TARGET PRODUCT PROFILES FOR NEEDED ANTIBACTERIAL AGENTS:

enteric fever, gonorrhoea, neonatal sepsis, urinary tract infections and meeting report

World Health Organization

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World Health Organization

Expert meeting on target product profiles for needed antibacterial agents

3–4 October 2019, Geneva, Switzerland

Meeting report

Introduction

This is the report of the scientific advisory group meeting on the development of target product profiles (TPPs) for needed antibacterial agents for enteric fever (typhoid fever), gonorrhoea, neonatal sepsis and urinary tract infections, that took place in Geneva, Switzerland, on 3–4 October 2019.

Antimicrobial resistance (AMR) has increased worldwide in recent decades, limiting treatment options for many bacterial infections. In 2015, AMR was recognized as a global public health challenge with the adoption of the Global Action Plan (GAP) by the sixty-eighth World Health Assembly, providing countries with a blueprint for action to combat AMR both nationally and internationally.[1]

In response to GAP objective 5, WHO developed the *Global priority list of antibiotic-resistant bacteria* and the report *Antibacterial agents in clinical development* in 2017, and the report *Antibacterial agents in preclinical development* in 2019, to provide evidence-based guidance and a public health perspective in developing new antibacterial therapies.[2,3]

WHO has subsequently formulated TPPs to meet the need for specific antibacterial agents. TPPs are used by drug developers to provide strategic guidance for product development programmes, and to specify the intended use, target populations and desired attributes of potential new products. In the regulatory context, TPPs help to frame development in relation to submission of product dossiers. In the context of public health, WHO TPPs set R&D targets for funders and developers by outlining the desired performance and operational characteristics of potential new products.

1 Global action plan on antimicrobial resistance. Geneva: World Health Organization; 2015 (https://www.who.int/antimicrobial-resistance/global-action-plan/en/, accessed 23 January 2020).

2 Prioritization of pathogens to guide discovery, research and development of new antibiotics for drug-resistant bacterial infections, including tuberculosis. Geneva: World Health Organization; 2017 (WHO/EMP/IAU/2017.12; https://www.who.int/medicines/areas/rational_use/prioritization-of-pathogens/en/, accessed 23 January 2020).

3 Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including tuberculosis. Geneva: World Health Organization; 2017 (WHO/EMP/IAU/2017.12; https://www.who.int/medicines/areas/rational_use/antibacterial_agents_clinical_development/en/, accessed 23 January 2020).

The TPP development process

The TPPs for new antibacterial agents were developed in line with the standard WHO procedure for TPPs (Fig. 1). In January 2019, an interdepartmental meeting of WHO experts was held, identifying five clinical syndromes for which new antibacterial therapies are urgently needed due to increased resistance to existing therapies. These five clinical syndromes are neonatal sepsis, gonorrhoea, typhoid fever, urinary tract infections (UTIs) and intensive care unit (ICU) patient-focused indications.

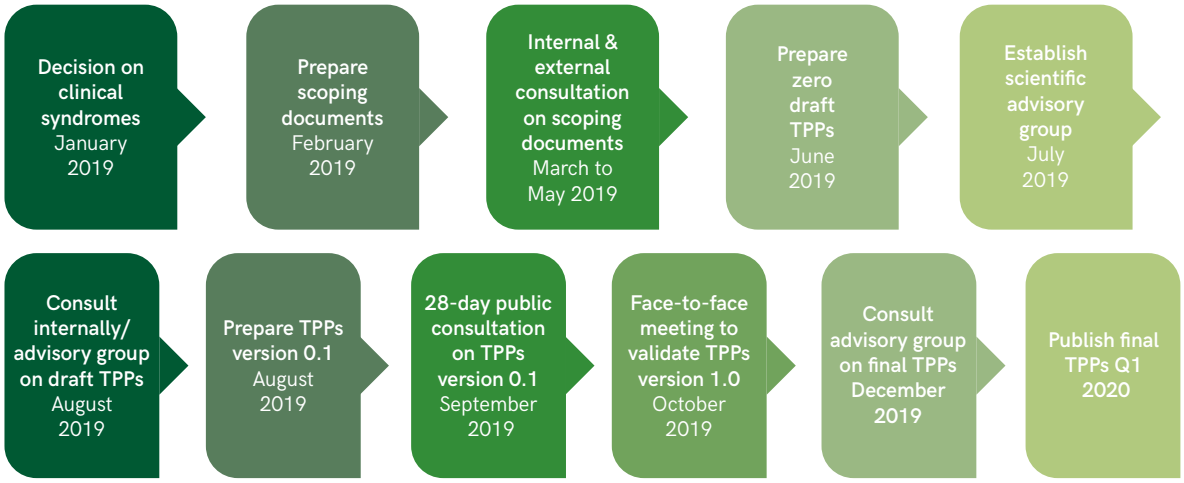
WHO then developed scoping documents for each of these five clinical syndromes, followed by an internal consultation with the WHO departments – Health Products, Policy and Standards; Immunization, Vaccines and Biologicals; Global HIV, Hepatitis and STI Programmes; and Maternal, Newborn, Child & Adolescent health and Ageing. This was followed by an external consultation process involving a broad set of clinical and drug-development experts. The proposed ICU patient-focused indication TPP was thereafter removed, as the scope was considered too broad. WHO prepared draft TPP documents for the remaining four clinical syndromes, reflecting the written comments received from the internal WHO experts.

A scientific advisory group of senior scientists, clinical and product development experts, public health officials and regulators was established following the WHO standard procedure for TPPs regarding geographical and gender balance, diversity in expertise and management of conflict of interest (see Annex 1). This group provided written feedback on the draft TPP documents, which, together with the feedback from the internal WHO consultation, informed subsequent amendments of the draft TPPs. From 1 to 29 September 2019, WHO published the following draft TPP documents for public consultation:

- empirical therapy of neonatal sepsis in high-resistance settings/targeted therapy for multidrug-resistant (MDR) Gram-negative neonatal sepsis;
- therapy of diagnosed uncomplicated gonorrhoea;
- therapy of uncomplicated typhoid fever; and
- oral therapy of acute uncomplicated UTI.

Following the public consultation period, WHO convened a face-to-face meeting of the scientific advisory group and the relevant internal WHO experts on 3–4 October 2019 in Geneva, Switzerland, to discuss the draft TPPs, validate the feedback received from the public consultation and update the TPP documents accordingly (Fig. 2). The list of participants is detailed in Annex 1.

Fig. 1. TPP development process



Summary of the meeting proceedings

The opening remarks were delivered by Haileyesus Getahun (director of WHO/GCP/AMR), focusing on WHO's role in providing the public health perspective and technical guidance on global health issues including the development of new antibiotic medicines. Peter Beyer (senior advisor, WHO/GCP/AMR) then presented WHO's work in R&D on AMR and introduced the draft TPPs for antibacterial agents to be discussed at the meeting. Priscilla Rupali (professor and senior consultant, Christian Medical College Vellore, India) chaired the discussions throughout the 2-day meeting. Ingrid Smith (technical officer, WHO/GCP/AMR), presented the meeting objectives, and Ingrid Smith, Sarah Paulin and Kwame Boaitey, all WHO/GCP/AMR, documented the discussions and consensus reached during the meeting.

Declarations of interest were recorded and assessed for potential conflicts by the WHO Secretariat. One expert, Prabha Fernandes, former CEO of CEMPRA, was partially excluded from the discussions on the TPP for gonorrhoea, due to previous employment by a commercial entity developing similar products within the past 4 years.

The draft TPPs were then discussed one by one, including a review of the feedback received on each during the public consultation. The draft TPP documents were updated at the meeting in real time. Following the discussions on each of the draft TPPs, a subsequent discussion was held on the topic of access and affordability, a subsection common to all four TPP documents.

Summary of discussions

1. **TPP for oral therapy of acute uncomplicated UTIs (cystitis and pyelonephritis)**

   Consensus was reached to divide this TPP into two TPPs: (1) oral treatment of lower UTI (cystitis) to substitute nitrofurantoin, fosfomycin trometamol and pivmecillinam, and (2) oral treatment of upper UTI (pyelonephritis) by acute uncomplicated infection or after intravenous (iv) treatment in hospitalized patients. Target populations for both TPPs are adolescents and adults (cystitis – women only) with suspected MDR Gram-negative pathogens.

2. **TPP for therapy of diagnosed uncomplicated gonorrhoea**

   Consensus was reached that co-infections with chlamydia would not be addressed with this TPP, and that the minimal (treatment of suspected gonorrhoea) and the preferred (treatment of diagnosed gonorrhoea) TPP would correspond to empirical and targeted treatment, respectively. Furthermore, adolescents were included in the target population for the TPP together with adults.

3. **TPP for empirical therapy of typhoid fever in high-risk settings**

   Consensus was reached that the typhoid fever TPP should be named enteric fever because the causative pathogen is *Salmonella enterica* (serovars Typhi and Paratyphi). Furthermore, any new treatment must have intracellular activity, achieve rapid clearance of acute infection with effective elimination of convalescent faecal shedding and have a low relapse rate. It should be suitable also for use in children and be available in both iv and oral formulation.

4. **TPP for empirical therapy of neonatal sepsis in high-resistance settings/TPP for targeted therapy for MDR Gram-negative neonatal sepsis**

   There were extensive discussions about these two TPPs. Consensus was reached not to pursue

finalization of the TPP for empirical therapy because large multinational observational studies are ongoing, which will provide data on the actual use of antibiotics versus WHO recommended regimens and on infection-causing pathogens and their resistance rates from a site, country and regional perspective. As such, the data will provide evidence to determine the requirements of future empirical treatment regimens. The absence of this evidence makes it difficult at present to select one empirical treatment for neonatal sepsis or to formulate the relevant TPP.

Consensus was also reached to amend the title of the second TPP (targeted therapy) to TPP for therapy in children including neonates with MDR Gram-negative infections. This is due to the following factors: It would be more meaningful to develop a pathogen-focused TPP that applies across all paediatric age ranges. Also, it would be very difficult to include a sufficient number of subjects with such a resistant infection if the inclusion criteria were restricted to neonates with MDR Gram-negative pathogens. Finally, "targeted" was deleted as it implied culture-confirmed disease, which would be unlikely in many low-resource settings with high levels of MDR Gram-negative bacteria. As an AMS measure, the target population was identified as hospitalized children with an emphasis on neonates with severe infections and failure on current treatment and at least highly suspected to have a MDR/XDR infection.

5. Access and affordability

To conclude, a discussion was held on access and affordability, an issue of particular concern for low- and middle-income countries with low levels of health insurance coverage and high levels of resistance. Consensus was reached that the following text should be included in the introductory section of all the TPPs:

- 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.[4] To ensure access to patients in many countries, developers are invited to collaborate with WHO, GARDP 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, 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 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 risk of spreading AMR.

6. Suggestions for potential future TPP development

The group discussed and suggested the following areas for potential future TPPs: Treatment of XDR (extensively drug resistant) Gram-negative bacteria in adults; treatment for (untreatable) *Helicobacter pylori* infections, especially for gastric cancer patients; treatment for drug-resistant shigella; treatment of syphilis; treatment of undiagnosed non-malarial febrile illness; treatment of bacterial meningitis; and treatment of fungal infections.

[4] Fair pricing of medicines. In: WHO essential medicines and health products [website] (https://www.who.int/medicines/access/fair_pricing/en/, accessed 23 January 2020).

Conclusion

The main outcomes of the meeting were: to develop separate TPPs for lower UTI (cystitis) and upper UTI (pyelonephritis); not to develop the TPP for empirical therapy of neonatal sepsis in high-resistance settings; and to include a separate paragraph on access and affordability in all the TPPs. The draft TPPs will be updated according to the meeting recommendations and, following a final review by the scientific advisory group, will be formally adopted and published on the WHO Global Observatory on Health R&D.

Fig. 2. Scientific advisory group meeting on TPPs for needed antibacterial agents, 3–4 October 2019, Geneva, Switzerland

Annex 1. Scientific advisory group and meeting participants

Name	Institution, country
External experts	
Angela Huttner*	Hôpitaux Universitaires de Genève, Switzerland
Chris Parry*	Liverpool School of Tropical Medicine, UK
Folasade Ogunsola*	University of Lagos, Nigeria
Guy Thwaites	Oxford University Clinical Research Unit, Viet Nam
Jeeva Sankar	All India Institute of Medical Sciences, New Delhi, India
Jennie Hood	Global AMR R&D Hub, Germany
Mark Goldberger	Washington DC, USA (independent)
Mical Paul*	Rambam Medical Center, Israel
Prabha Fernandes*	Chapel Hill NC, USA (independent)
Priscilla Rupali*	Christian Medical College Vellore, India
Seamus O'Brien*	GARDP, Geneva, Switzerland
Shabina Ariff	Aga Khan University, Karachi, Pakistan
Thomas Tangden	ReAct, Uppsala, Sweden
Queen Dube*	Queen Elizabeth Hospital, Blantyre, Malawi
WHO staff	
Adwoa Desma Bentsi-Enchill*	WHO headquarters
Haileyesus Getahun*	WHO headquarters
Ingrid Smith*	WHO headquarters
Kwame Boaitey*	WHO headquarters
Peter Beyer*	WHO headquarters
Sarah Paulin*	WHO headquarters
Teodora Elvira Wi*	WHO headquarters
Shamim Ahmad Qazi	WHO consultant
Ursula Theuretzbacher*	WHO consultant

*Attended the scientific advisory group meeting in Geneva on 3–4 October 2019.

World Health Organization

Target product profile for therapy of uncomplicated enteric fever

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).

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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).

World Health Organization

Target product profile for therapy of diagnosed uncomplicated gonorrhoea

Introduction

Disease burden

Gonococcal infection is the second most prevalent bacterial sexually transmitted infection (STI), and as such is a current public health problem worldwide.[1] *Neisseria gonorrhoeae* causes an estimated 87 million new cases annually, of which approximately half are asymptomatic. Symptomatic gonorrhoea results in urethritis in males and cervicitis in females. Untreated gonorrhoea can lead to epididymitis in males and pelvic inflammatory disease in females, which in turn can have serious sequelae such as infertility, ectopic pregnancy and chronic pelvic pain. Infants of mothers with gonococcal infection can be infected at delivery, resulting in neonatal conjunctivitis, which may lead to scarring and blindness if untreated. Untreated gonorrhoea can also lead to disseminated infection with polyarthralgia, polyarthritis or oligoarthritis, and rarely to endocarditis. Finally, gonorrhoea can increase the risk of contracting and transmitting HIV and other STIs.[2] Gonorrhoea affects high-, middle- and low-income countries. The African region has the highest rates of gonococcal infection worldwide.[3]

Antibiotic resistance

Widespread antibiotic resistance in *N. gonorrhoeae* strains has increasingly compromised the management and control of gonorrhoea.[4] *N. gonorrhoeae* has evolved and acquired or developed resistance to all oral antimicrobials used for treatment – sulphonamides, penicillins, tetracyclines, macrolides and fluoroquinolones – leading to treatment failures. *N. gonorrhoeae* continues to show high rates of non-susceptibility to azithromycin in many countries, and the increasing emergence of strains with decreased susceptibility, and resistance to ceftriaxone is concerning.[5] Resistance to both agents of the dual therapy (ceftriaxone and azithromycin) and to other antibiotic classes (extensively drug resistant isolates) has emerged but is still rare.

Available treatment options

Currently, the empirical therapy for gonorrhoea in most countries is the injectable third-generation cephalosporin ceftriaxone and azithromycin. But high levels of resistance to both ceftriaxone and azithromycin have been reported. The recently released World Health Organization (WHO) treatment guidelines for gonorrhoea recommend dual therapy over monotherapy where resistance surveillance data is not available. In 2019 the US Centers for Disease Control and Prevention recommended dual therapy with a single dose of ceftriaxone given intramuscularly (im) plus oral azithromycin.[6] Because of increasing resistance to last-line treatment options, choices for antimicrobial treatment are becoming limited. Gentamicin is an option for treating ceftriaxone-resistant gonorrhoea, but it is not as effective as ceftriaxone.

Therapies in development

Because of the inherent risk of emergence of resistance of *N. gonorrhoeae* to antibiotics, continuous efforts to develop new treatments for gonorrhoea are inevitable. The target product profile (TPP) development will be essential to increase the pipeline of new treatments. The current clinical pipeline for gonorrhoea treatment is severely depleted due to lack of economic attractiveness and recent failures in Phase 3 clinical studies. Only two new antibiotics are in clinical development (zoliflodacin and gepotidacin), but several preclinical programmes target *N. gonorrhoeae*. WHO is now facilitating the development of a gonorrhoea vaccine after a successful proof-of-concept trial with meningococcal group B vaccine, but it is still in the early phase of development. Drug-drug interactions (DDIs) must be considered in patients on HIV treatment, as CYP3A4 can be induced by HIV protease inhibitors, and CYP3A4 metabolizes many medicines, including macrolides.

Purpose of the TPP

An initial TPP for gonorrhoea was developed by WHO and the Global Antibiotic Research and Development Partnership (GARDP).[7] This TPP is hereby being updated to ensure realistic expectations following the new WHO standardized methodology for developing TPPs. Co-infections with chlamydia are not addressed by this TPP. The minimal and the preferred TPP correspond to empirical and targeted treatment, respectively.

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.[8] To ensure access to patients in many countries, developers are invited to collaborate with WHO, GARDP 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,[9] 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 (AMR).

TPP for therapy of diagnosed uncomplicated gonorrhoea

	Minimal TPP	Preferred TPP
Indication for use	Treatment of suspected or diagnosed uncomplicated urogenital gonorrhoea.	Treatment of diagnosed uncomplicated urogenital gonorrhoea and extra-genital gonorrhoea (anorectal and oropharyngeal).
Target population	Adults and adolescents in areas with resistance to the current recommended first-line treatment.	Adults and adolescents in areas with resistance to the current recommended first-line treatment.
Access and affordability	See Introduction and paragraph on Access and affordability.	See Introduction and paragraph on Access and affordability.
Safety/tolerability	No patient monitoring required post treatment. For oral route, low frequency of side effects, including nausea and vomiting (comparable to current treatment). For im use, good local tolerance.	No patient monitoring required post treatment. For oral route, low frequency of side effects, including nausea and vomiting (comparable to current treatment). For im use, good local tolerance. Acceptable for use in pregnancy and lactation based on nonclinical studies.
In vitro activity	In vitro activity against *N. gonorrhoeae* resistant to extended-spectrum cephalosporins and macrolides, no cross-resistance to any other known antibiotic class (best achieved by a new class and/or new target and/or new mode of action). Activity measured by minimum inhibitory concentration (MIC) and dynamic in vitro models that account for protein binding, intracellular penetration and activity against intracellular bacteria. Low potential for emergence of mutational resistance.	In vitro activity against *N. gonorrhoeae* resistant to extended-spectrum cephalosporins and macrolides, no cross-resistance to any other known antibiotic class (best achieved by a new class and/or new target and/or new mode of action). Activity measured by MIC and dynamic in vitro models that account for protein binding, intracellular penetration and activity against intracellular bacteria. Low potential for emergence of mutational resistance.
Clinical efficacy	Non-inferiority in clinical trials versus current standard of care, as in US Food and Drug Administration (FDA) guidance, for urogenital gonorrhoea.	Non-inferiority to current standard of care (as in FDA guidance) for urogenital gonorrhoea, and equivalent to current care for extra-genital gonorrhoea.
Dose regimen	1–3 doses, up to 3 days	Single dose preferred at least for urogenital gonorrhoea; but 1–3 doses, up to 3 days, acceptable to treat extra-genital gonorrhoea.
Route of administration	Oral or im	Oral or im
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).
Pharmacokinetics	Pharmacokinetic data available to support use in acute infection.	Pharmacokinetic data available to support use in acute infection and elimination of colonizing extragenital bacteria and show intracellular activity.
Drug interactions	Minimal relevant DDIs, including HIV medicines and other STI treatments.	No relevant DDIs, including HIV medicines and other STI treatments.

Important documents

WHO guidelines for the treatment of Neisseria gonorrhoeae. Geneva: World Health Organization; 2016 (https://apps.who.int/iris/bitstream/handle/10665/246114/9789241549691-eng.pdf?sequence=1, accessed 2 February 2020).

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Uncomplicated gonorrhoea: developing drugs for treatment guidance for industry. Silver Spring, MD: US Department of Health and Human Services, Food and Drug Administration; 2015 (https://www.fda.gov/media/88904/download, accessed 3 February 2020).

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World Health Organization

Target product profile for therapy of neonatal sepsis in high resistance settings

Introduction

Disease burden

Neonatal sepsis is a systemic infection occurring in infants ≤ 28 days old which accounts for 15% of deaths in neonates globally.[1,2] The highest burden of neonatal sepsis is in South Asia and sub-Saharan Africa,[3] although it is recognized that there may be some overdiagnosis due to the low specificity of clinical diagnosis. The aetiology of neonatal sepsis is largely unknown in low- and middle-income countries (LMICs), as surveillance data are sparse due to low rates of microbiological diagnostics being performed to confirm suspected neonatal sepsis and low detection rates of bacterial pathogens due to a very low number of positive blood cultures.[4,5,6]

The epidemiology of pathogens differs regionally and depends on time of onset of infection, but involves Gram-negative pathogens (mainly *Escherichia coli* and *Klebsiella* species, but also *Acinetobacter* species and *Pseudomonas aeruginosa*), *Staphylococcus aureus* and other Gram-positive cocci.[7]

Antibiotic resistance

Resistance rates are extremely variable, and only a few studies with adequate data exist. Nevertheless, multidrug-resistant (MDR) pathogens, resistant to more than one agent in three or more antibiotic categories, are estimated to account for approximately 30% of all global neonatal sepsis mortality.[8]

Available treatment options

Few antibiotics have been tested and licensed for either the empirical treatment of clinically diagnosed neonatal sepsis or for cases suspected or confirmed to be caused by MDR bacteria. The World Health Organization (WHO) recommended treatment of ampicillin or penicillin in combination with gentamicin may not be adequate in many places due to a global increase in resistance in Gram-negative pathogens.

Therapies in development

Regulatory requirements and incentives exist for paediatric studies with new drugs, but economic incentives are lacking for the development of new antibiotics overall. No registrational studies are under way for new antibiotic treatments for neonatal sepsis, and consequently public health studies are required with appropriate funding to fill this gap. Recently approved new antibiotics for use in adults (i.e. ceftazidime-avibactam, meropenem-vaborbactam) may potentially be suitable, and their use could be explored for neonatal infections. Development activities would be supported by an agreed target product profile (TPP) tailored to prioritize treatment in settings with a high prevalence of resistance.

Purpose of the TPP

A TPP developed by the Global Antibiotic Research and Development Partnership (GARDP) with World Health Organization (WHO) involvement, primarily focusing on empirical treatment of neonatal sepsis, already exists.[9] This process would build on that work following the new more inclusive WHO standard procedure for developing TPPs. Due to the incomplete knowledge around the wide variety of aetiology and resistance rates in different regions, and thus the types of target products and treatments required, this TPP addresses the known challenge of specific therapy for infections caused by different MDR and extensively drug resistant (XDR) organisms (resistant to all but one or two antibiotic categories), including carbapenem-resistant organisms. The expert meeting recommended postponing the TPP for empirical therapy of neonatal sepsis until more reliable data from ongoing epidemiological studies is available. Furthermore, the meeting recommended changing the title of the second TPP to TTP for therapy in children including neonates with MDR Gram-negative infections, to recognize the requirement of such a TPP to cover all XDR/MDR infections across age groups and to secure sufficient study subjects by not limiting the inclusion criteria to neonates only. Antibiotic research efforts should go hand in hand with the development of corresponding rapid diagnostics that are inexpensive and that 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.[10] To ensure access to patients in many countries, developers are invited to collaborate with WHO, GARDP 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,[11] 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 (AMR).

TPP for therapy in children including neonates with MDR Gram-negative infections

	Minimal TPP	Preferred TPP
Indication for use	Serious bacterial infections in environments with high prevalence of XDR Gram-negative bacteria for which there are limited or no treatment options.	All the criteria included in the minimal TPP, and neonatal sepsis/meningitis caused by MDR and XDR Gram-negative pathogens, including *K. pneumoniae* and *Acinetobacter* spp., failing on optimal current treatment.
Target population	Hospitalized children with an emphasis on neonates with severe infections and failure on current treatment.	Hospitalized children including neonates with severe infections, failure on current treatment and a very high likelihood of being caused by MDR/XDR Gram-negative pathogens.
Access and affordability	See Introduction and paragraph on Access and affordability.	See Introduction and paragraph on Access and affordability.
Safety/tolerability	The need for safety and tolerability data from animal juvenile toxicity models should be considered on a case-by-case basis.	The need for safety and tolerability data from animal juvenile toxicity models should be considered on a case-by-case basis. No requirement to routinely monitor drug levels.
In vitro activity	MDR and XDR Gram-negative pathogens, including *K. pneumoniae* and/or *Acinetobacter* spp., activity tested in bacteria with defined resistance mechanisms (especially β-lactams, aminoglycosides, fosfomycin). Low cross-resistance to currently used antibiotics, and low propensity for resistance development.	MDR and XDR Gram-negative pathogens, including *K. pneumoniae* and *Acinetobacter* spp., activity tested in bacteria with defined resistance mechanisms (especially β-lactams, aminoglycosides, fosfomycin) and clinical strains, especially carbapenem-resistant strains, no cross-resistance to currently used antibiotics. Low propensity for resistance development.
Clinical efficacy	Proven efficacy in adults, and showing safety and refining the pharmacokinetics (PK) in neonates and children. Demonstrate clinical efficacy in adults with confirmed XDR infections.	Proven efficacy in adults, and showing safety and refining the PK in neonates and children. Demonstrate clinical efficacy in adults with confirmed XDR infections.
Formulation/ presentation	Injectable and oral formulations	Injectable and oral formulations
Dose regimen	1–4x daily, treatment duration depending on initial clinical response to treatment and clinical focus on site of infections.	1–4x daily, treatment duration depending on initial clinical response to treatment and clinical focus on site of infections.
Route of administration	Intravenous injection or infusion	Intravenous injection or infusion and oral (step down)
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).
Pharmacokinetics	PK data available to support use in all age groups, including neonates, derived from population PK modelling in neonates and across all age groups.	PK data available to support use in all age groups, including neonates, population PK modelling in neonates and across all age groups, population PK modelling to support activity in cerebrospinal fluid.
Drug interactions	Minimal drug-drug interactions (DDIs) with common intensive care unit (ICU) drugs. For HIV, tuberculosis (TB) and malaria medication, DDIs should be studied if relevant, in addition to those that have already been studied.	No DDIs with common ICU drugs. For HIV, TB and malaria medication, DDIs should be studied if relevant, in addition to those that have already been studied.

WHO documents

WHO recommendations on newborn health guidelines approved by the WHO Guidelines Review Committee. Geneva: World Health Organization; 2017 (https://apps.who.int/iris/bitstream/handle/10665/259269/WHO-MCA-17.07-eng.pdf?sequence=1, accessed 30 January 2020).

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World Health Organization

Target product profiles for oral therapy of urinary tract infections

Introduction

Disease burden

Urinary tract infections (UTIs) are associated with significant disease burden, antimicrobial resistance (AMR) and cost.

Acute uncomplicated lower UTI, mainly cystitis in women, remains one of the most common indications for prescribing antibiotics.[1,2] *Escherichia coli* is the most common pathogen, followed by *Klebsiella pneumoniae*, *Proteus mirabilis* and other *Enterobacteriaceae*. A wide range of antibiotics are prescribed, which impacts resistance rates.

Acute pyelonephritis with community onset is an ascending UTI involving the kidneys and may be associated with bacteraemia.[3] Although pyelonephritis is less common than cystitis, it causes important short-term morbidity and can lead to severe and sometimes fatal complications. The incidence is highest among young women, followed by infants and the elderly.[4] Similarly to cystitis, the most common pathogen is *E. coli* followed by other *Enterobacteriaceae*, with a wide range of variation. Acute pyelonephritis may be treated with oral antibiotics that cover the same spectrum of pathogens as cystitis, but it requires adequate antibiotic concentrations in the upper urinary tract and bloodstream.[5]

Antibiotic resistance

Community-acquired infections, including UTIs, caused by extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*, are becoming more common and pose a major healthcare burden and treatment challenge. ESBL-producing *Enterobacteriaceae* are commonly co-resistant to fluoroquinolones. Resistance data shows high rates of resistance to ampicillin, amoxicillin/clavulanic acid, oral cephalosporins, co-trimoxazole and ciprofloxacin in many countries. Resistance patterns of *E. coli* strains, the dominant uropathogen, vary considerably among regions and countries.[6]

Available treatment options

Increasing resistance rates have reduced oral treatment options. Oral fluoroquinolones are no longer recommended for empirical therapy of lower UTI in many countries, due to increased resistance rates and its potential for selection pressure and co-resistance to unrelated antibiotic classes. Oral fluoroquinolones may still be recommended for empirical treatment of acute pyelonephritis in countries with low resistance rates.

Nitrofurantoin, fosfomycin trometamol and pivmecillinam have been revived for treatment of cystitis (e.g. high-risk patients, long-term care facilities) because of high resistance rates to other antibiotics and to avoid the emergence of further resistance to commonly used antibiotics (e.g. fluoroquinolones). The above three antibiotics have proven efficacy against ESBL-producing *Enterobacteriaceae*, which might expand their use. However, they are not universally available and increased resistance rates can be anticipated following increasing use, particularly for fosfomycin trometamol and pivmecillinam.

Oral treatment options for pyelonephritis are even more limited, as many of the available treatment options are only suitable or approved for cystitis. Moreover, resistance to co-trimoxazole and fluoroquinolones severely affects treatment options for upper UTI caused by ESBL-producing *Enterobacteriaceae*.

Therapies in development

New oral drugs are being developed mainly for complicated UTI in hospitalized patients as follow-on oral treatment after a few days of intravenous (iv) treatment. Though several oral antibiotics are in clinical development, i.e. oral sulopenem (penem) and tebipenem (carbapenem), they are mainly modified compounds of old classes. Consequently, they may suffer from some class-specific cross-resistance or exert strong selection pressure if widely used in the community. There are a few agents in preclinical development, and the recent clinical failure of oral eravacycline calls for a target product profile (TPP) to guide the development of new oral antibiotic agents for UTIs.

Purpose of the TPPs

Cystitis: New oral antibacterial drugs without cross-resistance to existing classes and without selection pressure on existing classes are needed to provide an alternative to nitrofurantoin, fosfomycin trometamol and pivmecillinam. Such new drugs would require high urinary concentrations and activity, but not necessarily high blood concentrations.

Pyelonephritis: New oral antibacterial drugs and oral follow-on treatment after iv treatment in hospitalized patients without cross-resistance to existing classes and without selection pressure on existing classes are needed. Patients with infections involving the upper urinary tract require drugs with adequate blood and renal parenchyma concentrations and activity in urine.

Both: Ideally, any new medicine for lower or upper UTI would exert minimal collateral effects on human microbiota, inducing little selection pressure for emergence of resistance, particularly among gastrointestinal flora.

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.[7] To ensure access to patients in many countries, developers are invited to collaborate with the World Health Organization (WHO), the Global Antibiotic Research and Development Partnership (GARDP) 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,[8] 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 AMR.

TPP for oral therapy of acute uncomplicated UTI (cystitis)

	Minimal TPP	Preferred TPP
Indication for use	Treatment of acute uncomplicated community-acquired lower UTI in women (cystitis).	Treatment of acute uncomplicated community-acquired lower UTI (cystitis) in women with confirmed or increased risk for multidrug-resistant (MDR) Gram-negative (incl. ESBL-producing) pathogens, or in need of an alternative therapy to nitrofurantoin, fosfomycin or pivmecillinam.
Target population	Adolescents and adults (women) with suspected MDR Gram-negative pathogens.	Adolescents and adults (women) with suspected MDR Gram-negative pathogens.
Access and affordability	See Introduction and paragraph on Access and affordability.	See Introduction and paragraph on Access and affordability.
Safety/tolerability	Comparable to current therapies with β-lactams, no toxicity signals in preclinical reproduction toxicity studies.	Comparable to current therapies with β-lactams, no indication for toxicity signals in preclinical reproduction toxicity studies.
In vitro activity	Activity against Enterobacteriaceae (especially *E. coli*, *Klebsiella* and *Proteus*, including ESBL producers); low cross-resistance to known antibiotic classes (new class/target/ mode of action), especially β-lactams, fluoroquinolones, co-trimoxazole, fosfomycin, nitrofurantoin; low propensity for mutational resistance development.	Activity against Enterobacteriaceae (especially *E. coli*, *Klebsiella* and *Proteus*, including ESBL producers); no cross-resistance to known antibiotic classes (new class/new target/new mode of action), especially β-lactams, fluoroquinolones, co-trimoxazole; low propensity for mutational resistance development.
Clinical efficacy	Non-inferior clinical activity to current therapies in acute infections with susceptible pathogens: ciprofloxacin, pivmecillinam and co-trimoxazole. Clinical trials should include elderly patients (> 65 years).	Non-inferior clinical activity to current therapies in acute infections with susceptible pathogens: ciprofloxacin, pivmecillinam and co-trimoxazole. Clinical trials should include elderly patients (> 65 years).
Formulation/ presentation	Suggestion: tablets/capsules/sachet	Suggestion: tablets/capsules/sachet
Dose regimen	1-3x daily, treatment duration 1-5 days	1-2x daily, treatment duration 1-5 days
Route of administration	Oral	Oral
Product stability and storage	Heat stable, 1-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).
Pharmacokinetics	Pharmacokinetic data available to support use in lower UTI (renal elimination), activity in urine.	Pharmacokinetic data available to support use in lower UTI (adequate concentrations and activity in urine, potentially concentrations in blood).
Drug interactions	Comparable to current therapies	Comparable to current therapies

TPP for oral therapy of acute pyelonephritis

	Minimal TPP	Preferred TPP
Indication for use	Oral treatment or oral follow-on of iv treatment of acute pyelonephritis.	Oral treatment or oral follow-on of iv treatment of acute pyelonephritis, in patients with confirmed or at high risk of having MDR (incl. ESBL-producing) Gram-negative pathogens.
Target population	Adolescents and adults (men and women) with suspected MDR Gram-negative pathogens.	Adolescents and adults (men and women) with suspected MDR Gram-negative pathogens.
Access and affordability	See Introduction and paragraph on Access and affordability.	See Introduction and paragraph on Access and affordability.
Safety/tolerability	Comparable to current therapies with β-lactams, no toxicity signals in preclinical reproduction toxicity studies.	Comparable to current therapies with β-lactams, no toxicity signals in preclinical reproduction toxicity studies.
In vitro activity	Activity against Enterobacteriaceae (including *E. coli*, *Klebsiella* and *Proteus*, including ESBL producers); low cross-resistance to known antibiotic classes (new class/target/mode of action), especially to β-lactams, fluoroquinolones, co-trimoxazole; low propensity for mutational resistance development.	Activity against Enterobacteriaceae (including *E. coli*, *Klebsiella* and *Proteus* including ESBL-producers); no cross-resistance to known antibiotic classes (new class/target/mode of action), especially to β-lactams, fluoroquinolones, co-trimoxazole; low propensity for mutational resistance development.
Clinical efficacy	Non-inferior clinical activity in acute infections to currently used therapies against susceptible strains, e.g. aminoglycosides, cephalosporins and ciprofloxacin, carbapenems. Clinical trials should include elderly patients (> 65 years).	Non-inferior clinical activity in acute infections to currently used therapies against susceptible strains, e.g. aminoglycosides, cephalosporins and ciprofloxacin, carbapenems. Clinical trials should include elderly patients (> 65 years).
Formulation/ presentation	Tablets/capsules/sachet	Tablets/capsules/sachet
Dose regimen	1-3x daily, treatment duration 3-10 days	1-2x daily, treatment duration 3-10 days
Route of administration	Oral	Oral, or iv + oral
Product stability and storage	Heat stable, 1-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).
Pharmacokinetics	Pharmacokinetic data available to support use in lower and upper UTI (adequate concentrations and activity in urine and blood).	Pharmacokinetic data available to support use in lower and upper UTI (adequate concentrations and activity in urine and blood).
Drug interactions	Comparable to current therapies	Comparable to current therapies

WHO documents

Urinary tract infections in infants and children in developing countries in the context of IMCI, 2005. Geneva: World Health Organization; 2005 (https://apps.who.int/iris/bitstream/handle/10665/69160/WHO_FCH_CAH_05.11.pdf?sequence=1, accessed 4 February 2020).

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