therapeutic indications

Children aged over 5 years and adults can take the Ty21a vaccine orally. The pack contains 3 capsules, to be taken every other day, with cold or lukewarm water, at least an hour before meals. The protection starts between 7 and 10 days after the third dose.
In countries where the risk of contracting the disease is high, vaccination is recommended every 3 years. Similarly, on the basis of new summary of product characteristics, those traveling to an endemic area should be vaccinated every 3 years [25]. The vaccination schedule must be completed at least one week before going to an endemic area.
Vivotif® may be administered concomitantly with yellow fever vaccine and oral polio vaccine.

Immunogenicity, efficacy and safety

It has been shown that the vaccine stimulates a good local production of IgA against the O antigen and that it induces good humoral and cell-mediated immunogenicity against the O antigen in adult male subjects [26].
The immunogenicity of Ty21a was evaluated in 634 Thai children, who underwent a three-dose vaccination schedule [27]. A seroconversion rate of 60% was found in 3-year-old children and of 91% in 6-year-old children ($p < 0.005$); these percentages were higher than the seroconversion rates in unvaccinated children of the same age. The data showed that seroconversion rates increased proportionally to the age of vaccinated children.
Gilman et al. [28] studied 155 male adults vaccinated with Ty21a and observed good seroconversion rates of antibodies to the O antigen, resulting in disease protection.
In another controlled trial, 32,388 children were recruited in order to evaluate Ty21a vaccine (16,486 received the vaccine, 15,902 received oral placebo, and 25,625 did not receive either) and it was reported that, out of 92,675 doses administered, there were 49 cases of vomiting among vaccinees, versus 21 in the placebo group; 1 case of fever after the vaccine and 3 cases in the control group, and finally 14 cases of abdominal pain in the vaccinated group, versus 2 cases in the placebo group [29]
Levine et al. described a randomized, placebo-controlled field efficacy trial in Santiago (Area West); a total of 65,674 schoolchildren (aged 6-17 years) received three doses of vaccine. Volunteers were randomly assigned to two groups, one of which received the three

capsules within 48 hours (22,170 subjects), and the other within 21 days (21,598). Children who received placebo (21,906) served as the comparator group. The study demonstrated that the best protection was seen in the group that received all three doses of the vaccine in enteric-coated capsules within one week; prolonging the interval between doses to 21 days did not enhance efficacy [30].
Subsequently, a liquid formulation was commercialized after it had been shown to provide greater protection than enteric-coated capsules over three years of follow-up in a randomized, placebo-controlled trial in Area South East and Area North, Santiago [31].
Surveillance in the Area West trial was continued for four additional years (i.e., total seven years of follow-up) and in the Area South East and Area North trial for two additional years (i.e., a total of five years of follow-up).
Over the course of a decade, it was possible to conduct separate large-scale trials to evaluate different immunization regimens and programs of Ty21a oral in vivo typhoid vaccine. The results showed that over 3 years of follow-up in Santiago (Area West), there were 68 cases of bacteriologically confirmed typhoid fever in the placebo group and 23 cases in the short-interval vaccine group, yielding a point estimate of vaccine efficacy of 67% (95% CI 47-79%; $p < 0.00001$). There were 34 cases of confirmed typhoid fever in the long-interval group, providing a point estimate of vaccine efficacy of 49% (95% CI 24-66%; $p = 0.0006$).
In a field trial, the three-dose regimen of enteric-coated capsules taken on alternate days was shown to have a protective efficacy of 71% (95% CI 35-87%) during the first year after vaccination, 67% (95% CI 47-79%) over 3 years, and 62% (95% CI 48-73%) over 7 years of follow-up, which definitively supports the efficacy reported in the vaccine summary of product characteristics [31].
Moreover, the data from the Area South East and Area North trial revealed that three doses of liquid formulation conferred 77% (95% CI 60 ± 87%; $p < 0.001$) protection over three years and 79% (95% CI 65 ± 87%; $p < 0.001$) over five years of follow-up, showing the efficacy of three doses of the liquid formulation of Ty21a [31].
Other studies of vaccine immunogenicity, safety and tolerability have demonstrated the good profile of Vivotif® [32-34].

Vi polysaccharide vaccine (Typhim Vi®)

Vi polysaccharide vaccine (Typhim Vi®) contains purified Vi capsular polysaccharide of Salmonella typhi (Ty 2 strain). Immunity appears within 1-3 weeks after injection and lasts around 3 years. A single dose of ViPS vaccine elicits high levels of serum IgG anti-Vi antibodies. The persistence of anti-Vi antibodies depends on endemicity, with a trend towards greater persistence in endemic areas (documented up to 10 years in 83 children at levels equal to or above the serological correlate of protection of 1 µg/mL). In non-endemic areas, anti-Vi antibodies persist for 2 to 3 years [33].

Therapeutic indications

Typhim Vi® can be used in adults and children over 2 years of age, administration being in a single dose of 0.5 ml, with re-administration required every 2–3 years in subjects who remain at risk of typhoid fever. The common route of administration of this vaccine is intramuscular, although it may be given subcutaneously. Vaccination should be carried out at least 2 weeks prior to potential exposure to *S. typhi* infection.
Typhim Vi® may be administered together with other common vaccines (yellow fever, diphtheria, tetanus, poliomyelitis, rabies prepared on Vero cells, meningitis A+C, hepatitis A and hepatitis B) during the same vaccination session [35].

Immunogenicity, efficacy and safety

A double-blind, randomized, controlled efficacy clinical trial was conducted in a highly endemic area of Nepal, in both pediatric and adult populations: 3,457 subjects received Typhim Vi®. The results indicated that the level of protection conferred by a single dose of the vaccine was 74% against blood culture-confirmed cases of TF throughout the 20 months of active surveillance, in comparison with the control group [36].
The seroconversion rate (defined as a 4-fold rise in anti-Vi antibody levels) was recorded in 19 clinical trials involving a total 2,137 pediatric and adult subjects in endemic and non-endemic areas. In the adult population, the seroconversion rate ranged from 62.5% to 100% four weeks after a single injection, with a similar magnitude of anti-Vi immune response in non-endemic areas and endemic areas. Similar results were obtained in the pediatric population.
During clinical development, more than 15,000 people received Typhim Vi® (first or second injection). The most common adverse reaction, in all age-groups, was injection site pain. In adults over 18 years of age, myalgia and fatigue were the most frequently reported systemic reactions. In children and adolescents (from 2 to 17 years of age), myalgia and headache were the most frequently reported systemic reactions. Most adverse reactions appeared within 3 days after vaccination and most resolved spontaneously within 1 to 3 days after onset [33, 37].

Cholera

Cholera is a rapidly-dehydrating diarrheal disease caused by intestinal infection by the toxin-producing bacterium *Vibrio cholerae.*
Vibrio cholerae strains are classified into serogroups on the basis of the structure of their cell surface lipopolysaccharides. Of the over 200 known serogroups of *Vibrio cholerae*, distinguished by the polysaccharides of the somatic (O) antigen, only the O1 and O139 serovars can produce the cholera toxin and cause pandemic disease [38]. There is no proven cross-protection between O1 and O139. On the basis of a number of phenotypic differences, including their susceptibility to polymyxin B and phage infection [39], the O1 serotype is further

classified into 2 biotypes, El Tor and classical O1. Both of these biotypes can be further classified into 2 cross-reacting serovars, Ogawa and Inaba [40]. El Tor persists for a longer time in the environment and is associated with a higher rate of asymptomatic cases. The classical strains are believed to have been responsible for the six previous cholera pandemics in modern history, the first of which started in 1817. The El Tor biotype is responsible for the longest and most severe seventh pandemic, which started in 1961 and continues today [41]. In 1992, a genetic derivative of the El Tor biotype, termed *Vibrio cholerae* O139 Bengal, caused extensive epidemics of cholera in India and Bangladesh and subsequently in other parts of south Asia [41]. The spread of the O139 serogroup is restricted to Asia and over the years its incidence has decreased following the appearance of a new El Tor strain in 1994 [42]. This serogroup switch has occurred several times over the past decade in cholera-endemic regions, suggesting that acquired immunity plays an important role in the emergence of specific serogroups. Moreover, the rapid evolution and genetic rearrangement of O1 and O139 strains contribute to the persistence and re-emergence of this disease.

In recent years, new pathogenic variants of *Vibrio cholerae* have emerged as the genetic backbone of El Tor strains and the higher infectivity of classical strains, and are associated with increased ecological persistence, infectivity, disease severity, and dispersion worldwide [41, 43-47]. This strain is responsible for the epidemic on Hispaniola and may cause more severe episodes of cholera and higher death rates [12].

As *Vibrio cholerae* strains continue to adapt and evolve, understanding the underlying factors that contribute to their enhanced environmental persistence and increased transmission will be essential, in order to predict outbreaks and establish preventive measures [48].

Cholera currently remains a serious public health problem in many countries, occurring as an endemic disease in some regions and causing major epidemics in some low/middle-income countries [49, 50].

Clinical features

Cholera displays an acute nature, leading to severe dehydration within hours, and death if not treated adequately. *Vibrios* are gram-negative, highly motile and comma-shaped, with a single polar flagellum. In affected individuals, *Vibrio cholerae* secretes a toxin (CT) that affects the small intestine. The toxic action of CT depends on a specific receptor, the monosialosyl ganglioside GM1. The binding (B) subunit of the toxin attaches to GM1 and releases the active (A) subunit; this enters the host cell and activates the G protein, which stimulates adenylate cyclase [50]. This activation increases the outflow of chloride and bicarbonate from the cell and reduces sodium influx, causing water molecules to flow into the lumen of the gut. The consequent net fluid loss causes watery diarrhea and rapid dehydration, which, if untreated, can lead to hypotonic shock and death within 12 hours of the first symptoms [38, 49, 51].

After an incubation period of approximately 18 h to 5 days, the illness typically starts suddenly with passage of watery stools and vomiting. Systemic manifestations, such as fever, are absent unless there is a co-infection. Depending on the severity of dehydration, the patient may be thirsty and irritable and, in later stages, display lethargy, a rapid radial pulse, loss of skin turgor, diminished urine output, low blood pressure, rapid breathing and sunken eyes. When severely dehydrated, the patient may progress to hypovolemic shock. Complications of cholera include electrolyte imbalance, including hypokalemia, hyponatremia, hypocalcemia and acidosis. Children can develop hypoglycemia due to depleted hepatic glycogen reserves and insufficient gluconeogenesis, which may cause seizures [52]. Other complications include various manifestations of diminished perfusion of end organs, including acute renal failure, stroke and, in pregnant patients, miscarriage, premature delivery and stillbirth [12].

Susceptibility to infection by *Vibrio cholerae* depends both on adaptive immune responses, induced by previous infection or vaccination, and on innate host factors. A low gastric acid level has been associated with more severe cholera disease. The immune response in individuals with cholera is directed primarily against bacterial surface molecules and against cholera toxin. The response includes intestinal-mucosal secretory IgA (SIgA) and serum IgA, IgG, vibriocidal antibodies, antibody-secreting cells, T cells and, of special importance for long-term protection, memory B cells and T cells [40].

Intriguingly, not all individuals infected with pathogenic *Vibrio cholerae* exhibit symptoms of cholera, and several host factors appear to impact on immunity to the disease. Both retinol deficiency and blood type O have been associated with an increased susceptibility to infection [53-56]. Regardless of blood type, higher transmission rates of cholera are observed between first-degree relatives than between less closely related contacts living in the same household, indicating that additional genetic factors play a role in the susceptibility to cholera [55].

Laboratory tests are not essential for the diagnosis of cholera, as the clinical picture of acute, non-bloody, profuse, watery diarrhea quickly leading to dehydration does not occur in many other scenarios [57]. Cholera is confirmed through culture of a stool specimen or rectal swab [12].

Treatment for cholera is relatively cheap and simple. Intravenous rehydration with Ringer's lactate solution should be administered aggressively in order to restore the circulation. With adequate and timely rehydration, case-fatality rates (CFRs) are < 1%. The oral rehydration solution recommended by the WHO contains glucose as a source of carbohydrates, and has reduced osmolarity, which is associated with reduced stool output. Antiemetics have no role, and might interfere with rehydration because of their sedating effects. Antibiotic treatment should be dictated by local antimicrobial susceptibility profiles. Azithromycin and ciprofloxacin are commonly used, although azithromycin has been shown to be more effective than ciprofloxacin in terms of shortened

duration of diarrhea, reduced stool volume, lower frequency of vomiting and cessation of fecal excretion of vibrios [12, 40].

Epidemiology

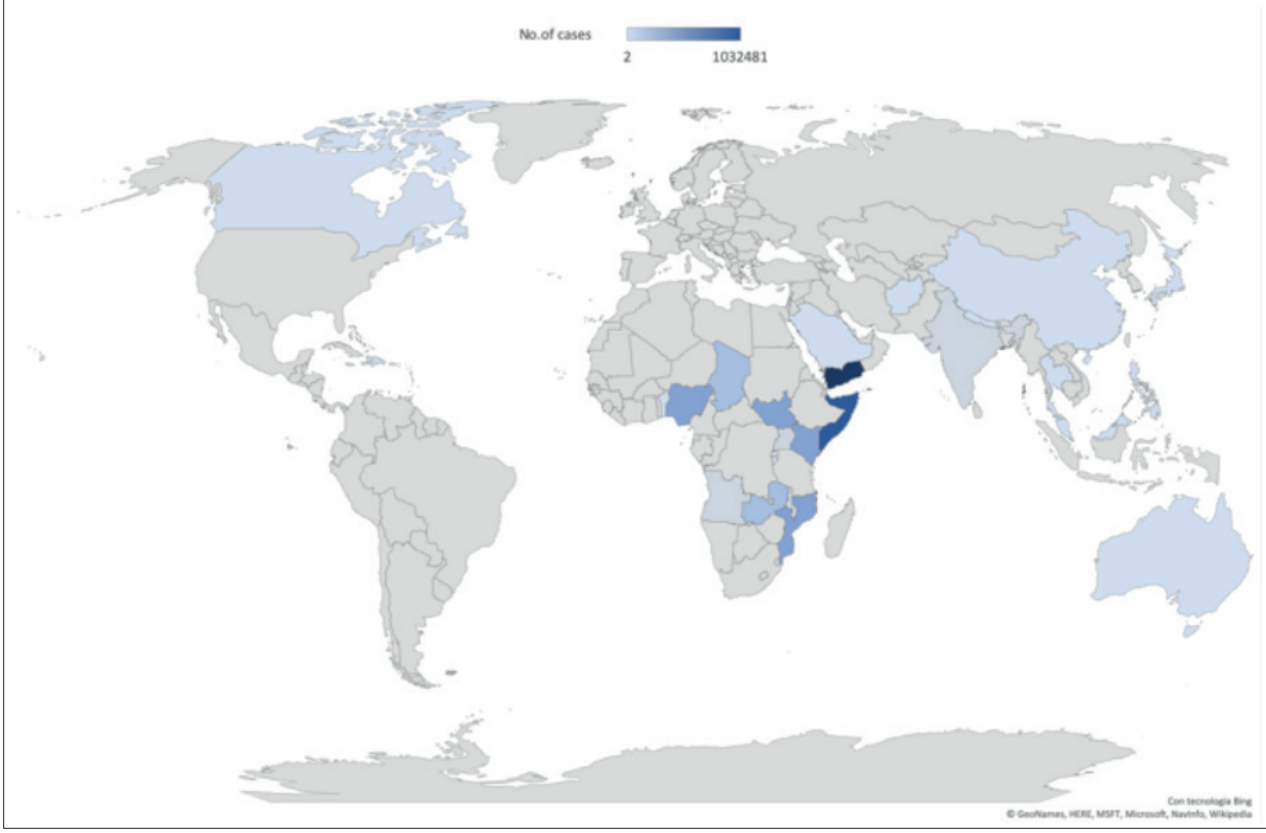
The disease typically affects regions where housing is overcrowded and water and sanitation are poor, or where conflicts or natural disasters have led to the collapse of the water, sanitation and healthcare systems [58]. Access to safe water and improved sanitation facilities has eliminated the transmission of *Vibrio cholerae*, the causative agent, in high-income countries. However, the bacteria continue to afflict millions of people in less developed countries where adequate water and sanitation infrastructure are not widely available [59].

Cholera epidemics are superimposed on the endemic disease in long cycles. These cycles are determined by waning levels of population immunity and periods of climate variability. When introduced into a cholera-naive population, large-scale epidemics can occur, such as the ongoing Haitian epidemic that began in 2010. In epidemic settings where natural immunity is scant or absent, all age-groups are equally affected by the disease although mortality in children < 5 years is higher [59]. Epidemics occur unpredictably and are often associated with natural disasters and humanitarian emergencies that disrupt the supply of water and sanitation. [58].

The global burden of cholera is largely unknown, as the majority of cases are not reported [59]. The WHO estimates that only 5-10% of cases occurring annually are officially reported [60]. The main factors for this low reporting efficiency include the limited capacity of epidemiological surveillance systems and laboratories, and social, political and economic disincentives to reporting [61-63]. While safe drinking water and advanced sanitation systems have made the Global North cholera-free for decades, the disease is still endemic in many regions, including Asia, Africa and the Americas, with 1.3 billion people at risk, Sub-Saharan Africa being the worst affected [64].

As mentioned above, *V. cholera* originated in the Indian subcontinent and caused six pandemics from 1827 through 1923. The seventh pandemic has been ongoing since 1961, reaching South America and most of the Western Hemisphere in 1991 [65]. The WHO estimates 2.8 million cases and 91,000 deaths annually. Recently, cholera has struck vulnerable communities, such as post-earthquake Haiti (2010), Iraq and Yemen, where natural disasters, refugee movements, war and conflict increase the risk of infection and outbreaks [66]. In 2017, the WHO gathered data on cholera from 71 countries worldwide: 34 countries reported a total of 1,227,391 cases and 5,654 deaths (global case-fatality rate (CFR): 0.5%) (Fig. 3), and 37 countries reported cases for the year [62].

Fig. 3. Countries reporting cholera cases in 2017 (Adapted from WHO, 2018) [67]. The colors indicate different values of incidence; a darker shade corresponds to a higher incidence.



Yemen accounted for 84% of all suspected cases reported and for 41% of cholera-attributed fatalities. Excluding cases related to Yemen, an increase of 45% in the number of cases and 33% in the number of deaths over the 2016 global totals was observed in Member States. The increase in 2017 was due largely to severe epidemics in the Democratic Republic of the Congo (DRC), Nigeria, Somalia and South Sudan [68].
Since the last Communicable Disease Threats Report (CDTR), updated on 24 August 2018, the countries reporting the most cases have been Yemen (38,269 cases, 63 deaths), Nigeria (7,966 cases, 224 deaths), the DRC (2,918 cases, 65 deaths), Niger (1,592 cases, 36 deaths) and Ethiopia (1103 cases). Since the last CDTR update, the WHO has declared the cholera outbreaks in Kenya and Uganda to be under control. Two countries have recently reported new cholera outbreaks within their territories: Algeria and Zimbabwe [68].

Natural disasters and epidemics

Epidemics occur unpredictably and are often associated with natural disasters and humanitarian emergencies that disrupt access to water and sanitation supplies. [57].
The WHO defines natural disasters as "catastrophic events with atmospheric, geologic and hydrologic origins", including earthquakes, volcanic eruptions, storm surges, landslides, tsunamis, wildfires, floods and droughts [69, 70].
In humanitarian crises and emergencies, the lack of infrastructures often forces victims to seek refuge in temporary accommodation, without adequate access to food, safe water and sanitation. Obviously, in such situations, public health surveillance systems may be suboptimal, disrupted or even non-existent, exacerbating the risk of transmission of communicable diseases [71]. Furthermore, the lack of electricity, laboratory equipment and supplies can make conventional testing for water-borne pathogens impossible [72].
Moreover, susceptibility to many diseases, including cholera, may be due to pre-existing health conditions, such as malnutrition, especially in infants and children. Indeed, a 2011 study [73] showed that cholera cases (or worse epidemics) are more likely to arise in malnourished populations with limited food availability owing to famine, war or natural disasters [74]. A poor nutritional status may have many causes, such as a deficient macro/micronutrient intake, malabsorption, metabolic disturbances and other health issues (e.g., HIV/AIDS); for example, children with zinc and vitamin A deficiency are more susceptible to cholera [75].
Moreover, natural disasters affect the ecology of pathogens, mainly by increasing the risk of exposure to them, but also by facilitating their growth in aquatic environments, which are the main *reservoir* of pathogenic cholera bacteria [70, 76, 77]. In this regard, changes in the aquatic environment, such as plankton concentration, variations in salinity, temperature, pH, sediments and their re-suspension/transport and other physico-chemical factors, can promote the survival of the pathogen, especially in coastal zones [78].
In recent years, as a consequence of climate change and human activities (e.g., rapid urbanization, deforestation, etc.), the incidence of natural disasters has increased [69, 78, 79]. An estimate derived from the International Disaster Database suggests that about 270 million people each year are affected by natural disasters [70, 80, 81].
However, not all disasters are followed by cholera epidemics; environmental conditions need to be conducive to the rapid growth of this bacterium, the pathogenic strains of which are susceptible to many factors, as seen above. Furthermore, societal structure, prevailing climatic processes and the spatio-temporal seasonal variability of natural disasters play a very important role in predicting cholera outbreaks. Indeed, an already "fragile" area is at greater risk of suffering an epidemic than a high-income area, which, by contrast, will be able to help the victims of a disaster promptly and can recover from it relatively quickly, before an outbreak can occur [70].

Vaccination

In order to prevent cholera, it is important to vaccinate both travelers to endemic areas and people who live in such areas. Currently, the available vaccine for European travelers is cholera inactivated vaccine (Dukoral®), that is administered orally.

Cholera inactivated vaccine (Dukoral®)

Cholera inactivated vaccine (Dukoral®) contains killed whole *Vibrio cholerae* O1 bacteria and the recombinant non-toxic B-subunit of the cholera toxin (CTB) [82].
Bacterial strains of both Inaba and Ogawa serovars and of El Tor and classical biotypes are included in the vaccine. Dukoral® is taken orally together with a bicarbonate buffer, which protects the antigens from the gastric acid. The vaccine acts by inducing antibodies against both the bacterial components and CTB. The intestinal antibacterial antibodies prevent the bacteria from attaching to the intestinal wall, thereby impeding colonization by *Vibrio cholerae* O1. The intestinal anti-toxin antibodies prevent the cholera toxin from binding to the intestinal mucosal surface, thereby preventing the toxin-mediated diarrheal symptoms.
The heat-labile toxin (LT) of enterotoxigenic E. coli (ETEC) is structurally, functionally and immunologically similar to CTB. The two toxins cross-react immunologically.

Therapeutic indications

Dukoral® is indicated for active immunization against disease caused by Vibrio cholerae serogroup O1 in adults and children from 2 years of age who will be visiting endemic/epidemic areas.
As reported in the summary of product characteristics, the use of Dukoral® should be determined on the basis of official recommendations, taking into consideration the variability of epidemiology and the risk of contracting the disease in different geographical areas and traveling conditions. However, Dukoral® should not replace stan-

dard protective measures (such as washing hands, eating well-cooked foods, avoiding raw foods, eating only beverages from sealed bottles, and if not boil them; remember: "boil it, cook it, peel it or forget it).

The standard primary course of vaccination with Dukoral® against cholera consists of 2 doses for adults and children from 6 years of age. Children from 2 to below 6 years of age should receive 3 doses. Intervals of at least one week between doses are necessary. If more than 6 weeks have elapsed between doses, the primary immunization course should be re-started.

For continuous protection against cholera, a single booster dose is recommended within 2 years for adults and children from 6 years of age, and within 6 months for children aged 2 to 6 years. No clinical efficacy data have been generated on repeat booster dosing. However, immunological data and data on the duration of protection suggest that if up to 2 years have elapsed since the last vaccination in adults, and up to 6 months in children aged 2-6 years, a single booster dose should be given. If more than 2 years have elapsed since the last vaccination (more than 6 months in children aged 2-6 years) the primary course should be repeated.

Immunogenicity safety and tolerability

Safety and immunogenicity were studied in Bangladeshi children ($n = 340$) aged 6-18 months. The results showed that two doses of the vaccine were safe and induced antibacterial (vibriocidal) antibody responses in 57% of the children and antitoxin responses in 85%. Immune responses were comparable after the administration of one and two doses. Administering the vaccines without buffer or in water did not affect vibriocidal responses. This study demonstrates that the vaccine is safe and immunogenic in children under 2 years of age and that simple interventions can enhance immune responses in young children [83].

In the Bangladesh Field Trial (1985) protective efficacy against cholera in adults and children aged ≥ 6 years was evaluated, and short-term protection was detected in 85% of subjects [84].

In children aged 2-5 years in Mozambique, Dukoral® provided protection for 6 months [78% protection (CI 39-92%)] [85]. Herd immunity was also registered in non-vaccinated individuals [86, 87].

Recently, Dukoral® was evaluated in a clinical trial: healthy volunteers (n = 21) and renal transplant recipients (n = 30) were vaccinated with the oral whole cell/recombinant B subunit cholera vaccine Dukoral®. The vaccine was administered at the baseline and on day 14. The results showed that more than half of the transplant recipients seroconverted, and adverse events were mild to moderate and transient [88].

Several studies have investigated the cross-protection of Dukoral® against enterotoxigenic Escherichia coli [84, 89, 90]. In particular, one study found that the protective efficacy against cholera was 85% and protection against the toxin of enterotoxigenic Escherichia coli reached 67% [90].

S. typhi and cholera: similarities and differences

Concerning similarities, TF and cholera are both transmitted through the oro-fecal route. Owing to poor sanitary conditions and lack of safe drinking water, which are often associated with poverty and deprivation, developing countries are most severely affected by these diseases [91].

In the 19th and 20th centuries, oro-fecal transmissible diseases were endemic in many areas of the world, including Europe and the Americas. After the widespread introduction of chlorination, sand filtration and other practical preventive methods of water sanification, the spread of oro-fecal diseases decreased drastically worldwide. Today, the WHO is actively involved in reducing the transmission of diseases caused by critical health conditions, particularly in middle- and low-income countries.

The new WHO Guidelines on Sanitation and Health [92] summarize the evidence on the effectiveness of a range of sanitation interventions and provide a comprehensive framework for health-protecting sanitation; this covers policy and governance measures, the implementation of sanitation technologies, systems and behavioral interventions, and monitoring approaches.

Critically, the guidelines detail the role of the health sector in identifying gaps in sanitation interventions, in order to guide future research efforts and to improve and maximize the effectiveness of sanitation interventions on the health of the population (a WHO study in 2012 calculated that for every US$ 1.00 invested in sanitation there was a return of US$ 5.50 in lower health costs, increased productivity, and fewer premature deaths). Indeed, the benefits of improved sanitation extend well beyond reducing the risk of diarrheal disease.

Importance of vaccination in fighting antimicrobial resistance

Today, antimicrobial resistance has grown enormously, and many pathogenic bacteria are resistant to multiple antibiotics, including such micro-organisms as *Vibrio cholerae* and *S. typhi*. Consequently, multi-drug resistance is now one of the most alarming emerging problem associated with infectious diseases. On the other hand, vaccines can prevent infectious diseases and can yield a much longer-lasting control of infections. Indeed, vaccines can control infections over a long period of time without becoming obsolete. This characteristic is due to the fact that vaccines work prophylactically and prevent the start of infections, while drugs work therapeutically on an ongoing infection in which bacteria proliferate and mutate, allowing the drug to select resistant variants [93].

Regarding *S. typhi*, since 2001, the complete genome sequence of multiple drug-resistant *S. typhi* has been mapped and the genes of resistance to the antibiotics commonly used in the treatment of typhoid fever, especially fluoroquinolones, have been identified [94]. Infection caused by multiple drug-resistant strains has

been documented to be associated with more severe illness and higher rates of complications and death, and with a higher rate of prolonged asymptomatic carrier status [95].
In 2016 in Pakistan, an outbreak of Salmonella enterica (ssp. enterica serovar typhi), resistant to chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole, fluoroquinolones and third-generation cephalosporins, was observed. More than 1000 cases were registered and laboratory confirmed. The outbreak was caused by the H58 clade, a multidrug-resistant haplotype of S. typhi, common in Asia and in some African areas. As reported by the authors, multi-resistant *S. typhi* involved a densely populated area of Asia where adequate sanitation, water and infrastructure were lacking [96].
With regard to cholera, multidrug-resistant isolates are emerging, particularly in Southern Asia, with resistance to quinolones, trimethoprim-sulfamethoxazole and tetracycline.
A variety of mechanisms of antimicrobial resistance have been identified in *Vibrio cholerae*, including efflux pumps, chromosomal mutations and mobile genetic elements such as plasmids and SXT elements. Antibiotics are often used in combination with rehydration therapy, as they are believed to relieve the symptoms of cholera faster than rehydration treatment alone, and because a shorter disease duration lessens the transmission of infectious *Vibrio cholerae*. Because antibiotics are widely used as part of the cholera treatment regimen, the number of pathogenic *Vibrio cholerae* strains resistant to one or more antibiotics is increasing [97]. To prevent the spread of resistance, it is crucial to limit the use of antibiotics in cholera patients and to implement alternative strategies and novel approaches in managing this disease.
The WHO does not advise the prophylactic administration of antibiotics in travelers coming from or going to a country affected by cholera. Indeed, routine treatment with antibiotics, or preventive chemoprophylaxis, has no effect on the spread of cholera. On the contrary, the use of antibiotics can have adverse effects by increasing antimicrobial resistance.
Although TF and cholera seem to be similar diseases, they display some different features in terms of geographical distribution, pathogenesis, clinical presentation, prognosis and mortality.
Regarding their geographical distribution, TF has a high incidence in sub-Saharan Africa, India and south-east Asia, while cholera has a high incidence in a few African countries, particularly in the Horn of Africa and the Arabian Peninsula (Fig. 1 and Fig. 3).
Cholera has a worse prognosis than TF during the acute phase of the disease, mainly owing to profuse watery diarrhea and vomiting, which cause massive dehydration. If untreated, 50% of severe cases are fatal, while proper treatment and fluid replacement reduce mortality to less than 1% [98]. Mortality is higher in children, especially those under 5 years of age.

International travel and migration

With modern air travel, transmissible diseases can spread across continents and oceans in a few days, constituting a threat to public health. Indeed, it takes only 36 hours to travel around the world by plane; a time much shorter than the incubation period of most infectious diseases [99].
In 1950, international travelers numbered just over 25 million, while according to estimates by the United Nations World Tourism Organization (UNWTO) they could become 1.3 billion by 2020. Over 700 million travelers could be exposed to an increased risk of contracting infectious diseases, owing to changes in their habits, different weather conditions (cold, heat, humidity, exposure to the sun or wind) and the consumption of unsafe food. Asia and the Pacific area, which account for 37% of the world's international tourism expenditure and nearly one-fourth of global arrivals, play a vital role in global tourism, as both an inbound and an outbound market. The increase in international travel in these areas is due to major infrastructure and socio-economic development [100].
Nowadays, people travel for many reasons, such as tourism and business. Several surveys have shown that a high proportion of travelers, whether tourists or businesspeople, lack adequate information on safety issues, such as timely vaccination and prophylactic medications. Indeed, only a small number of travelers seek advice from the Travel Medicine clinic, particularly with regard to vaccinations. Notably, the pre-travel planning of vaccinations is a complex operation that requires adequate medical support and proper timing.
In a cross-sectional, multicenter study, the European Travel Health Advisory Board (ETHAB) used a self-administered anonymous questionnaire to evaluate current travel health knowledge, attitudes and practices and to determine where travelers to developing countries obtained travel health information, what information they received, and what preventive health measures they implemented. The survey was conducted at several airports in Europe, Asia, South Africa and the United States. The questionnaire [101], which was distributed at the departure gate, gathered information on: personal characteristics (age, gender, nationality, country of residence and profession); the journey undertaken (destination countries, type of region, purpose, duration, travel companions) and travelers' knowledge, attitudes and practices (timing of travel preparation, source and timing of travel health information, planned food habits and restrictions, perceived risk of specific infectious diseases, perception and status of vaccinations, contents of travel health kit) regarding malaria and vaccine-preventable travel-related diseases. The results obtained from a total of 5,465 questionnaires showed that the majority of travelers (73.3%) had sought general information about their destination prior to departure, but only just over half of the respondents (52.1%) had sought travel health advice. Tourists and people traveling for religious reasons had sought travel health advice more often, whereas those visiting

friends and relatives were less likely to do so. Hepatitis A was perceived as the most common infectious disease, followed by HIV and hepatitis B. When all participants were asked to score the risk of vaccine-preventable diseases, between one-quarter and one-third of respondents stated that they did not know the risk concerning the respective diseases; some 40% could not assess the risk at all, and 10% to 15% did not answer this question. Ignorance was highest with regard to rabies, TF and cholera [101].

Many characteristics of the journey (duration, destination, etc.) can influence decisions regarding the preventive and prophylactic strategies to adopt. For example, the strongest and most consistent predictor of typhoid risk in travelers is the trip destination: 1/3,000 in travelers to South Asia (high risk), 1/50,000-100,000 Sub-Saharan Africa, North Africa and the Middle East or South America (intermediate risk) and < 1/300,000 in travelers to the Caribbean and Central America (low risk) [102].

A review published in 2005 confirmed that the risk to travelers appears to vary by geographic region visited, with travel to the Indian subcontinent accounting for the greatest risk of acquiring typhoid fever. The overall risk of contracting TF during travel to the Indian subcontinent was 18 times higher than in any other geographic area [103]. Many cases acquired in the Indian subcontinent were multidrug-resistant, as fluoroquinolone resistance is on the rise in this geographical area.

A special category at higher risk of contracting TF is that of travelers who visit relatives (emigrants returning to their homeland). These subjects are less likely to have received pre-travel advice, less likely to adopt food and water precautions and, perhaps most importantly, by and large do not perceive their risk or undergo typhoid vaccination before traveling [104].

Regarding the risk of cholera, with the growth of international travel by sea and air, cases of food-borne transmission of cholera have increased. Indeed, in addition to contaminated water, certain foodstuffs are particularly at risk of transmitting the disease: seafood, including fish, shellfish, crabs, oysters and clams, and other foods that can easily be contaminated during preparation in unhygienic food factories or by infected food handlers [105]. Transportation systems and trade routes have greatly improved and expanded worldwide, and the ease and speed of migration mean that cholera is still a global health challenge. Confirmation that cholera is still a public health threat associated with migration and the rapid movement of people is provided by the recent outbreak reported in Algeria. As referred by the European Centre for Disease Prevention and Control, as of 30 August 2018, Algeria reported 74 confirmed cholera cases in six northern and coastal areas of the country. This was the first cholera outbreak reported in Algeria in more than 20 years. Cases were reported in both rural and urban areas, including the capital. A water source was found to be contaminated with *Vibrio cholerae*. On the basis of the number of cases and the geographical extension of the outbreak, additional cases are expected to be reported.

Conclusion

Not only are cholera and TF a severe threat to the populations of low- and middle-income countries, these diseases may also affect travelers to endemic areas. The preventive measures to be adopted in the case of travel to countries where these diseases are still endemic are well known: the adoption of safe practices and vaccinations [24]. It is important to stress that an effective strategy should be based both on vaccinations and on hygiene travel guidelines. It is commonly believed that chances of developing gastrointestinal illness will be reduced considerably by being counselled to "boil it, cook it, peel it, or forget it." However, surveys of returning travellers have shown that receiving advice about food and drink safety appears to have no significant effect on rates of diarrhoea. Indeed, many travellers will commit a food and beverage indiscretion within 72 hours after arrival in a developing country, despite pre-departure counselling. Standard protective measures are always recommended such as: wash your hands thoroughly before eating food, avoid consuming raw foods (meat, fish, shellfish, vegetables and more), with the exception of personally peeled fruits, take well-cooked foods and not re-warmed; avoid milk that has not been previously boiled, pasteurized or sterilized, ice creams, cakes with cream, cream, raw egg sauces (like mayonnaise), fresh cheeses. Don't buy food and drinks from street vendors and drink only from sealed bottles (if this is not possible, boil the water) [106, 107].

TF is one of the main causes of death due to food-borne infections, and results in the greatest loss of Disability-Adjusted Life years (DALYs) worldwide [24]. Given that man is the only host of *S. typhi*, an effective vaccination strategy could limit the spread of disease and reduce its burden, especially in endemic areas [6]. Furthermore, the emergence of multidrug-resistant strains is becoming a serious problem in the clinical treatment of the disease. For this reason, vaccination is the main solution.

The WHO has set the goal of eliminating cholera by 2030. To achieve this objective, it is essential to support the efforts of low-income countries to strengthen their capacities for preparedness, early detection, laboratory confirmation and immediate effective response to outbreaks. In addition, travelers must be fully informed of the risk of disease and be vaccinated before their departure for at-risk areas. Although safe drinking water and advanced sanitation systems have made cholera a treatable and limited illness in Europe and North America, the emergence of new *Vibrio cholerae* strains, the ease of travel and the increased migration of possibly infected individuals have raised serious public health concerns.

Today, people of all ages commonly travel to developing countries for a variety of different reasons. The common objective should be to help travelers stay healthy while abroad, and thus also to reduce the potential importation of infectious diseases and its consequent implications for public health and society [108]. Indeed, the consequences of returning from abroad with an infectious disease can extend beyond the infected individual, in that

they may also involve travelers' relatives, people with whom they have close contact, or the wider community. Thus, prophylactic travel health measures do not only benefit individuals, but also public health [101, 109].
Initiatives to enhance the awareness of travelers should target all groups, including business travelers, those visiting friends and relatives, and the elderly. Nowadays, travelling isn't just a matter for young and adult people: in the last years, the number of older travelers have increased. Older travelers have been encouraged by the greater ease of access to cheap and rapid modes of transport [110].
Obviously, older travels are often patients, with chronic diseases and other medical conditions: for example, lower respiratory tract infections, urinary tract infections and cardiovascular disease. in order to taking account of the special considerations for safe prescription, general practitioners, geriatricians and other healthcare professionals should cooperate with specialist travel medicine clinics [111]. Moreover, the immunosenescence in elderly people is also important in travel medicine, because it could reduce vaccines immunogenicity and could increase the risk of travel-related infectious diseases. For this reason older travelers, need a pre-travel consultation, preferably earlier than others travelers, to have an adequate time to respond to vaccinations, even if they are healthy, without immunosuppressing/immunocompromising conditions [112]. Additionally, the providers of travel health advice should continue to urge travelers to comply with the pertinent recommendations.
A large and growing number of "free and independent travelers", identifiable as a "consumer class", especially young travelers aged 15-34 years ("millennials"), use online travel agencies and mobile technology to make faster and simpler bookings through online (and more affordable) tourism platforms. These changes in travel habits should prompt different information strategies, e.g. the use of social media and collaboration between public health organizations and the most widely used travel websites.

Acknowledgements

Funding sources: the Department of Health Sciences, University of Genoa, received a grant from Emergent, Italy.

Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

DA and DP conceived and designed the overview. All the authors contributed to the literature search and the writing of the manuscript. DA, DP and RTM critically revised the manuscript. All authors read and approved the final version of the manuscript.

References

[1] GBD Diarrhoeal Diseases Collaborators. Estimates of global, regional, and national morbidity, mortality, and aetiologies of diarrhoeal diseases: a systematic analysis for the Global Burden of Disease Study 2015. Lancet Infect Dis 2017;17:909-48. https://doi.org/10.1016/S1473 3099(17)30276-1

[2] CDC. Newton AE, Routh JA, Mahon BE. Infectious Diseases Related Travel. Chapter 3. Typhoid & Paratyphoid fever. Available at: https://wwwnc.cdc.gov/travel/yellowbook/2016/infectious-diseases-related-to-ravel/typhoid-paratyphoid-fever [Accessed on 30/05/2019].

[3] Popoff MY, Bockemühl J, Gheesling LL. Supplement 2002 (no. 46) to the Kauffmann-White scheme. Res Microbiol 2004;155:568-70.

[4] World Health Organization (WHO). Guidelines on the quality, safety and efficacy of typhoid conjugate vaccines. Available at: http://www.who.int/biologicals/areas/vaccines/TYPHOID_BS2215_doc_v1.14_WEB_VERSION.pdf?ua=1&ua=1 [Accessed on 21/02/2019].

[5] Crump JA, Sjölund-Karlsson M, Gordon MA, Parry CM. Epidemiology, clinical presentation, laboratory diagnosis, antimicrobial resistance, and antimicrobial management of invasive Salmonella infections. Clin Microbiol Rev 2015;28:901-37. https://doi.org/10.1128/CMR.00002-15

[6] Anwar E, Goldberg E, Fraser A, Acosta CJ, Paul M, Leibovici L.Vaccines for preventing typhoid fever. Cochrane Database Syst Rev 2014;(1):CD001261. https://doi.org/10.1002/14651858.CD001261.pub3

[7] CDC. Health information for international travel. The yellow book 2016. Oxford University Press. Available at: https://wwwnc.cdc.gov/travel/page/yellowbook-home-2014/ [Accessed on 30/05/2019].

[8] Crump JA, Mintz ED. Global trends in typhoid and paratyphoid fever. Clin Infect Dis 2010;50:241-6. https://doi.org/10.1086/649541

[9] World Health Organization. The diagnosis, treatment and prevention of typhoid fever. WHO/V&B/03.17. Geneva, Switzerland: WHO, 2003.

[10] Bhan MK, Bahl R, Bhatnagar S. Typhoid and paratyphoid fever. Lancet 2005;366:749-62.

[11] Maskey AP, Day JN, Tuan PQ, 2 Thwaites GE, Campbell JI, Zimmerman M, Farrar J, Basnyat B. Salmonella enterica Serovar Paratyphi A and S. enterica Serovar typhi cause indistinguishable clinical syndromes in Kathmandu, Nepal. Clinical Infectious Diseases 2006;42:1247-53.

[12] CDC. Health information for international travel. The yellow book 2016. Oxford University Press. Available at: https://wwwnc. cdc.gov/travel/page/yellowbook-home-2014/ [Accessed on 20/01/2017].

[13] Steele AD, Hay Burgess DC, Diaz Z, Carey ME, Zaidi AK. Challenges and opportunities for typhoid fever control: a call for coordinated action. Clin Infect Dis 2016;62(Suppl 1):S4-8. https://doi.org/10.1093/cid/civ976

[14] GBD 2017 Typhoid and Paratyphoid Collaborators. The global burden of typhoid and paratyphoid fevers: a systematic analysis for the Global Burden of Disease Study 2017. Lancet Infect Dis 2019;19:369-81. https://doi.org/10.1016/S1473-3099(18)30685-6

[15] Buckle GC, Walker CL, Black RE. Typhoid fever and para- typhoid fever: Systematic review to estimate global morbidity and mortality for 2010. J Glob Health.2012;2:010401. https://doi.org/10.7189/jogh.02.010401

[16] Kirk MD, Pires SM, Black RE, Caipo M, Crump JA, Dev-

leess- chauwer B, Döpfer D, Fazil A, Fischer-Walker CL, Hald T, Hall AJ, Keddy KH, Lake RJ, Lanata CF, Torgerson PR, Havelaar AH, Angulo FJ. World Health Organization estimates of the global and regional disease burden of 22 foodborne bacterial, protozoal, and viral diseases, 2010: a data synthesis. PLoS Med 2015;12:e1001921. https://doi.org/10.1371/journal.pmed.1001921. eCollection 2015

[17] Wain J, Hendriksen RS, Mikoleit ML, Keddy KH, Ochiai RL. Typhoid fever. Lancet 2015;385:1136-45. https://doi.org/10.1016/S0140-6736(13)62708-7

[18] Prüss-Ustün A, Bartram J, Clasen T, Colford JM Jr, Cumming O, Curtis V, Bonjour S, Dangour AD, De France J, Fewtrell L, Freeman MC, Gordon B, Hunter PR, Johnston RB, Mathers C, Mäusezahl D, Medlicott K, Neira M, Stocks M, Wolf J, Cairncross S. Burden of disease from inadequate water, sanitation and hygiene in low- and middle-income settings: a retrospective analysis of data from 145 countries. Trop Med Int Health 2014;19:894-905. Epub 2014 Apr 30. https://doi.org/10.1111/tmi.12329

[19] Mogasale V, Maskery B, Ochiai RL, Lee JS, Mogasale VV, Ramani E, Kim YE, Park JK, Wierzba TF. Burden of typhoid fever in low-income and middle-income countries: a systematic, literature-based update with risk-factor adjustment. Lancet Glob Health 2014;2:e570-80. https://doi.org/10.1016/S2214-109X(14)70301-8

[20] Antillón M, Warren JL, Crawford FW, Weinberger DM, Kürüm E, Pak GD, Marks F, Pitzer VE. The burden of typhoid fever in low- and middle-income countries: a meta-regression approach. PLoS Negl Trop Dis 2017;11:e0005376. https://doi.org/10.1371/journal.pntd.0005376

[21] Marchello CS, Hong CY, Crump JA. Global typhoid fever incidence: a systematic review and meta-analysis. Clin Infect Dis 2019;68(S2):S105-16. https://doi.org/10.1093/cid/ciy1094

[22] Franco-Paredes C, Khan MI, Gonzalez-Diaz E, Santos-Preciado JI, Rodriguez-Morales AJ, Gotuzzo E. Enteric fever: a slow response to an old plague. PLoS Negl Trop Dis 2016;10:e0004597. https://doi.org/10.1371/journal.pntd.0004597

[23] Amicizia D, Arata L, Zangrillo F, Panatto D, Gasparini R. Overview of the impact of Typhoid and Paratyphoid fever. Utility of Ty21a vaccine (Vivotif®). J Prev Med Hyg 2017;58:E1-E8.

[24] Levine MM. Typhoid fever vaccines. In: Plotkin SA, Orenstein WA, Offit PA, eds. Vaccines. 6t^{h} ed. Philadelphia, PA: Elsevier Saunders 2012, pp. 812-36.

[25] AIFA. Summary of the product Characteristic. Available at: https://farmaci.agenziafarmaco.gov.it/aifa/servlet/PdfDownloadServlet?pdfFileName=footer_004969_025219_RCP.pdf&retry=0&sys=m0b1l3. [Accessed on 23/07/2019].

[26] Nisini R, Biselli R, Matricardi PM, Fattorossi A, D'Amelio R. Clinical and immunological response to typhoid vaccination with parenteral or oral vaccines in two groups of 30 recruits. Vaccine 1993;11:582-6.

[27] Cryz SJ, Jr, Vanprapar N, Thisyakorn U, Olanratmanee T, Losonsky G, Levine MM, Chearskul S. Safety and immunogenicity of Salmonella typhi Ty21a vaccine in young Thai children. Infection Immunity 1993;61:1149-51.

[28] Gilman RH, Hornick RB, Woodard WE, DuPont HL, Snyder MJ, Levine MM, Libonati JP. Evaluation of a UDP-glucose-4-epimeraseless mutant of Salmonella typhi as a liver oral vaccine. J Infect Dis.1977;136:717-23.

[29] Wahdan MH, Serie C, Germanier R, Lackany A, Cerisier Y, Guerin N, Sallam S, Geoffroy P, el Tantawi AS, Guesry P. A controlled field trial of live oral typhoid vaccine Ty21a. Bulletin of the World Health Organization 1980;58:469-74.

[30] Levine MM, Ferreccio C, Black RE, Germanier R. Large-scale field trial of Ty21a live oral typhoid vaccine in enteric-coated capsule formulation. Lancet 1987;1:1049-52.

[31] Levine MM, Ferreccio C, Abrego P, Martin OS, Ortiz E, Cryz S. Duration of efficacy of Ty21a, attenuated Salmonella typhi live oral vaccine. Vaccine 1999;17(Suppl 2):S22-27.

[32] Bhuiyan TR, Choudhury FK, Khanam F, Saha A, Sayeed MA, Salma U, Lundgren A, Sack DA, Svennerholm AM, Qadri F. Evaluation of immune responses to an oral typhoid vaccine, Ty21a, in children from 2 to 5 years of age in Bangladesh. Vaccine 2014;32:1055-60. https://doi.org/10.1016/j.vaccine.2014.01.001

[33] Jackson BR, Iqbal S, Mahon B; Centers for Disease Control and Prevention (CDC). Updated recommendations for the use of typhoid vaccine - Advisory Committee on Immunization Practices, United States, 2015. MWR Morb Mortal Wkly Rep 2015;64:305-8.

[34] Date KA, Bentsi-Enchill A, Marks F, Fox K. Typhoid fever vaccination strategies. Vaccine 2015;33(Suppl 3):C55-61. https://doi.org/10.1016/j.vaccine.2015.04.028.

[35] FDA Typhoid VI polysaccharide vaccine Typhim vi®. Available at https://www.fda.gov/media/75993/download [Accessed on 20/02/2019].

[36] Acharya IL1 Lowe CU, Thapa R, Gurubacharya VL, Shrestha MB, Cadoz M, Schulz D, Armand J, Bryla DA, Trollfors B. Prevention of typhoid fever in Nepal with the Vi capsular polysaccharide of Salmonella typhi: a preliminary report. N Engl J Med 1987;317:1101-4.

[37] Tacket CO, Ferreccio C, Robbins JB, Tsai CM, Schulz D, Cadoz M, Goudeau A, Levine MM. Safety and immunogenicity of two Salmonella typhi Vi capsular polysaccharide vaccines. J Infect Dis 1986;154:342-5.

[38] Kaper JB, Morris JG, Levine MM. Cholera. Clin Microbiol Rev 1995;8:48-86.

[39] Faruque SM, Albert MJ, Mekalanos JJ. . Epidemiology, genetics, and ecology of toxigenic Vibrio cholerae. Microbiol Mol Biol Rev 1998;62:1301-14.

[40] Clemens JD. Cholera vaccines. In: Plotkin SA, Orenstein WA, Offit PA, eds. Vaccines. 7th edition. Philadelphia, PA: WB Saunders Company 2017, Chapter 14.

[41] Mukhopadhyay AK, Takeda Y, Nair GB. Cholera outbreaks in the El Tor biotype era and the impact of the new El Tor variants. Curr Top Microbiol Immunol 2014;379:17-47.

[42] Faruque AS, Fuchs GJ, Albert MJ.Changing epidemiology of cholera due to Vibrio cholerae O1 and O139 Bengal in Dhaka, Bangladesh. Epidemiol Infect 1996;116:275-8.

[43] Siddique AK, Zaman K, Akram K, Mutsuddy P, Eusof A, Sack RB. Emergence of a new epidemic strain of Vibrio cholerae in Bangladesh. An epidemiological study. Trop Geogr Med 1994;46:147-50.

[44] Grim CJ, Hasan NA, Taviani E, Haley B, Chun J, Brettin TS, Bruce DC, Detter JC, Han CS, Chertkov O, Challacombe J, Huq A, Nair GB, Colwell RR. Genome sequence of hybrid *Vibrio cholera* O1 MJ-1236, B-33, and CIRS101 and comparative genomics with *V. cholerae*. J Bacteriol 2010;192:3524-33.

[45] Kanungo S, Sah BK, Lopez AL, Sung JS, Paisley AM, Sur D, Clemens JD, Nair GB. Cholera in India: an analysis of reports, 1997-2006. Bull World Health Organ 2010;88:185-91.

[46] Siddique AK, Nair GB, Alam M, Sack DA, Huq A, Nizam A, Longini IM, Qadri F, Faruque SM, Colwell RR, Ahmed S, Iqbal A, Bhuiyan NA, Sack RB. El Tor cholera with severe disease: a new threat to Asia and beyond. Epidemiol Infect. 2010;138:347-52.

[47] Piarroux R, Barrais R, Faucher B, Haus R, Piarroux M, Gaudart J, Magloire R, Didier R. Understanding the Cholera Epidemic, Haiti. Emerg Infect Dis 2011;17:1161-7.

[48] Conner JG, Teschler JK, Jones CJ, Yildiz FH. Staying alive: vibrio cholerae's cycle of environmental survival, transmission, and dissemination. Microbiol Spect. 2016;4(2). https://doi.org/10.1128/microbiolspec

[49] Barr AJ. The biochemical basis of disease. Essays Biochem 2018;62:619-42. https://doi.org/10.1042/EBC20170054

[50] Cholera vaccines: WHO position paper – August 2017. Wkly Epidemiol Rec 201;92:477-98.

[51] Charles RC, Ryan ET. Cholera in the 21st century. Curr Opin Infect Dis 2011;24:472-7.

[52] Clemens JD, Nair GB, Ahmed T, Qadri F, Holmgren J. Cholera. Lancet 2017;390:1539-49. https://doi.org/10.1016/S0140-6736(17)30559-7

[53] Chowdhury F, Khan AI, Harris JB, LaRocque RC, Chowdhury MI, Ryan ET, Faruque ASG, Calderwood SB, Qadri F. A comparison of clinical and immunologic features in children and older patients hospitalized with severe cholera in Bangladesh. Pediatr Infect Dis J 2008;27:986-92.

[54] Harris JB, Khan AI, LaRocque RC, Dorer DJ, Chowdhury F, Faruque ASG, Sack DA, Ryan ET, Qadri F, Calderwood SB. Blood group, immunity, and risk of infection with Vibrio cholerae in an area of endemicity. Infect Immun 2005;73:7422–7.

[55] Harris JB, LaRocque RC, Chowdhury F, Khan AI, Logvinenko T, Faruque ASG, Ryan ET, Qadri F, Calderwood SB. Susceptibility to Vibrio cholerae infection in a cohort of household contacts of patients with cholera in Bangladesh. PLoS Negl Trop Dis 2008;2:e221. https://doi.org/10.1371/journal.pntd.0000221

[56] Holmner A, Mackenzie A, Krengel U. Molecular basis of cholera blood-group dependence and implications for a world characterized by climate change. FEBS Lett 2010;584:2548-55.

[57] Hannah G. Davies, Conor Bowman, Stephen P. Luby. Cholera – management and prevention. J Infect 2017;74: S66-S73.

[58] Watson JT, Gayer M, Connolly MA. Epidemics after natural disasters. Emerg Infect Dis 2007;13:1-5.

[59] Ali M, Nelson AR, Lopez AL, Sack DA. Updated global burden of cholera in endemic countries. PLoS Negl Trop Dis 2015;9:e0003832. https://doi.org/10.1371/journal.pntd.0003832

[60] WHO (2014) Cholera surveillance and number of cases. Geneva: World Health Organization.

[61] Griffith DC, Kelly-Hope LA, Miller MA. Review of reported cholera outbreaks worldwide, 1995-2005. Am J Trop Med Hyg 2006;75:973-7.

[62] Zuckerman JN, Rombo L, Fisch A. The true burden and risk of cholera: implications for prevention and control. Lancet Infect Dis 2007;7:521-30.

[63] Masuet Aumatell C, Ramon Torrell JM, Zuckerman JN Review of oral cholera vaccines: efficacy in young children. Infect Drug Resist 2011;4:155-60. https://doi.org/10.2147/IDR.S10339

[64] Legros D; Partners of the Global Task Force on Cholera Control. Global cholera epidemiology: opportunities to reduce the burden of cholera by 2030. J Infect Dis 2018;218(suppl_3):S137-S140. https://doi.org/10.1093/infdis/jiy486_

[65] Hamilton KL. Robert K. Crane-Na(+)-glucose cotransporter to cure? Front Physiol 2013;4:53.

[66] Dutta D, Chowdhury G, Pazhani GP, Guin S, Dutta S, Ghosh S, Rajendran K, Nandy RK, Mukhopadhyay AK, Bhattacharya MK, Mitra U, Takeda Y, Nair GB, Ramamurthy T. Vibrio cholerae non-O1, non-O139 serogroups and cholera-like diarrhea, Kolkata, India. Emerging Infect Dis 2013;19:464-7.

[67] World Health Organization. Cholera, 2017. Wkly Epidemiol Rec 2018;93:489-500.

[68] Communicable Disease Threats Report Week 38, 16-22 September 2018.

[69] World Health Organization. Communicable diseases following natural disasters [Internet]. 1211 Geneva 27 Switzerland; 2006. Report No.: WHO/CDS/NTD/DCE/2006.4. Available at: http://www.who.int/diseasecontrol_emergencies/guidelines/CD_Disasters_26_06.pdf. [Accessed on 30/03/2019].

[70] Jutla A, Khan R, Colwell R. Natural disasters and cholera outbreaks: current understanding and future outlook. Curr Environ Health Rep 2017;4:99-107. https://doi.org/10.1007/s40572-017-0132-5

[71] Outbreak surveillance and response in humanitarian emergencies WHO guidelines for EWARN implementation. Geneva, 2012.

[72] Amar PK. Ensuring safe water in post-chemical, biological, radiological and nuclear emergencies. J Pharm Bioallied Sci 2010;2:253-66. https://doi.org/10.4103/0975-7406.68508

[73] Hove-Musekwa SD, Nyabadza F, Chiyaka C, Das P, Tripathi A, Mukandavire Z. Modelling and analysis of the effects of malnutrition in the spread of cholera. Mathematical and Computer Modelling 2011;53:1583-95. https://doi.org/10.1016/j.mcm.2010.11.060

[74] Cholera: risk factors. Available at: http://www.mayoclinic.com/health/cholera/ds00579/dsection=risk-factors. [Accessed 20/02/2019].

[75] Gaffga NH, Tauxe RV, Mintz ED. Cholera: a new homeland in Africa? Am J Trop Med Hyg 2007;77:705-13.

[76] Alam M, Hasan NA, Sadique A, Bhuiyan NA, Ahmed KU, Nusrin S, Nair GB, Siddique AK, Sack RB, Sack DA, Huq A, Colwell RR. Seasonal cholera caused by Vibrio cholerae serogroups O1 and O139 in the coastal aquatic environment of Bangladesh. Appl Environ Microbiol 2006;72:4096-104. https://doi.org/10.1128/AEM.00066- 06

[77] Singleton FL, Attwell RW, Jangi MS, Colwell RR. Influence of salinity and organic nutrient concentration on survival and growth of Vibrio cholerae in aquatic microcosms. Appl Environ Microbiol 1982;43:1080-5.

[78] Lara RJ, Neogi SB, Islam MS, Mahmud ZH, Yamasaki S, Nair GB. Influence of catastrophic climatic events and human waste on vibrio distribution in the Karnaphuli Estuary, Bangladesh. Eco Health 2009;6:279. https://doi.org/10.1007/s10393-009-0257-6

[79] Leaning J, Guha-Sapir D. Natural disasters, armed conflict, and public health. N Engl J Med 2013;369:1836-42. https://doi.org/10.1056 /NEJMra1109877

[80] McMichael A. Human population health: sentinel criterion of environmental sustainability. Curr Opin Environ Sustain. 2009;1:101- 6. https://doi.org/10.1016/j.cosust.2009.07.001

[81] EM DAT. The OFDA/CRED International Disaster Database [Internet]. 2016. Available at: http://www.emdat.be/classification [Accessed on 30/03/2019].

[82] EMA. Summary of the product Characteristic. Available at: https://ec.europa.eu/health/documents/community-register/2015/20150408131570/anx_131570_en.pdf. [Accessed on 20/02/2019].

[83] Ahmed T, Svennerholm AM, Al Tarique A, Sultana GN, Qadri F. Enhanced immunogenicity of an oral inactivated cholera vaccine in infants in Bangladesh obtained by zinc supplementation and by temporary withholding breast-feeding.Vaccine 2009;27:1433-9. https://doi.org/10.1016/j.vaccine.2008.12.036

[84] Clemens JD, Sack DA, Harris JR, Chakraborty J, Khan MR, Stanton BF, Kay BA, Khan MU, Yunus M, Atkinson W. Field trial of oral cholera vaccines in Bangladesh. Lancet 1986;2:124-7. https://doi.org/10.1016/S0140-6736(86)91944-6.

[85] Lucas ME, Deen JL, von Seidlein L, Wang XY, Ampuero J, Puri M, Ali M, Ansaruzzaman M, Amos J, Macuamule A, Cavailler P, Guerin PJ, Mahoudeau C, Kahozi-Sangwa P, Chaignat CL, Barreto A, Songane FF, Clemens JD. Effectiveness of mass oral cholera vaccination in Beira, Mozambique. N Engl J Med 2005;352:757-67.

[86] Ali M, Emch M, von Seidlein L, Yunus M, Sack DA, Rao M, Holmgren J, Clemens JD. Herd immunity conferred by killed oral cholera vaccines in Bangladesh: a reanalysis. Lancet 2005;366:44-9.

[87] Longini IM Jr, Nizam A, Ali M, Yunus M, Shenvi N, Clemens JD. Controlling endemic cholera with oral vaccines. PLoS Med 2007;4:e336.

[88] Jonker EFF, Uijlings MAC, Visser LG, Soonawala D. Comparison of the immunogenicity of Dukoral® oral cholera vaccine between renal transplant recipients on either a calcineurin inhibitor or mycophenolate - A controlled trial. Vaccine

2019;37:3133-9. https://doi.org/10.1016/j.vaccine.2019.04.010

[89] Clemens JD, Harris JR, Sack DA, Chakraborty J, Ahmed F, Stanton BF, et al. Field trial of oral cholera vaccines in Bangladesh: results of one year of follow-up. J Infect Dis 1988;158:60–9. https://doi.org/10.1093/infdis/158.1.60

[90] Jeline T, Kollaritsch H. Vaccination with Dukoral against travelers' diarrhea (ETEC) and cholera. Expert Rev Vaccines 2008;7:561-7. https://doi.org/10.1586/14760584.7.5.561

[91] WHO Water, sanitation and hygiene interventions and the prevention of diarrhea. Available at https://www.who.int/elena/titles/bbc/wsh_diarrhoea/en/. [Accessed on 22/03/2019].

[92] WHO Guidelines on sanitation and health. Available at: https://www.who.int/water_sanitation_health/sanitation-waste/sanitation/sanitation-guidelines/en/ [Accessed on 30/03/2019].

[93] Tagliabue A, Rappuoli R. Changing Priorities in Vaccinology: Antibiotic Resistance Moving to the Top. Front Immunol 2018; 9:1068. https://doi.org/10.3389/fimmu.2018.01068

[94] Parkhill J, Dougan G, James KD, Thomson NR, Pickard D, Wain J, Churcher C, Mungall KL, Bentley SD, Holden MT, Sebaihia M, Baker S, Basham D, Brooks K, Chillingworth T, Connerton P, Cronin A, Davis P, Davies RM, Dowd L, White N, Farrar J, Feltwell T, Hamlin N, Haque A, Hien TT, Holroyd S, Jagels K, Krogh A, Larsen TS, Leather S, Moule S, O'Gaora P, Parry C, Quail M, Rutherford K, Simmonds M, Skelton J, Stevens K, Whitehead S, Barrell BG. Complete genome sequence of a multiple drug resistant Salmonella enterica serovar Typhi CT18. Nature 2001;413:848-52.

[95] WHO. Typhoid vaccines: WHO position paper. Wkly Epidemiol Rec 2008;83:49-59.

[96] ClinicalTrials.gov Available at: https://clinicaltrials.gov/ct2/show/NCT03220737?term=CVD103-HgR&cond=Cholera&rank=8

[97] Kitaoka M, Miyata ST, Unterweger D, Pukatzki S. Antibiotic resistance mechanisms of Vibrio cholerae. J Med Microbiol 2011;60(Pt 4):397-407. https://doi.org/10.1099/jmm.0.023051-0

[98] Saulat J. Cholera - Epidemiology, Prevention and Control 2016 Capter 6. https://doi.org/0.5772/63358

[99] Epicentro. Salute in viaggio. Available at: https://www.epicentro.iss.it/viaggiatori/. [Accessed on 22/03/2019].

[100] World Tourism Organization and Global Tourism Economy Research Centre (2018), UNWTO/GTERC Asia Tourism Trends – 2018 Edition, UNWTO, Madrid, DOI: https://doi.org/10.18111/9789284420032

[101] Van Herck K, Zuckerman J, Castelli F, Van Damme P, Walker E, Steffen R; European Travel Health Advisory Board. Travelers' knowledge, attitudes, and practices on prevention of infectious diseases: results from a pilot study. J Travel Med 2003;10:75-8.

[102] Statement on international travelers and typhoid: an Advisory Committee Statement (ACS) Committee to Advise on Tropical Medicine and Travel (CATMAT). Available at: http://publications.gc.ca/collections/collection_2014/aspc-phac/HP40-98-2014-eng.pdf [Accessed on 22/02/2019].

[103] Connor BA, Schwartz E. Typhoid and paratyphoid fever in travellers. Lancet Infect Dis 2005;5:623-8.

[104] Angell SY, Cetron MS. Health disparities among travelers visiting friends and relatives abroad. Ann Intern Med 2005;142: 67-72.

[105] Awofeso N, Aldabk K. Cholera, migration, and global health – a critical review. Int J Travel Med Glob Health 2018;6:92-9. https://doi.org/10.15171/ijtmgh.2018.19

[106] International travel health guide 2019 online edition. Disponibile all'indirizzo: https://www.travmed.com/pages/health-guide-chapter-6-travelers-diarrhea. [ultimo accesso 27/11/2019.

[107] Kozicki M, Steffen R, Schar M. 'Boil it. Cook it. Peel it or forget it': does this rule prevent travellers' diarrhoea? Int J Epidemiol 1985;14:169-72.

[108] Van Herck K, Van Damme P, Castelli F, Zuckerman J, Nothdurft H, Dahlgren AL, Gisler S, Steffen R, Gargalianos P, Lopéz-Vélez R, Overbosch D, Caumes E, Walker E. Knowledge, attitudes and practices in travel-related infectious diseases: the European airport survey. J Travel Med 2004;11:3-8.

[109] Leggat PA. Sources of health advice given to travelers. J Travel Med 2000;7:85-8.

[110] Lee TK, Hutter JN, Masel J, Joya C, Whitman TJ. Guidelines for the prevention of travel-associated illness in older adults. Trop Dis Travel Med Vaccines.2017;3:10.

[111] Flaherty GT, Rossanese A, Steffen R, Torresi J. A golden age of travel: advancing the interests of older travellers. J Travel Med 2018;25(1).

[112] Han CT, Flaherty G. Profile of travelers with preexisting medical conditions attending a specialist travel medicine clinic in Ireland. J Travel Med 2015;22:312-7.

Received on June 21, 2019. Accepted on September 4, 2019.

Correspondence: Donatella Panatto Department of Health Sciences, University of Genoa, via Pastore 1, 16132 Genoa, Italy - Tel. +39 01 08109 - E-mail: panatto@unige.it

How to cite this article: Amicizia D, Micale RT, Pennati BM, Zangrillo F, Iovine M, Lecini E, Marchini F, Lai PL, Panatto D. Burden of typhoid fever and cholera: similarities and differences. Prevention strategies for European travelers to endemic/epidemic areas. J Prev Med Hyg 2019;60:E271-E285. https://doi.org/10.15167/2421-4248/jpmh2019.60.4.1333