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Review

Typhoid fever infection – Antibiotic resistance and vaccination strategies: A narrative review

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ABSTRACT

Typhoid fever is a bacterial infection caused by the Gram-negative bacterium *Salmonella enterica* subspecies enterica serovar Typhi (*S*. Typhi), prevalent in many low- and middle-income countries. In high-income territories, typhoid fever is predominantly travel-related, consequent to travel in typhoid-endemic regions; however, data show that the level of typhoid vaccination in travellers is low. Successful management of typhoid fever using antibiotics is becoming increasingly difficult due to drug resistance; emerging resistance has spread geographically due to factors such as increasing travel connectivity, affecting those in endemic regions and travellers alike.

This review provides an overview of: the epidemiology and diagnosis of typhoid fever; the emergence of drug-resistant typhoid strains in the endemic setting; drug resistance observed in travellers; vaccines currently available to prevent typhoid fever; vaccine recommendations for people living in typhoid-endemic regions; strategies for the introduction of typhoid vaccines and stakeholders in vaccination programmes; and travel recommendations for a selection of destinations with a medium or high incidence of typhoid fever.

1. Introduction

Typhoid is a bacterial infection caused by the Gram-negative bacterium *Salmonella enterica* subspecies enterica serovar Typhi (*S*. Typhi). Typhoid fever is usually contracted by ingestion of food or water contaminated by faecal or urinary carriers excreting *S*. Typhi [1]. The predominant symptom of infection is high fever, with other symptoms including nausea, abdominal pain and abnormal bowel movements [2]. Once prevalent worldwide, improvements in the provision of clean water and sewerage systems has led to a dramatic decrease in the incidence of typhoid fever with the burden of disease now predominantly residing in low- and middle-income countries where sanitary conditions may be poor [1].

In developed countries, typhoid fever is a predominantly travel-associated disease [3], impacting travelling populations such as tourists, military personnel, temporary workers, or travellers visiting friends or relatives (VFR) in endemic areas, with risk varying by the geographical region visited [3–6], the duration of travel, integration with local cultures, traveller concurrent diseases or medications.

Successful management of typhoid fever using antibiotics is becoming increasingly difficult due to drug resistance [7,8]; emerging resistance has spread geographically due to factors such as increasing travel connectivity, affecting those in endemic regions and travellers alike.

The aim of this article is to provide an overview of: the epidemiology and diagnosis of typhoid fever; the emergence of drug-resistant typhoid strains in the endemic setting; drug resistance observed in travellers; vaccines currently available to prevent typhoid fever; vaccine recommendations for people living in typhoid-endemic regions; strategies for the introduction of typhoid vaccines and stakeholders in vaccination programmes; and travel recommendations for a selection of destinations with a medium or high incidence of typhoid fever.

Abbreviations: AE, adverse event; CI, confidence interval; Ig, immunoglobulin; MDR, multidrug resistance/resistant; PCR, polymerase chain reaction; *S*. Typhi, *Salmonella enterica* subspecies enterica serovar Typhi; TCV, typhoid conjugate vaccine; TMP-SMX, trimethoprim-sulfamethoxazole; UDP, uridine-diphosphate; VFR, travellers visiting friends or relatives; Vi-CRM_{197}, Vi polysaccharide conjugated with CRM_{197}; Vi-DT, Vi polysaccharide conjugated to diphtheria toxoid; ViPS, Vi polysaccharide; Vi-rEPA, Vi polysaccharide bound to the recombinant exoprotein of *Pseudomonas aeruginosa*; XDR, extremely drug resistant; WHO, World Health Organization.

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2. Methodology

An original literature search was conducted on March 19, 2019 in PubMed and EmBase, limited to English-language articles and studies of human individuals. The search terms were 'Typhoid [Title] AND resistan*[Title]', limited to the last 15 years, and 'Typhoid [Title] AND vaccin* [Title/Abstract] AND resistan* [Title/Abstract]', limited to the last 20 years. Reference lists of relevant articles were also screened to identify other additional sources. Apart from abstracts listed in EMBASE, grey literature (e.g. government resources and congress publications) was not included, and duplicate articles were removed. The search results were screened by a non-blinded reviewer to exclude articles that did not provide information about typhoid in humans. Possible articles of interest were retrieved, reviewed and relevant data extracted. Dual validation was not performed as the intention was not to provide a quantitative meta-analysis. Owing to the time since the original search was run, the literature included in this review was updated in the week commencing November 16, 2020 and relevant additional literature added.

3. Overview of the epidemiology of typhoid fever

An estimated 26.9 million episodes of typhoid fever occur annually worldwide (interquartile range 18.3–35.7 million) [9], although precise estimates are difficult to establish. This is due to the non-specific presenting symptoms and signs, under-reporting of cases (screening procedures are not undertaken if the patient is asymptomatic), and lack of suitable diagnostics in many regions (see section 3.1 "Diagnosis of typhoid fever"). The highest burden of typhoid fever is thought to be on the Indian subcontinent, however there is considerable heterogeneity in the distribution of typhoid fever [10]. In sub-Saharan Africa, the incidence of typhoid has historically been poorly described [11]. Indeed, data from the Typhoid Surveillance in Africa Program and other groups have shown that the incidence in African regions may be as high as (or exceed) that in Asia [12–14], affecting both rural and urban populations [14,15].

At the regional level, modelling data from Antillon and colleagues estimate that the incidence of typhoid fever in the Eastern sub-Saharan Africa region could be 620 cases per 100,000 person-years (95% confidence interval [CI] 213–2921), approximately three-fold higher than the Southeast Asia region (217 cases per 100,000 person-years; 95% CI 88–571) [13]. An analysis by the GBD 2017 Typhoid and Paratyphoid Collaborators estimated that, in 2017, South Asia had the highest age-standardised incidence rate (549 [481–625] cases per 100,000 person-years) and the largest number of cases (10.3 million [9.0–11.7]), accounting for 71.8% of global cases, while the sub-Saharan Africa region accounted for 12.1% (1.73 million [1.45–2.06]) of global cases (Fig. 1) [16]. A multicentre population-based prospective study across 13 sites in 10 African countries highlighted that children aged 2–14 bear the greatest burden of typhoid fever [17]. The degree of uncertainty is considerable in regions where typhoid surveillance is weak or non-existent [13], emphasising the importance of capturing wide-ranging surveillance data to fully understand typhoid incidence and the likely outcome of different interventions.

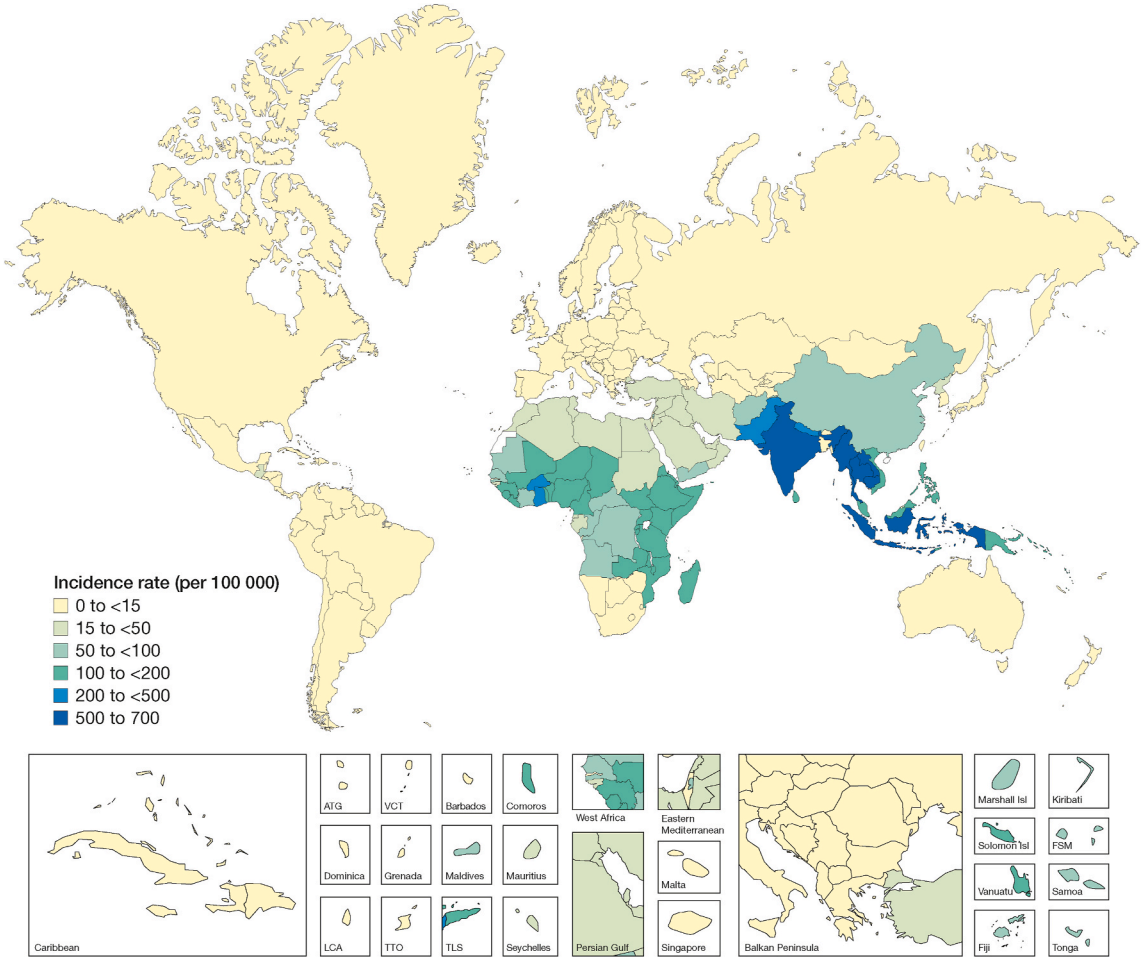

Fig. 1. Incidence rates (per 100,000) of typhoid and paratyphoid fevers, by country, in 2017. Reproduced with permission, Copyright © 2019 The Author(s). Published by Elsevier Ltd. This is an Open Access article under the CC BY 4.0 license [16].

Along with paratyphoid fever (caused by *Salmonella enterica* subspecies serovar Paratyphi A, Paratyphi B and Paratyphi C), typhoid fever is a type of enteric fever [18]. *S.* Typhi is estimated to cause 76.3% (95% CI 71.8–80.5) of cases of enteric fever globally in 2017, with an estimated mean all-age global case fatality of 0.95% (95% CI 0.54–1.53), with higher fatality among children and older adults, and among those living in low income countries [16].

During the course of infection, carriage can be split into three periods – convalescence, temporary and chronic [19]. As many as 10% of convalescent carriers shed bacilli in faeces for up to 3 months post-infection [1]. Following resolution of the disease, approximately 1–4% of typhoid patients progress to the carrier state, excreting the bacilli for more than 1 year [1]. Typhoid fever-causing *Salmonella* have no known environmental reservoir, but it is thought that the chronic asymptomatic carrier is responsible for continued maintenance of the bacteria within human populations [19]. The carrier state has not been extensively studied as the majority of chronic carriers in endemic settings are asymptomatic [1] and a substantial proportion may have had no clinical history of typhoid [19]. However, it is known that chronic carriage is more common in women and increases with age [20]. It is likely that breach of the intestinal epithelial barrier, evasion of early innate immune-mediated killing, and localisation to the biliary tract and gallbladder are requirements for development of the carrier state [19]. Approximately 90% of carriers present with gallstones [21]. Mechanistic studies have shown that *S.* Typhi forms biofilms on gallstones [22], the formation of which is proposed to aid in their survival and persistence during this phase of the transmission cycle [23].

Recent outbreaks, such as the ongoing outbreak in Zimbabwe (active since 2017), demonstrate how poor sanitation and overcrowding are drivers of seasonal outbreaks of typhoid fever and other waterborne diseases [24]. In addition to water-related and socio-economic risks, improper food handling is a risk factor [25,26], underlying the importance of detecting index cases to allow education (and vaccine strategies) to be appropriately targeted.

Typhoid fever is extremely uncommon in countries that have access to treated water supplies and sanitation systems that remove human waste [27]. In non-endemic regions, typhoid is a predominantly travel-associated disease [28–33]. In 2016, 22 countries from the EU reported over 1100 cases (typhoid and paratyphoid combined), with France, Italy and the UK accounting for approximately 70% of those cases [33]. Of those with available information, 82.5% were travel-related, with India and Pakistan accounting for the majority of cases [33]. In the USA, 79% (240/303) of typhoid fever patients travelled or lived outside of the country in the 30 days prior to illness [31]. Previously it was estimated that the incidence of typhoid among travellers to a selection of low- and middle-income countries was $\leq$1 case per 100,000 travellers, except for those who visited Nepal or India where the case rate was 7.9 or 27–81 cases per 100,000 travellers, respectively [3]. The most common reason to travel abroad for patients who subsequently contracted typhoid fever was to visit friends or relatives [29,31,33]. The literature suggests that VFR are at higher risk of contracting travel-related illness, compared with other groups of travellers, due to factors including an increased likelihood of travelling for longer periods of time, travel to rural destinations and being more likely to drink untreated water [34]. Additionally, as VFR may co-habit with their friends and family, they may have greater exposure to asymptomatic carriers in the endemic population (and possibly experience lower levels of sanitation in the home setting), contributing to their increased risk of typhoid fever compared with other travellers.

Another group of travellers potentially at risk of typhoid are military personnel deployed to typhoid-endemic regions. A review of the typhoid fever cases reported in the US military (1998–2011) revealed 205 cases of typhoid fever among military service members, for an incidence of 1.09 per 100,000 person-years, consistent with the incidence of typhoid in the general US population during that same time period, the majority of which was travel-related [35]. Increases in deployment of military personnel to countries with medium or high incidence estimates could be expected to increase the risk of typhoid fever, however this has not been shown, in part due to deployed troops not experiencing the living conditions of the local population [35].

The risk of acquiring typhoid increases with the duration of stay. Correspondingly, in a study of travellers from Greece to typhoid-endemic areas (such as sub-Saharan Africa and Southeast Asia), it was shown that typhoid vaccine administration is statistically associated with the duration of stay [36] as travellers look to mitigate their risks. Approximately 20% of travellers who stayed <1 month underwent vaccination compared with nearly 35% who stayed $\geq$6 months [36]. However, data show that typhoid fever is a risk even for short-term travel – 5% (31/626) of travellers from the USA with typhoid fever reported that their travel outside of the USA lasted $\leq$1 week compared with 60% (376/626) whose travel lasted $\leq$6 weeks [37]. Therefore, behaviours and expected exposure to typhoid fever at the destination should be considered, not only the length of travel.

Travellers who acquire typhoid fever are rarely immunised. Previous data of travellers who developed typhoid fever show that just 4% (36/1027) reported having received a typhoid vaccination at any point during the previous 5 years preceding travel [37]. Data from the US military revealed that 26% (53/205) of military personnel had a documented *S.* Typhi vaccination within 2 years of typhoid fever diagnosis [35]. More recent data of young Canadian travellers with typhoid fever revealed that 0% (0/39) had a record of typhoid vaccination [30]. This low rate of vaccination is therefore one of the key factors that contribute to the occurrence of typhoid infection in travellers [30,37].

3.1. Diagnosis of typhoid fever

Isolation of *S.* Typhi from blood is the current gold standard for determining typhoid fever infection [38]. Bacterial culture from bone marrow is more sensitive but is difficult to obtain, invasive and is impractical for routine use [38]. Although blood cultures remain the gold standard for diagnosis, this method has poor sensitivity [38]. In addition, culturing takes at least 48 h to generate results, and optimal usage is hampered by lack of healthcare infrastructure and adequately trained laboratory personnel in resource-limited countries where typhoid fever is common [38,39].

The Widal test is a serological test that detects agglutinating antibodies against the O and H antigens [38]. It is widely used due to its simplicity and low cost [38] but has low sensitivity [40] and is highly operator dependent [41], with values varying considerably between geographical areas [1]. In addition, the background level of antibodies in a normal healthy population within a typhoid-endemic region means that proper interpretation of the Widal test results entails collection of sera from two visits (spaced 10–14 days apart) and requires each country to determine the appropriate antibody titre with which to diagnose typhoid [39,42], since there is no universal titre cutoff to define the disease. With the emergence of antibiotic resistance (see Section 4, "Overview of the treatment of typhoid fever and the emergence of drug-resistant typhoid strains"), the Widal test is inadequate as it does not provide susceptibility results [43].

Nucleic acid amplification tests, including conventional polymerase chain reaction (PCR), nested, multiplex and real-time PCR, have been developed for the detection of *S.* Typhi DNA in blood [39]. The main challenges preventing widespread use in low-resource settings are the high costs associated with this technology [39].

There are several commercially available typhoid rapid antibody tests that can generate results in as little as 2 min [44] allowing prompt treatment with antimicrobials for those with a positive result. One qualitative test, Typhidot®, uses pre-dotted antigen strips to detect the presence of immunoglobulin (Ig)M and -G antibodies to an outer membrane protein [44]. A semi-quantitative colourimetric test (IDL TUBEX® TF) relies on visual and subjective examination of colour reactions to detect *anti*-O:9 antibody titres [44]. However, in comparative

studies of performance utilising blood culture as the comparator, this type of testing can perform poorly [44]. A recent meta-analysis reported an average sensitivity of 78% (95% CI 71–85; the ability to identify true positives) and specificity of 87% (95% CI 82–91; the ability to identify true negatives) for TUBEX [38]. Analysis of all Typhidot variants as a group showed an average sensitivity of 84% (95% CI 73–91) and specificity of 79% (95% CI 70–87) [38]. A recent study conducted in Bangladeshi patients revealed that the sensitivity of typhoid rapid antibody tests may be as low 60.2% (95% CI 49.3–71.2) and 59.6% (95% CI 50.1–69.3), respectively [45]. These results emphasise the difficulties of laboratory diagnosis of typhoid.

At present there is no gold standard for the detection of chronic typhoid carriers. Standard practice has been to detect typhoid carriage through serial analysis of stool and urine samples (using culturing), however this is logistically challenging and suffers from low sensitivity [19].

The presenting signs and symptoms of typhoid fever are shared with other febrile illnesses (such as malaria, dengue or other arbovirus fevers) [46], and thus differentiating *S*. Typhi infection from other sources of fever in endemic areas is a diagnostic challenge [38]. In most endemic areas (at least in Africa), the only means for diagnosis of a febrile patient is the Widal test for typhoid fever or the thick blood smear for malaria and, as has been shown, the Widal test performs poorly. The lack of diagnosis (because tests are not ordered), misdiagnosis (due to the use of insensitive methods), poor surveillance and inadequate healthcare infrastructure are common problems in resource-limited settings. New strategies that are specific, sensitive, scaleable and cost-effective are required to correctly identify both acute sufferers and chronic carriers of typhoid, in order to stop expansion of the disease and determine the real global burden of *S*. Typhi.

For patients in countries where typhoid is not endemic, determination of the patient's travel history is crucial [1].

4. Overview of the treatment of typhoid fever and the emergence of drug-resistant typhoid strains

The treatment of typhoid fever normally consists of antibiotics [1,11]; early initiation of effective antimicrobial therapy has been shown to shorten the duration of the illness and reduce the risk of complications and death [47]. Because of the high risk of morbidity and mortality if left untreated [48], clinicians may administer antibiotics to patients in the absence of a confirmed diagnosis (on the clinical suspicion of typhoid fever). However, large surveillance studies from Asia and Africa indicate that only 1–4% of people with suspected typhoid actually have culture-confirmed typhoid [49], which suggests that there might often be substantial overtreatment with unnecessary antibiotics.

One of the effects of empiric prescribing of antimicrobials has been an increase in selective pressure on *S.* Typhi [49,50]. Since 1948, when the efficacy of chloramphenicol to treat typhoid was discovered, there has been a pattern of antibiotic usage and resultant development of resistance to antimicrobial therapies [7]. Subsequently, antimicrobial resistance has become a major threat to the treatment of typhoid with increasing levels of treatment failure [7,8] (Fig. 2).

Multidrug resistance (MDR) is historically used to describe combined resistance to the first-line antibiotics chloramphenicol, co-trimoxazole (trimethoprim-sulfamethoxazole) and ampicillin [2]. *S.* Typhi can harbour complex MDR elements, either on self-transmissible plasmids carrying a cassette of antimicrobial resistance genes [51], or integrated into the chromosome (which is more common than previously thought) [52]. While antibiotic selection maintains resistance genes on the plasmid, there also appears to be competition between plasmids encoding the same resistance phenotype [53].

MDR *S.* Typhi is now considered endemic in many developing countries, especially in areas of South and Southeast Asia [2], mediated by the dissemination of the specific H58 lineage across Asian and African countries [8]. As with the disease incidence, antimicrobial agent susceptibility patterns vary geographically [54]. High incidences of MDR *S.* Typhi are found in areas with a high burden of typhoid, particularly in children aged under 15 years [55]. There is a paucity of data on the geographical distribution, incidence and phylogenetics of MDR *S.* Typhi in sub-Saharan Africa [55], however the H58 clade of *S*. Typhi is associated with the MDR phenotype [56] and with much of the typhoid occurring in the last decade in East and Southern Africa [54].

Longitudinal studies show that the proportion of MDR strains decrease over time as clinicians respond to resistance and use alternative drugs [57]. Correspondingly, MDR *S*. Typhi is on the decline in South and Southeast Asia, because of the reduced usage of these first-line drugs in this region [54].

In response to the development and spread of MDR *S*. Typhi, the use of fluoroquinolones, (ciprofloxacin, ofloxacin, fleroxacin and pefloxacin) became widely accepted as an alternative to treat typhoid fever [2]. However reports of decreased susceptibility to fluoroquinolone soon followed both in endemic areas and in travellers returning from such areas [2]. In areas with a high prevalence of both MDR and fluoroquinolone resistance, azithromycin (an azalide antimicrobial) and extended-spectrum cephalosporins (e.g. ceftriaxone) tend to be used for treatment [2].

The first outbreak of an extremely drug resistant (XDR) H58 clone

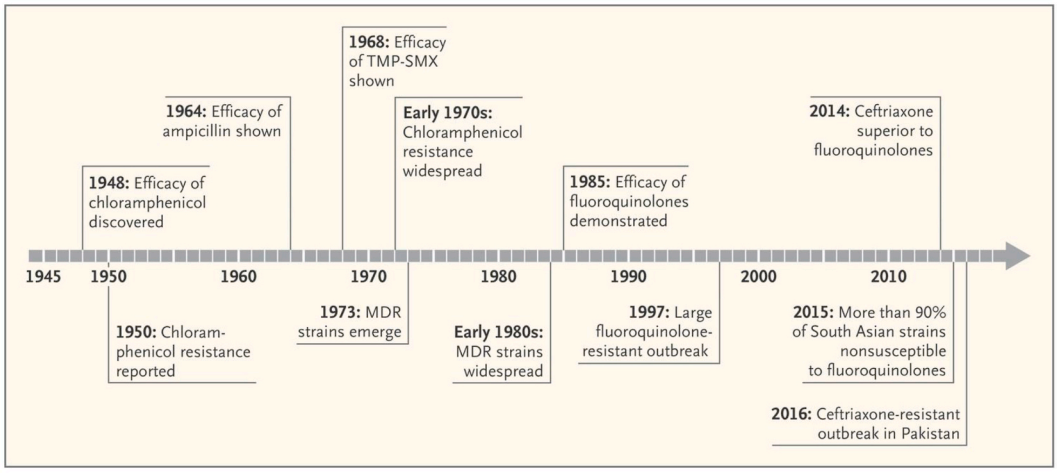

Fig. 2. History of antibiotic efficacy studies and the emergence of antimicrobial resistance in *Salmonella* typhi. Abbreviations: MDR; multidrug resistant; TMP-SMX, trimethoprim-sulfamethoxazole. Strains noted to be "nonsusceptible" are intermediately or fully resistant. Reproduced with permission, copyright © 2018 Andrews et al. [7].

harbouring resistance to not only the three first-line drugs (chloramphenicol, co-trimoxazole and ampicillin), but also fluoroquinolones, and extended-spectrum cephalosporins, began in Sindh province, Pakistan in 2016 [43,58,59]. All of the XDR isolates belonged to the H58 clade and it is thought that the plasmid conferring resistance originated in *Escherichia coli* and was acquired by an MDR H58-endemic *S.* Typhi clone in Pakistan [43]. This outbreak resulted in 5372 XDR *S.* Typhi cases reported from 2016 to 2018 [60]. First reported in June 2019, several areas of Sindh province are again suffering from an outbreak of typhoid, with two child deaths and illness in more than 150 people already recorded. Thus far, five of 51 typhoid cases have been reported as XDR, with results of several other cases awaiting. Health authorities are planning to launch a mass vaccination drive to gain control of this current outbreak [61]. Where patients experience resistance to all first- and second-line drugs, the carbapenems (e.g. imipenem, meropenem and ertapenem) and tigecycline are considered potential alternatives [2].

In addition to the difficulties of ensuring patients receive effective treatment, there are also cost implications associated with resistance: the cost of therapy for resistant cases can be approximately 70% greater than the cost of sensitive typhoid cases, driven mostly by an increase in physician and nursing care [62]. Even with appropriate treatment, the risk of relapse remains, with approximately 5–10% of immunocompetent patients relapsing [63]. Typhoid relapse cases have been reported in typhoid-endemic countries and in travellers returning from those regions [48,63,64]. In one small study from India, patients with drug-resistant typhoid who initially received ineffective therapy had a higher relapse rate following effective treatment compared with those infected with pan-sensitive strains [63].

For the treatment of chronic carriers, eradication has been achieved with some success using ampicillin or amoxicillin, sometimes combined with probenecid or co-trimoxazole (dependent upon the susceptibility of the strain) [2]. A small study of 12 chronic *S.* Typhi carriers revealed a 92% cure rate with a 4-week regimen of fluoroquinolones (ciprofloxacin orally twice a day for 28 days) [65]. At present, there are few data on this subgroup and more research is necessary to determine the best approach for treatment.

4.1. Drug-resistance in travellers

Resistance to antibiotics has been observed in travellers from non-endemic regions with typhoid fever, with patterns reflecting the conditions in typhoid-endemic countries. Case reports of travellers returning to Spain from Guatemala [66], and to Germany from Iraq [67], have documented infections of an extended-spectrum beta lactamase-producing *S.* Typhi strain.

Data gathered in the USA from the National Typhoid and Paratyphoid Fever Surveillance System and National Antibiotic Resistance Monitoring System revealed that antimicrobial resistance was common [68]. Among *S.* Typhi isolates, 314 (29%) were susceptible to all clinically relevant antimicrobial agents, 750 (69%) were resistant to nalidixic acid or had decreased susceptibility to ciprofloxacin, 127 (12%) were MDR, and 108 (10%) were both nalidixic acid resistant/decreased susceptibility to ciprofloxacin and MDR [68]. Isolates resistant to nalidixic acid (a synthetic quinolone that is a marker of decreased susceptibility or resistance to fluroquinolones) originated mainly in southern Asia whilst MDR cases originated from southern Asia and Africa [68].

The afore-mentioned typhoid fever outbreak of 2016–2018 in Sindh province resulted in five travel-related cases in children visiting relatives in Pakistan and returning to the USA [69], and one in the UK [43]. In April 2019, a ceftriaxone-resistant *S.* Typhi case was detected in a pregnant woman returning to Denmark from a family visit to Sindh province [70]. In August 2019, the first case of XDR typhoid was reported in Australia [71].

Collectively, the occurrence of resistant cases necessitates heightened vigilance and re-consideration of treatment strategies for those who have visited a region that has high levels of antimicrobial resistance. *S.* Typhi is quickly able to acquire new resistance mechanisms. As long-distance travel becomes more accessible and migration between endemic and non-endemic regions increases, access to information regarding local and regional susceptibility is important to guide empirical treatment [10]. Consequently, the landscape of resistance is dynamic. The World Health Organization (WHO) has recommended that the surveillance of typhoid fever be strengthened, including surveillance to monitor known resistance, detect new and emerging resistance, and mitigate its spread [72].

5. Vaccines available for typhoid

To stop the expansion of typhoid, interventions should mostly focus on prevention. Along with improvements in antibiotic stewardship, public sanitation, availability of clean drinking water, safe food handling practices and public health education, vaccination in endemic areas is one strategy to prevent typhoid fever. The WHO recommends programmatic use of typhoid vaccines for the control of typhoid fever [73].

Two typhoid vaccines are widely available – Vivotif® (Emergent BioSolutions), an enteric-coated capsule formation of the live attenuated Ty21a vaccine, and TYPHIM Vi® (Sanofi Pasteur), a liquid formulation of the unconjugated Vi polysaccharide (ViPS) vaccine [74,75]. Other vaccines available include the combination typhoid-hepatitis A vaccine VIVAXIM® (Sanofi Pasteur) [76]. There are also two newer generation ViPS-tetanus toxoid conjugate vaccines (typhoid conjugate vaccines [TCVs]) currently licensed, Typbar-TCV™ (Bharat Biotech) and PedaTyph™ (Bio-Med) [77,78]. Selected vaccines are summarised in Table 1.

5.1. Ty21a vaccine

The Ty21a vaccine was developed by chemical-induced mutagenesis of the *S.* Typhi Ty21 strain, resulting in a *galE* mutant and the inability to express the Vi polysaccharide antigen [109]. Inactivation of the *galE* gene generates a lack of uridine-diphosphate (UDP)-galactose-4-epimerase [110], which is responsible for the conversion of UDP glucose into UDP galactose. Consequently, there is intracellular accumulation of galactose derivatives and subsequent bacterial lysis, thus eliminating virulence of the vaccine strain [110,111]. Lipopolysaccharide synthesis is preserved [109].

S. Typhi is an intracellular bacterium and thus needs T cell-dependent immunological response for resolution [112]. Vaccination with Ty21a activates a broad immune response, with both humoral and systemic cell-mediated immune responses. The serum antibody response to Ty21a is a rise in serum IgG antibody against the O polysaccharide of *S.* Typhi [113]. Data have shown that the rate of seroconversion of IgG *anti*-O antibodies increases as more doses are administered within a period of 7 days [88] and that the humoral response is dose-dependent [114].

Following oral immunisation, mucosal antibody responses have been reported. Vaccination studies in healthy adult volunteers have revealed that oral Ty21a immunisation results in an increase in the concentration of IgG anti-lipopolysaccharide [115,116] as well as an increase in levels of faecal IgA (total and/or specific) [115–117]. Data have also shown that after oral vaccination antibody-secreting cells that produce specific IgA to *S.* Typhi O-polysaccharide bear homing receptors which commit them to migrate to the intestinal mucosa [118]. Cell-mediated responses include contributions from $CD4^+$ helper T cells and $CD8^+$ cytotoxic T cells [27].

In the late 1980s–1990s, a series of large-scale randomised, double-blind, controlled field trials (pre-licensure) of Ty21a efficacy were conducted assessing different dosage regimens (single or multiple doses), dosing intervals and formulations. The evidence from the trials that assessed the dosing regimen currently recommended for the Ty21a

Table 1
Typhoid vaccines [74,75,77–103].

Brand and manufacturer	Vivotif® Emergent BioSolutions	TYPHIM Vi® Sanofi Pasteur	Typbar-TCV™ Bharat Biotech	PedaTyph™ Bio-Med
Formulation	• Enteric-coated capsules [74]	• Liquid [75]	• Liquid [77]	• Liquid [78]
Type	• Live attenuated Ty21a strain of *S.* Typhi [74]	• Purified Vi capsular polysaccharide from the Ty2 *S.* Typhi strain [75]	• Vi polysaccharide conjugated with nontoxic tetanus toxoid carrier protein [77]	• Purified Vi capsular polysaccharide from the Ty2 *S.* Typhi strain conjugated with nontoxic tetanus toxoid protein [78]
Route of administration	• Oral [74]	• Injectable	• Injectable	• Injectable
		• Intramuscular [75]	• Intramuscular [77]	• Intramuscular [78]
Recommended dose/regimen	• Three dose regimen, taken on alternate days [74]	• One dose [75]	• One dose [77]	• One dose [78]
	• Four dose regimen in USA and Canada [79][a]	• Optimum antibody protection may be reached 2 weeks after administration [75]	• Prevention is effective 2–3 weeks after immunisation [77]	• Prevention becomes effective 4 weeks after immunisation [78]
	• Entire vaccination schedule to be completed at least one week prior to travel to endemic area [74]			
Efficacy of recommended dose regimen	***Randomised, double-blind placebo-controlled field study* [80,101]** Vivotif vaccination arm: n = 22,170 school-children, aged 6–21, three doses.	***Randomised, double-blind placebo-controlled field study* [82]**. TYPHIM Vi vaccination arm: n = 3457 individuals, aged 5–44	***Randomised human challenge study* [85]** Typbar-TCV vaccination arm: n = 37 healthy adult volunteers, aged 18–60, one dose	***Cluster randomised field study* [86]** Mitra, 2015, Kolkata, India. PedaTyph vaccination arm: n = 905 school children, aged 6 months–12 years, one or two doses
	• Year 1: 71% (95% CI 35–87) • Year 2: 61% (95% CI 12–82) • Year 3: 67% (95% CI 47–79) • Total years 1–3: 67% (95% CI 47–79)	• 17 months post-vaccination: 75% (95% CI unreported)	• 72 h post-challenge: 87.1% (95% CI 47.2–96.9)	*Two dose*[d] • Year 1: 100% (95% CI 97.6–99.5)
	Additional follow-up • Years 1–7: 62% (95% CI 48–73) • Years 4–7: 61% (95% CI 34–73)	***Randomised, double-blind placebo-controlled field trial* [83,84]** TYPHIM Vi vaccination arm: n = 5692 children, aged 5–15/16[c]	***Randomised controlled Phase 3 trial* [104]** Typbar-TCV vaccination arm: 10, 005 individuals, aged 9 months–16 years, one dose	
	***Randomised, double-blind placebo-controlled field study* [87].**[b] Vivotif vaccination arms: n = 34,696 school children, aged 5–19, three doses	• Year 1: 61% (95% CI 6–82) • Year 2: 52% (95% CI 5–76) • Year 3: 50% (95% CI 0–78) • Total years 1–3: 55% (95% CI 30–71)	• Year 1: 81.6% (95% CI 58.8–91.8)	
	• Year 3: 33.2% (95% CI 0–57)			
Revaccination	• 3 years following the most recent vaccination for all individuals [74]	• 3 years under conditions of repeated or continuous exposure [75]	• Booster dose may be given after 3 years [77]	• Booster dose may be given from 2.5 to 3 years [78]
Indirect (herd) protection	• Yes [88]	• Unclear[e]	• Unknown	• Unknown
Cross-protection against paratyphoid	• Moderate protection against paratyphoid B fever (efficacy 49% 95% CI 8–73) [89]	• No [75]	• No [77]	• Unknown [78]
Recommended target age for vaccination	*Highest level of recommendation: 2b* • Indicated for use in adults and children >5 years of age [74] [f]	*Highest level of recommendation: 2b* • Adults and children ≥2 years of age [75]	*Highest level of recommendation: 4* • Adults and children ≥6 months to ≤45 years of age [77]	*Highest level of recommendation: 4* • Children of all age groups from 6 months to 12 years of age [86]
Safety	*Post-marketing surveillance* [90] Most common AEs reported in the USA, July 1990–June 2002[g]	*Monograph*[h] [75] TYPHIM Vi vaccination arm: children aged 12–144 months (n = 175) and adults aged 18–40 years old (n = 152)	*Human challenge study* [85] Typbar-TCV vaccination arm: adults, n = 41	*Randomised comparative trial* [91] PedaTyph vaccination arm: children aged 3 months−5 years, n = 400
	• Diarrhoea (n = 51), nausea (n = 47), fever (n = 42), abdominal pain (n = 42), headache (n = 31), rash (n = 26), vomiting (n = 21), pain (n = 20), asthenia (n = 17), myalgia (n = 17)	• No serious or unusual side effects in either children or adults	• No serious adverse events related to vaccine administration	• Non-severe and recoverable reactions within 48 h • One dose, n = 400, ≥1%: erythema (1.5%), induration (1%), fever (13%), lethargy (1.5%) • Two dose, n = 168, ≥1%: erythema (2%), fever (18%), lethargy (1%)
		Post-marketing surveillance [90] Most common AEs reported in the USA, July 1990–June 2002&	*Randomised, double-blind Phase 3 study* [92] Typbar-TCV vaccination arm: children and adults, n = 667	
		• Fever (n = 11), headache (n = 11), dizziness (n = 9), rash (n = 9), urticaria (n = 9), myalgia (n = 6), pain (n = 6), abdominal pain (n = 6), pruritis (n = 6), injection site pain (n = 5)	• No serious adverse events related to vaccine administration	
			Adverse event reporting during mass vaccination campaign [105] Typbar-TCV vaccination arm: children aged 6 months–10 years, n = ~207,000	
			• Significantly higher rate of AEs in children aged 6–12 months vs those aged 2–3 years (0.54%	

(*continued on next page*)

Table 1 (*continued*)

Brand and manufacturer	Vivotif® Emergent BioSolutions	TYPHIM Vi® Sanofi Pasteur	Typbar-TCV™ Bharat Biotech	PedaTyph™ Bio-Med
			and 0.33%, respectively; $p < 0.001$) • Most common AEs detected via 14-day active follow-up were fever (2.89%) and local reactogenicity (1.88%) • No serious AE was observed	
Availability	• First licensed within Europe in 1983 and in the USA in 1989 [93] • Licensed for sale in 26 countries worldwide [94] • Recommended by the WHO since 2008 for the control of typhoid in endemic and epidemic settings [73]	• Licensed in the USA in 1994 [73] • Licensed in over 100 countries [95] • Recommended by the WHO since 2008 for the control of typhoid in endemic and epidemic settings [73]	• Licensed in India in 2013 [96] and Nepal [97] • Attained WHO prequalification status in 2018 [97]	• Licensed in India in 2008 [73]

[Δ]Injection site pain was statistically significant, $p = 0.0499$ [85].

Abbreviations: CI, confidence interval; AE, adverse event; *S*. Typhi, *Salmonella enterica* subspecies enterica serovar Typhi; WHO, World Health Organization.

[a] The four dose regimen was registered in the USA and Canada in 1987 as a result of the study by Ferreccio and colleagues [81].

[b] Note that information from three additional studies has been excluded as the formulation, dose regimen or time interval between doses does not reflect those in current recommendations. Black and colleagues evaluated the efficacy of one or two doses of Ty21a in a randomised placebo-controlled field study in >80,000 children in Santiago, Chile [102]. Simanjuntak and colleagues evaluated three doses at weekly intervals [98]. Wahdan and colleagues evaluated a liquid formulation in <30, 000 children in Egypt [99].

[c] Reference [83] states ages 5–16, reference [84] states ages 5–15.

[d] Efficacy for one dose not reported.

[e] Indirect herd protection has been demonstrated for Typherix® (GlaxoSmithKline), a Vi polysaccharide vaccine [103,106]. Typherix has been withdrawn in some countries [107,108].

[f] This can be used from 3 years of age according to technical data, however as the user has to be able to swallow the whole capsules it is recommended from 5 years of age.

[g] Adverse events for the vaccine when given alone (not in combination with any other vaccine).

[h] This monograph includes data from 2 clinical trials [84,100] as well as data held on file by Sanofi Pasteur.

vaccine is presented in Table 1 and briefly described below. A large-scale randomised, controlled field trial in Santiago, Chile was performed in which school children (n = 22,170) received three doses of Ty21a, taken orally every other day, or placebo [80,101]. Results indicated that this regimen confers long-lived protection with 3-year efficacy of 67% [80]. With 7 years' follow-up, efficacy was 62% [101]. Vaccine efficacy increased with age at the time of vaccination, from 59% (95% CI 16–80) in children aged 5–9 years, to 67% (95% CI 35–83) in those aged 10–14, and 85% (95% CI 42–96) in those ≥15 years old [80]. In another study, analysis of efficacy by age showed increased efficacy in children ≥10 years versus those aged 5–9 years (53.5% [95% CI 7–77] vs 16.9% [95% CI 0–53]) [87]. The justification for the four-dose regimen employed in the USA and Canada originates from a large randomised field study of Chilean school children, which assessed the comparative efficacy of a two-, three- or four-dose regimen of Ty21a [81]. The incidence of typhoid fever in recipients of two or three doses was significantly higher than in those who received four doses (48% vs 40%, $p < 0.002$) [81]. A subsequent analysis of vaccine efficacy, using data from the two-dose group as standard, reported efficacy of 13% (95% CI 0–33; years 1–3) for those who received three doses and 48% (95% CI 29–62; years 1–3) for those who received four doses [88].

The effectiveness of public health vaccination programmes can depend on both the vaccinated and unvaccinated population. Herd protection is the reduction in infection or disease in the non-immunised proportion of the population as a result of vaccination in another proportion of the population [119]. Evidence that Ty21a can provide indirect herd immunity comes from a field trial in Santiago, Chile, that used one or two doses, during which the incidence of typhoid fever in the control group fell during the follow-up period [102]. The incidence rate in the randomised placebo group in the first year of surveillance was 227 cases per 100,000 school children [102]. The incidence in the second year fell to 139 cases per 100,000 school children [102]. The data suggest that large-scale vaccination appears to cause indirect herd immunity in non-vaccinated subjects [88].

Data regarding co-administration with malaria prophylaxis were determined using the previously developed liquid formulation, rather than the capsule formulation in current usage, and suggested that the vaccine can be administered concurrently with malaria prophylaxis using atovaquone/proguanil [120]. Current manufacturer recommendations state that vaccination should be completed prior to malaria prophylaxis, with an interval of at least 3 days between the last dose of vaccine and the start of malaria prophylaxis [74].

Ty21a can be administered to immunologically stable HIV-positive individuals (CD4% >25% for children aged <5 years or CD4 count ≥200 cells/mm^3 if aged ≥5 years) [73,121]. Ty21a is not recommended for individuals with a known depression of cell-mediated immunity [73]. Ty21a may be given concurrently with the yellow fever vaccine, CVD 103-HgR cholera vaccine and oral polio vaccine [74]. No data are available regarding the interaction with other live attenuated vaccines.

Due to the potential inhibition of the growth of the vaccine organisms and potential attenuation of the immune response, vaccination with Ty21a should be postponed during, and for at least 3 days before and after, antibiotic or antibacterial sulphonamide treatment [74]. For longer-acting antibiotics, eg azithromycin, a longer postponement should be considered [74].

At present there are no data on the safety and immunogenicity of any of the typhoid vaccines in pregnant or lactating women [122]. Generally, live vaccines, and therefore Ty21a, should not be given during pregnancy due to theoretical safety concerns [122], however the manufacturer suggests that it could be administered in cases of increased risk of infection [74].

The efficacy trials of the three- or four-dose alternate-day regimen did not specifically include safety monitoring. However, safety of the Ty21a vaccine can be assessed from post-marketing surveillance data. Post-marketing surveillance data collected in the USA through the Vaccine Adverse Event Reporting System (July 1990 to June 2002; four-dose regimen) revealed 345 reports of adverse events (AEs) related to the administration of Ty21a alone or in combination with other vaccines [90]. The rate of AEs or serious AEs was 9.7 or 0.59 per 100,000 doses, respectively and AEs included diarrhoea, nausea, fever and abdominal

pain [90]. Of 38 million immunisations administered between 1990 and 2000, the total number of spontaneously reported adverse drug reactions was 0.001954% (i.e. ~20 in every million immunisations will result in an adverse drug reaction) [123].

During the early pre-licensure field trials in Chile, there was a considerable level of paratyphoid fever due to *S*. Paratyphoid B, allowing estimation of cross-protection. The Ty21a vaccine has also been shown to confer moderate protection against *S*. Paratyphi B (efficacy 49%) [89]. A randomised double-blind field trial of 20,543 subjects in Plaju, Indonesia (one dose per week for 3 weeks) suggests that Ty21a does not offer cross-protection against *S*. Paratyphi A [98].

5.2. Vi polysaccharide vaccine

ViPS vaccines are based on the purified capsular polysaccharide, S. Typhi Vi antigen [11]. The Vi antigen of *S*. Typhi is well recognised as a factor for virulence and as an antigen that confers immunity against the typhoid fever [124]. The ViPS induces T cell-independent immune responses against *S*. Typhi, thus resulting in a lack of prolonged protection [97].

Evidence of the efficacy of ViPS vaccines comes from studies that utilised vaccines from two different manufacturers, TYPHIM Vi® (Table 1) and Typherix® (GlaxoSmithKline) vaccines. Typherix vaccine is no longer commercialised in some countries and may be unavailable for use [107,108]. Early pre-licensure randomised studies demonstrated that ViPS vaccines offer a moderate level of protection. A Nepalese study of TYPHIM Vi in subjects aged 5–44 years reported a total efficacy (blood culture proved and clinically suspected) of 75% [82]. A double-blind randomised trial of TYPHIM Vi in South African school children aged 5–15 years reported an efficacy of 55% [84]. A meta-analysis of four individually randomised clinical trials (including the two studies mentioned above plus two additional trials in China utilising locally produced ViPS) demonstrated efficacy of 69% (95% CI 63–74) in year 1 (three trials) and 59% (95% CI 45–69) in year 2 (four trials) [11].

Subgroup analysis by age in a cluster-randomised trial conducted in India using Typherix post-licensure showed the efficacy as: 80% (95% CI 53–91) in children under 5 years; 56% (95% CI 18–77) in those aged 5–14 years; and 46% (95% CI -43–79) in those aged ≥15 and above [103]. To the contrary, a cluster-randomised trial conducted in Pakistan showed no protection among children aged 2–4 years (efficacy −38% [95% CI -192−35]) and 57% (95% CI 6–81) for children 5–16 years old [125].

An outbreak of typhoid fever in previously vaccinated French soldiers stationed in Cote d'Ivoire revealed that an interval of >3 years from the time of vaccination may result in reduced immunity [126].

Hypo-responsiveness or immunotolerance to re-vaccination is the inability of an individual to mount an immune response equal or greater than the immune response induced by primary vaccination [127]. This phenomenon has been described for polysaccharide vaccines [127]. Roggelin and colleagues assessed the influence of previous vaccinations with a ViPS (not more than 5 years ago) on post-vaccination antibody concentrations [128]. Thirty-six of the participants had been vaccinated once, nine had been vaccinated at least twice. There was no evidence of immunotolerance with multiple versus primary vaccination using a ViPS vaccine. However this was a small study, and the subgroup of those who had been previously vaccinated once showed the highest post-vaccination geometric mean antibody concentration compared with those who had been vaccinated twice before or received their primary vaccination [128].

A post-licensure cluster randomised trial in Kolkata, India, indicated that Typherix offers herd immunity. Among unvaccinated members of the vaccine clusters (geographical units that served as units of randomisation), the level of protection was 44% (95% CI 2–69, model based on 25,083 subjects) [103].

ViPS vaccines, because of their poor immunogenic and T cell-independent properties, are not suitable for immunisation of infants [112]. ViPS vaccines are safe and recommended for HIV-infected individuals [73,121], however elicitation of protective antibodies is directly correlated with the levels of $CD4^+$ T cells and thus the proportion of individuals with protective antibody concentrations will be lower than in healthy controls [129]. Antibody responses are severely impaired in those with CD4 <200 cells/μL [129].

ViPS vaccines can be co-administered with other vaccines, including inactivated or attenuated, which is relevant for international travellers and routine childhood vaccination schedules [73]. As previously mentioned, there are no data on the safety of typhoid vaccines in pregnant women [122] and thus the manufacturer of TYPHIM Vi recommends that it should only be administered if clearly required and following risk assessment [75].

Post-marketing surveillance data collected in the USA through the Vaccine Adverse Event Reporting System (July 1990 to June 2002) revealed 321 reports of adverse events related to the administration of TYPHIM Vi alone or in combination with other vaccines [90]. The rate of AEs or serious AEs was 4.5 or 0.34 per 100,000 doses, respectively [90]. Common AEs included fever, headache and dizziness [90]. Serious side effects were rare [90].

Neither *S*. Paratyphi A or B express the Vi capsular antigen therefore there is no biological plausibility for cross-protection [27]. Theoretically, ViPS should offer protection against *S*. Paratyphi C, which does express the Vi capsular polysaccharide, although this is a rare cause of enteric fever and no data from field trials have reported protection [27].

5.3. Typhoid conjugate vaccines

TCVs combine the Vi-polysaccharide capsule with a protein carrier [85]. For example, each dose of PedaTyph contains 5 μg of Vi polysaccharide of *S*. Typhi conjugated to 5 μg of tetanus toxoid [91], a recombinant inactive form of tetanus toxin produced by *Clostridium tetani* [97]. Covalently conjugating ViPS to carrier proteins overcomes the limitation of the ViPS vaccine by changing the immune response from T cell-independent to T cell-dependent, enabling immunisation even in young children [97]. Several conjugate subunit vaccines combining ViPS with another protein antigen (typically inactive forms of bacterial exotoxins) are under investigation [97]. At present, hyporesponsiveness is not thought to be a feature of repeated vaccination with conjugate vaccines [127]. Limited data are currently available – large field studies are required and further investigations are being conducted by the Typhoid Vaccine Acceleration Consortium [130].

Since TCVs are less well established for typhoid vaccination, data are comparatively limited. A Phase 2b randomised controlled trial showed that the efficacy of Typbar-TCV was 54.6% in a controlled human infection model of typhoid fever in adult volunteers aged from 18 to 60 years; a post hoc analysis of these data revealed that if alternative diagnostic criteria were applied, such as fever of 38.0 °C or higher followed by bacteraemia, the estimated efficacy would be 87.1% [85]. In a report of two trials (randomised controlled and an open-label trial), adverse events for Typbar-TCV were uncommon [92]. Fever was the most common, with 4.3% (14/340) of subjects experiencing this AE [92]. Post-marketing surveillance data reported fever, pain and swelling in 1–10% of vaccinees in any age group (no serious AEs were reported) [131]. Whether Typbar-TCV offers herd immunity is unknown at present, however herd immunity has been observed with other conjugate vaccines due to mucosal immunity and will need to be addressed in future studies.

The efficacy of PedaTyph was determined in a single cluster open-label randomised control trial in 950 children aged 6 months to 12 years: year 1 efficacy was reported to be 100% (95% CI 97.6–100) [86]. A study of 400 children to assess the safety and immunogenicity of PedaTyph reported non-severe AEs in 17% of children with one dose, recoverable within 48 h [91]. At present, there is no evidence of interference with other vaccines (e.g. the trivalent measles, mumps and

rubella vaccine) [122]. Although there are no data to this effect, like the ViPS vaccine, it is not biologically plausible for cross-protection to be induced against *S*. paratyphoid A and B. Theoretically, cross-protection against *S*. paratyphoid C is possible.

5.4. Other typhoid conjugate vaccines

There are several other typhoid vaccines available, or in the development pipeline, that utilise a variety of carrier proteins. Vi-rEPA, Vi polysaccharide bound to the recombinant exoprotein of *Pseudomonas aeruginosa*, showed efficacy of >90% in a Phase 3 study of Vietnamese children aged 2–5 years [132] and will be available in China soon [133]. Vi-CRM_{197}, Vi polysaccharide conjugated with CRM_{197} (a non-toxic mutant of diphtheria toxin), has completed Phase 2 trials in infants, children and adults [134] and is in clinical development [135]. Vi-DT vaccine, Vi polysaccharide conjugated to diphtheria toxoid, is currently undergoing assessment in a Phase 2 trial in children ages 3–23 months [136]. A Phase 3 trial in children and adults is due to complete in January 2020 [137]. In a Phase 1 study in adults aged 18–40 years old and children aged 2–5 years old [138], and in Phase 2 studies in children aged 6 to ≤24 months [139,140], the Vi-DT vaccine has been shown to be well tolerated and immunogenic.

In summary, there are several vaccines available for the prevention of typhoid, the choice of which will include factors such as the local availability and age of the intended recipient.

6. Vaccination strategies

A combined approach to typhoid health security based on public health that includes the use of typhoid vaccines, improvements in sanitation and safe water supply is necessary [141]. Vaccination has the potential to decrease the use of antibiotics, limit the emergence of resistant *S*. Typhi strains and create a herd immunity. Consequently, it should be offered to those who reside in endemic regions as well as to travellers to destinations where antibiotic-resistant strains of *S*. Typhi are prevalent [142]. As it is difficult to obtain the output from monitoring and reporting information in real time, and because typhoid fever may not have the highest priority due to competition from other diseases with higher morbidity/mortality, vaccination should be offered irrespective of the intensity of other control strategies [142].

Feedback from regions and countries on the implementation of the Strategic Advisory Group of Experts recommendations on typhoid identified that, as the incidence of *S*. Typhi declines, there has been a concomitant rise in the incidence of *S*. Paratyphi [143]. This increases the uncertainty of the value of typhoid vaccination in the absence of a vaccine against *S*. Paratyphi. In this context, vaccines that offer cross-protection against *S*. Paratyphi (Ty21a for example) may be considered to be of greater value.

6.1. Global recommendations for vaccination in endemic areas

The WHO currently recommend vaccination, using Ty21a, ViPS or TCV, to control endemic typhoid fever and outbreaks. The WHO recommends TCV in all ages due to its improved immunological properties, suitability for use in younger children and expected longer duration of protection [73]. Use of ViPS vaccine in individuals aged ≥2 years, and Ty21a vaccine for individuals aged >6 years, is also suitable [73].

6.1.1. Strategies for the introduction of typhoid vaccines

Routine typhoid fever vaccination for public health use has been very limited in the past, even in endemic areas, hampered by the lack of an effective vaccine for young children and relatively short duration of protective efficacy [144–146]. Typbar-TCV attained WHO pre-qualification in 2017 so the current landscape of typhoid vaccine usage is set to change (see Section 6.1.2, "Stakeholders in typhoid vaccine programmes") [147]. The introduction of TCVs should be prioritised in countries with the highest burden of typhoid disease or a high burden of antimicrobial resistant *S*. Typhi [73]. Data from Breiman and colleagues showed a high disease burden in densely populated urban slums compared with a low incidence in rural areas, supporting a typhoid immunisation strategy with a geographically and environmentally targeted approach [148].

Studies are ongoing to demonstrate whether the programmed introduction of an effective typhoid vaccine into countries with high burden of disease or significant antimicrobial resistance could have a dramatic impact, protecting children from infection and reducing antimicrobial usage [149]. Health-economics and cost-effectiveness studies suggest that vaccination (using a TCV) is likely highly cost-effective in high-burden settings (>100 cases per 100,000 population) [49]. An age-structured transmission and cost-effectiveness model that simulated multiple vaccination strategies with a TCV showed that TCVs would be highly cost-effective in low-income countries in settings of moderate typhoid incidence (50 cases/100,000 annually) [150].

In countries with epidemiological evidence of high incidence in well-defined subpopulations, a vaccination strategy based on risk assessment should be considered [142]. An evaluation of the cost-effectiveness of ViPS vaccination against typhoid in multiple Asian sites demonstrated that a vaccination programme targeting children would be "very cost-effective" (e.g. costs per disability-adjusted life-years averted less than per-capita gross national income), but programmes that also target adults are less cost-effective (albeit due to the lower incidence in adults than children) [151]. Recent cost-effectiveness analysis in five endemic, low- and middle-income settings showed that routine vaccination with TCVs, as well as one-time catch-up campaigns, would be cost-effective in most settings [152].

A recent study has modelled the predicted impact of TCVs on antimicrobial resistance, using the relative fitness of the resistant strain(s), prevalence of chronic carriers, and rates of recovery without treatment as variables. Notably, herd immunity was not included in the model. The study found that increasing vaccination coverage would decrease the total number of antimicrobial-resistant typhoid infections but not affect the proportion of cases that were antimicrobial resistant [153]. Further evaluation in real-world typhoid-endemic settings is necessary to confirm the model's predictive results. However, in low-resource settings (where typhoid is endemic), there is little chance of being able to confirm these results. As such, the likely impact of TCVs on antimicrobial resistance remains to be determined.

As asymptomatic carriers are thought to be responsible for maintenance of *S*. Typhi in the human population, a strategy for reducing this reservoir could be of interest. Stratification of carriers by age could support the vaccination strategy in endemic countries.

Interestingly, concomitant administration of Ty21a and ViPS has also been explored [154]. The enhanced immune response observed suggests that usage in this manner should elicit higher protective efficacy, although this is still to be investigated. The authors suggest that concomitant use should be encouraged for those at significant risk [154].

Recent findings from Bhutta and colleagues, studying surveillance data from several countries, documented substantial reductions in typhoid fever burden over recent decades which may be associated with improvements in economic conditions, education and environmental health [155]. It is likely that public health programmes of vaccination could also impact the burden of disease, as has been seen with other pathogens. However, it is possible that differing patterns of urbanisation, and resultant population densities, could impact on the success of vaccination strategies.

Like typhoid, cholera is a bacterium transmitted by faecally contaminated water and it has a high burden of disease, predominantly in areas that lack access to safe water [156]. In 2011, the first low-cost oral cholera vaccine obtained WHO pre-qualification status and efforts began to stockpile the vaccine for use in endemic and epidemic settings [157]. There were operational challenges that hampered the subsequent

vaccination campaigns, including regulatory hurdles, cold chain logistics, and vaccine coverage and uptake, however from 2011 to 2015, 4.8 million doses of cholera vaccine were administered globally [157]. Whilst it may be too early to assess the impact of these vaccinations, surveillance data from Malawi has shown that cholera outbreaks were absent in vaccinated high-risk areas (despite a national outbreak during the surveillance period), suggesting the suitability of this approach [158]. Vaccines have been used with great effect for other endemic diseases, such as polio. Since 1988, when the sustained use of polio vaccines began, the number of countries with endemic polio has reduced from 125 to just two in 2015 (Afghanistan and Pakistan) [93]. Concerted and sustained efforts concerning typhoid vaccinations might similarly result in substantial reductions in the decades to come.

6.1.2. Stakeholders in typhoid vaccine programmes

Several global activities support the introduction of vaccines, with efforts ongoing to make new typhoid vaccines available and accessible to those that need them.

As part of their vaccine investment strategy, Gavi, the Vaccine Alliance, prioritised typhoid vaccines in 2008 but did not make a financial commitment at that time [147]. All vaccines supported by Gavi are supplied through the United Nations procurement process and so pre-qualification is necessary for purchase and subsequent introduction into Gavi-eligible countries [159]. Following the WHO pre-qualification of the TCV vaccine Typbar-TCV in 2017 [147], Gavi approved US$85 million in funding to support eligible countries to introduce TCVs [160]. At present, there are 58 countries eligible for Gavi funding – to be eligible, a country's gross national income per capita must be ≤US $1580 over the previous 3 years [161]. A country's Gavi-eligibility status may have a large influence on a country's vaccine introduction decision and the introduction of TCVs may be more difficult in Gavi-ineligible countries [162].

The Coalition against Typhoid was created with the aim of preventing typhoid among vulnerable populations through research, education and advocacy [163]. The Typhoid Vaccine Acceleration Consortium aim to facilitate the introduction of TCVs into Gavi-eligible countries to reduce the burden of typhoid using an integrated, proactive approach [164]. Through the efforts of these groups and others, progress towards the reduction in typhoid fever is being made.

6.2. Recommendations for travellers to high-risk areas

For individuals in non-endemic areas, typhoid fever impacts travelling populations such as tourists, military personnel, or travellers VFR in endemic areas. Travel destination is the main factor for assessing the risk of acquiring typhoid fever [36]. Other factors include area of stay, duration of stay, purpose of travel and type of accommodation [36]. There are also risk factors intrinsic to the traveller, including age and diagnosed/undiagnosed underlying medical conditions [36]. In those travellers with impaired immunity (e.g. HIV), vaccination is less effective [129].

Vaccination has the potential to decrease the use of antibiotics (both standby and therapeutic use) and limit the emergence of resistant *S.* Typhi strains, and should be offered to travellers to destinations where

Table 2
General vaccine recommendations to prevent typhoid fever for travellers to selected middle and high incidence typhoid fever countries [94,171–188] (incidence as per [14]).

	Country recommendations											
	Australia* [171] Department of Foreign Affairs and Trade	Canada [172] Department of Foreign Affairs, Trade and Development	France [173] Institut Pasteur	Germany [175,188] German Society of Tropical Medicine	Ireland [178,179] Tropical Medicine Bureau	Portugal* [176,177] Sociedade Portuguesa de Medicina do Viajante	Spain∞ [180,181] Asociación Española de Vacunología	 Fundacion IO	Switzerland [182,183] Federal Office of Public Health	The Netherlands [184] GGD	UK [185,186] National Travel Health Network and Centre	USA [187] Centers for Disease Control and Prevention
	Vaccines											
	Vivotif, TYPHIM Vi, VIVAXIM	Vivotif, TYPHIM Vi, VIVAXIM	Vivotif§, TYPHIM Vi	Vivotif=, TYPHIM Vi	TYPHIM Vi, VIVAXIM	Vivotif&, TYPHIM Vi, VIVAXIM	Vivotif, TYPHIM Vi		Vivotif, TYPHIM Vi	Vivotif	Vivotif, TYPHIM Vi, VIVAXIM$	Vivotif,
	Destinations in Africa and associated risk factors											
Kenya	All travellers	Some travellers	Some travellers	Some travellers	All travellers	Most travellers	All travellers		Some travellers	None	Most travellers	Most travellers
		A, B, C, D	C, E	E, F, J, L		D, G, H	C, I, J	F, K	G, L		B, C, E, L, M	B, I, N
South Africa	All travellers	Some travellers	Some travellers	Some travellers	All travellers	Most travellers	All travellers	All travellers	Some travellers	None	Most travellers	Most travellers
		A, B, C, D	C, E	E, F, J, L		D, G, H	C, I, J	F, K	B		B, C, E, L, M	B, I, N
	Destinations in Asia and associated risk factors											
China	All travellers	Some travellers	Some travellers	Most travellers	All travellers	Most travellers	All travellers	All travellers	Some travellers	Some travellers	Most travellers	Most travellers
		A, B, C, D	C, E	C, E, F, J, L		D, G, H	C, I, J	F, K	G, L	D, O, P	B, C, E, L, M	B, I, N
Malaysia	All travellers	Some travellers	Some travellers	Most travellers	All travellers	Most travellers	All travellers	All travellers	Some travellers	None	Some travellers	Most travellers
		A, B, C, D	C, E	C, E, F, J, L		D, G, H		F, K	G, L		B, C, E, L, M	B, I, N
	Destinations in the Indian subcontinent and associated risk factors											
India	All travellers	Most travellers	Some travellers	All travellers	All travellers	Most travellers	All travellers		Some travellers	All travellers	Most travellers	Most travellers
			C, E			D, G, H		F, K	Q	D, O, P	B, C, E, L, M	B, I, N
Pakistan	All travellers	Most travellers	Some travellers	All travellers	All travellers	Most travellers	All travellers		All travellers	All travellers	Most travellers	Most travellers
			C, E			D, G, H		F, K		D, O, P	B, C, E, L, M	B, I, N

*Recommendations are for typhoid-endemic regions, not country-specific
∞Recommendations are for tropical areas, not country-specific
§Vivotif was granted marketing authorization in May 2019 [94] but has not yet been launched
=Local market name for Vivotif is Typhoral L®
$Local market name for VIVAXIM is ViATIM®
▪Note the licenses for Typherix and Hepatyrix were cancelled July 2019 [175]
&Vivotif was granted marketing authorization in May 2019 [94] and has recently been launched

Risk factor codes: A. Children; B. VFR; C. Extended/longer duration of stay; D. Existing illness/medical condition; E. Poor hygiene conditions/sanitation; F. Increased exposure (e.g. cooperative trips, backpacking, trekking); G. Duration of stay (>4 weeks); H. Activities; I. Visiting small cities/rural areas; J. Contact with the local population; K. Duration of stay (>3 weeks); L. Poor food hygiene; M. Frequency of stays; N. Adventurous eating; O. Duration of stay; P. Circumstance of stay; Q. Duration of stay (>1 week).

antibiotic-resistant strains of *S*. Typhi are prevalent [142]. This is particularly important given that standby antibiotics encourage less cautious use of antibiotics [165]. One of the available licensed products should be offered, namely Ty21a, ViPS or TCV. Licensed combination unconjugated ViPS-hepatitis A vaccines, where available, may also be used for travellers [73].

There is relatively little evidence of the effect of vaccinations in preventing typhoid in travellers who have visited typhoid-endemic areas. Data from 4 years of US national surveillance reported by Mahon and colleagues showed moderate protection (80%) from typhoid fever in vaccinated US travellers who travelled to southern Asia [166]. As the vaccination information gathered from reports did not specify the vaccine administered, the effectiveness of each individual vaccine could not be estimated. In the UK, between 2007 and 2012, >99% of typhoid vaccines prescribed were ViPS vaccines (TYPHIM Vi, Typherix, Hepatyrix® or VIVAXIM®) [167]. In travellers from England (children ≥2 years and adults) the overall effectiveness of typhoid ViPS vaccines was 65% (95% CI 53–73) [167].

In Canada, the Committee to Advise on Tropical Medicine and Travel suggest that typhoid vaccine (Ty21a or ViPS) be used for Canadian travellers visiting South Asia [168]. In the UK, the National Travel Health Network and Centre generally recommend vaccination for most travellers to typhoid-endemic countries where there is a "medium" disease incidence and the access to improved sanitation is <80% [169]. In the USA, guidelines were updated in 2015, and continue to recommend vaccination for travellers to certain countries, close contacts of chronic carriers, and certain laboratory workers [170].

At present, recommendations worldwide are not harmonised and can be generic or tailored for risk groups (Table 2). Experts must assess vaccination of travellers based on current country-specific recommendations and travel characteristics. Regardless of the incidence rate of typhoid in individual countries, European countries have different vaccination recommendations for travellers to those countries, with the need for vaccination based on travel duration, travel destination, circumstances of travelling or a combination of these factors.

Interviews with staff members from migrant resource centres have revealed that, paradoxically, migrants may believe that they are at lower risk than non-VFR travellers [34]. This is in part due to a generalised perception of immunity that they hold [34]. Efforts should be increased to target this sub-group of travellers.

As typhoid vaccines do not offer complete protection, safe water, sanitation and hygiene interventions are critical to preventing the spread of typhoid, both in endemic settings and among travellers [189]. A multidisciplinary strategy of public health based on personal protection and infrastructure interventions is needed.

7. Conclusion

Resistance has become a major threat to the treatment of typhoid, leading to treatment failure and subsequent changes in antimicrobial policy. The increasing prevalence of MDR *S*. Typhi strains is an important factor in the development of vaccination strategies for the prevention of typhoid infection in high-risk populations. The use of TCVs in endemic regions may be the best defence against MDR *S*. Typhi [54]. There is a need for worldwide surveillance and access to information on resistant strains, parallel to improvements in antibiotic usage and stewardship.

Country-level decision-making and programme planning are critical for local uptake and sustainability of vaccination strategies [122]. National decisions on the preferred vaccination strategy should be based on an analysis of the disease burden and risk factors for transmission, availability and quality of surveillance data, affordability, and operational feasibility. In parallel to vaccination, efforts to improve sanitation should continue.

For travellers, harmonisation of recommendations is likely to be of benefit. In particular, greater effort should be made to encourage vaccination for those visiting family and friends.

Author contributions

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Declaration of competing interest

The authors declare no conflicts of interest.

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