TARGET PRODUCT PROFILE FOR THERAPY OF UNCOMPLICATED ENTERIC FEVER

World Health Organization

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Introduction

Disease burden

Enteric fever, mostly referred to as typhoid fever, is a systemic infection caused by *Salmonella* Typhi (*S. enterica* subsp. *enterica*, serovar Typhi) or *Salmonella* Paratyphi (*S.* enterica subsp. *enterica*, serovar Paratyphi). Enteric fever is a poverty-related disease, common in countries with inadequate water and sanitation infrastructure. Infection with *S*. Typhi or the less common *S*. Paratyphi is estimated to have caused 14.3 million cases and 135,900 deaths worldwide in 2017[1] with higher case fatality estimates among children and older adults, and among those living in lower-income countries.[2,3] The highest burden of disease occurs in South and South-East Asia and in sub-Saharan Africa, and in children < 5 years old and, in some countries, young adults.[1] Food-related outbreaks occur in high-income countries (HICs) as well as in travellers who return from countries where enteric fever is endemic.

Antibiotic resistance

Multidrug-resistant (MDR) *S.* Typhi strains, resistant to three or more antibiotic categories, are common.[4] Extensively drug resistant (XDR) *S*. Typhi strains, resistant to all but one or two antibiotic categories, have emerged in Pakistan. The XDR strains are resistant to all major antibiotic categories used for treatment over the last 7 decades and have a large number of resistance determinants.[5] In addition to chromosomal resistance determinants, resistance genes can also be carried on transferable plasmids. The evolution and spread of MDR strains can take different paths in different regions of the world.[6] In some Asian countries, ciprofloxacin resistance in *S.* Typhi or *S.* Paratyphi is close to 100%.[7]

Available treatment options

Traditional therapies, including ampicillin, chloramphenicol, co-trimoxazole and fluoroquinolones, are not effective in many regions. In particular, fluoroquinolones are not effective against *S.* Typhi or *S.* Paratyphi in South Asia. Antibiotic treatment options for MDR strains are usually cefixime (an oral cephalosporin), azithromycin (an oral azalide) and ceftriaxone (an intravenous/intramuscular cephalosporin). The only active treatments for XDR strains documented in Pakistan are azithromycin and carbapenems.[8] Intravenous treatment with carbapenems is not available or affordable for most patients in countries endemic for enteric fever.

Therapies in development

Current research and investment focuses not on new antibiotic treatments, but on vaccine development and, to a lesser degree, diagnostics. An improved conjugate vaccine (Typbar TCV) was

pre-qualified by the World Health Organization (WHO) in December 2017. However, resistance to first- and second-line antibiotics is a public health concern and requires the development of new antibiotics. There are potentially suitable antibiotics in preclinical development, but not in clinical development. The target product profile (TPP) for a new antibiotic against *S*. Typhi and *S.* Paratyphi should address the need for a new class of drug with no cross-resistance to existing drugs used for treatment of enteric fever.

Purpose of the TPP

This TPP should guide the clinical development of a new antibiotic for the treatment of acute infection and prevention of carrier state in endemic or outbreak settings with bacteriologically confirmed MDR and XDR *S.* Typhi or *S.* Paratyphi. The new treatment should have excellent penetration into intracellular (preferred) and extracellular compartments, and lead to rapid clinical (fever defervescence) and microbiological clearance (blood culture negativity). It should be suitable for use in children with intravenous and oral formulations with a good bioavailability. Hepatic clearance is preferred, as a high liver clearance is required to eliminate convalescent faecal shedding and carrier state.

A new antibiotic against *S*. Typhi and *S*. Paratyphi may also be effective against invasive non-typhoidal *Salmonella* infection and potentially in *Shigella* infection. The predicted rise in environmental disasters, such as flooding, could significantly increase the risks of enteric fever and the need for new antibiotics in the future. Antibiotic research efforts should go hand in hand with the development of corresponding rapid diagnostics that are inexpensive and identify the pathogen as well as the susceptibility profile.

Access and affordability

- Access to new essential antibacterial treatments is an essential part of universal health coverage. Developers should commit to an access and stewardship strategy that promotes availability at fair prices. A fair price is one that is affordable for health systems and patients, but at the same time provides sufficient market incentive for industry to invest in innovation and the production of quality essential health products.[9] To ensure access to patients in many countries, developers are invited to collaborate with WHO, the Global Antibiotic Research and Development Partnership and the Medicines Patent Pool where appropriate.
- Governments need to commit to ensure availability and affordability of essential new antibiotic treatments. In particular for reserve antibiotics,[10] governments should explore models where procurement and reimbursement are linked to availability instead of volume to foster appropriate use.
- Stewardship and appropriate use are essential to preserve the effectiveness of any new antibacterial treatment. Developers should not register the product for use in animals or plants or develop a treatment of the same class for use in animals or plants. The above-mentioned access and stewardship plan should be based on ethical promotion and distribution. Manufacturing should be in line with best industry practices in the management of emissions to the environment to minimize the risks of spreading antimicrobial resistance.

TPP for therapy of uncomplicated enteric fever

	Minimal TPP	Preferred TPP
Indication for use	Suspected or confirmed uncomplicated enteric fever.	Suspected or confirmed uncomplicated enteric fever (diagnosed by blood culture). Treatment of acute infection, including prevention of carrier state.
Target population	Adults, children	Adults, children
Access and affordability	See Introduction and paragraph on Access and affordability.	See Introduction and paragraph on Access and affordability.
Safety/tolerability	Clinical safety comparable to current therapies.	Clinical safety comparable to current therapies, good tolerability in children.
In vitro activity	In vitro activity against *S.* Typhi and *S.* Paratyphi, low cross-resistance to known antibiotic classes, intracellular activity. Low propensity for mutational resistance development.	In vitro activity against *S.* Typhi and *S.* Paratyphi, no cross-resistance to known antibiotic classes, intracellular activity. Low propensity for mutational resistance development.
Clinical efficacy	Non-inferior clinical activity in acute enteric fever to current therapies in susceptible strains, low relapse rate (< 5%), clinical activity in infections due to pathogens resistant to current therapies.	Non-inferior clinical activity in acute enteric fever to current therapies in susceptible strains, low relapse rate (< 5%), prevent convalescent faecal shedding, clinical activity in infections due to pathogens resistant to current therapies.
Formulation/ presentation	Tablets/capsules, injectables	Tablets/capsules, paediatric suspension with acceptable taste, injectables
Dose regimen	1–3x daily, treatment duration up to 14 days	1–2x daily, treatment duration up to 7 days
Route of administration	Oral, or oral + intravenous (iv)	Oral, or oral + iv
Product stability and storage	Heat stable, 3-year shelf life in hot tropic/ humid climate (simulated with 30°C and 65% relative humidity).	Heat stable, 3-year shelf life in hot tropic/ humid climate (simulated with 30°C and 65% relative humidity). Stability of formulated suspension for multiple days without refrigeration.
Pharmacokinetics	Pharmacokinetic data available to support use in acute infections, intracellular penetration and biliary excretion.	Pharmacokinetic data available to support use in acute infections, including children, older patients (> 65 years), patients with some renal or hepatic insufficiency, intracellular penetration and biliary excretion.
Drug interactions	Comparable to current therapies, no drug-drug interactions (DDIs) with commonly prescribed drugs in the patient population.	Comparable to current therapies, no DDIs with commonly prescribed drugs in the patient population.

Important documents

Typhoid vaccine prequalified [website]. Geneva: World Health Organization; 2018 (http://www.who.int/medicines/news/2017/WHOprequalifies-breakthrough-typhoid-vaccine/en/, accessed 30 January 2020).

Kirk MD, Pires SM, Black RE, Caipo M, Crump JA, Devleesschauwer B, et al. 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, accessed 4 February 2020).

References

1 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. 2019;19(4):369-81 (https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(18)30685-6/fulltext, accessed 30 January 2020).

2 GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1211-59.

3 GBD 2016 Causes of Death Collaborators. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017;390(10100):1151-210.

4 Karkey A, Thwaites GE, Baker S. The evolution of antimicrobial resistance in Salmonella Typhi. Curr Opin Gastroenterol. 2018;34(1):25-30.

5 Klemm EJ, Shakoor S, Page AJ, Qamar FN, Judge K, Saeed DK et al. Emergence of an extensively drug-resistant Salmonella enterica serovar Typhi clone harboring a promiscuous plasmid encoding resistance to fluoroquinolones and third-generation cephalosporins. MBio. 2018;9(1):e00105-18.

6 Dyson ZA, Klemm EJ, Palmer S, Dougan D. Antibiotic resistance and typhoid. Clin Infect Dis. 2019;68 (Suppl 2):S165-70.

7 Cuypers WL, Jacobs J, Wong V, Klemm EJ, Deborggraeve S, Van Puyvelde S. Fluoroquinolone resistance in Salmonella: insights by whole-genome sequencing. Microb Genom. 2018;4(7):e000195.

8 Chatham-Stephens K, Medalla F, Hughes M, Appiah GD, Aubert RD, Caidi H et al. Emergence of extensively drug-resistant Salmonella typhi infections among travelers to or from Pakistan - United States, 2016-2018. Morb Mortal Wkly Rep. 2019;68(1):11-3.

9 Fair pricing of medicines. In: WHO essential medicines and health products [website]. Geneva: World Health Organization; 2020 (https://www.who.int/medicines/access/fair_pricing/en/, accessed 30 January 2020).

10 WHO model list of essential medicines, 20th list (March 2017). Geneva: World Health Organization; 2017 (https://www.who.int/medicines/publications/essentialmedicines/20th_EML2017.pdf, accessed 3 February 2020).