Typhoid fever - priorities for research and development of new treatments

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Enteric infections

- Enteric infections vary in symptoms and are caused by a diverse range of organisms
- Significant disease burden, disproportionally affecting the world’s poor in low- and middle-income countries
- Growing problem with antibiotic resistance among many of the causative pathogens
- GARDp initial evaluation focused on typhoid fever, invasive non-typhoidal salmonellosis (iNTS) and Shigella infections
General Objectives

- Review current epidemiological situation and clinical management, most pressing medical needs, research and development gaps, and collaboration opportunities in enteric infections
- Identification of entry points for R&D, if available
- Define short, medium and long term opportunities in R&D for new treatments
Typhoid fever

• Potentially fatal multi-systemic illness

• Caused primarily by Salmonella enterica, subspecies enterica serovar typhi and, to a lesser extent, related serovars paratyphi A, B, and C.

• Family: Enterobacteriaceae (gram negative, facultative anaerobic, nonmotile, rod-shaped bacteria)
Significant disease burden, disproportionally affecting the world’s poor in low- and middle-income countries

- 11 and 21 million cases and 145,000-161,000 deaths globally each year

- Estimates seem to under-estimate the real number of cases and the degree of uncertainty

Antillón et al, Plos NTD 2017
History of treatment and acquisition of resistance

- 1980’s - simultaneous plasmid-mediated resistance to chloramphenicol, ampicillin and TMP-sulfa

- Resistance to first-generation fluoroquinolones now widespread in many parts of Asia - specific mutations in gyrA and parC, which code for the binding region of DNA gyrase and topoisomerase IV, respectively.

- Growing numbers of extended-spectrum beta-lactamase (ESBL)-resistant Salmonella
Antibiotic resistance

- Reports quickly outdated
- Surveys of resistance of limited scope – often hospital-based
- Differences in pattern of resistance across different geographic areas

Nigeria - invasive bacterial isolates

Obaro SK et al, CID 2015

400 km distance between sites
Rural versus Urban
Malawi – antimicrobial resistance trends in bloodstream infections

Musicha P, Lancet ID 2017
WHO Priority Pathogen for R&D

WHO PRIORITY PATHOGENS LIST
FOR R&D OF NEW ANTIBIOTICS

Priority 1: CRITICAL

- Acinetobacter baumannii, carbapenem-resistant
- Pseudomonas aeruginosa, carbapenem-resistant
- Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

- Enterococcus faecium, vancomycin-resistant
- Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant
- Helicobacter pylori, clarithromycin-resistant
- Campylobacter, fluoroquinolone-resistant
- Salmonella spp., fluoroquinolone-resistant
- Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: MEDIUM

- Streptococcus pneumoniae, penicillin-non-susceptible
- Haemophilus influenzae, ampicillin-resistant
- Shigella spp., fluoroquinolone-resistant
R&D Landscape

- Research and investment focused on vaccine development and, to a lesser degree, diagnostics, but much less on treatment

Treatment will remain an important component of disease management and role in disease control should be further explored.
R&D Priorities

Short and Medium Term

1. Systematic review of existing in-vitro; pharmacokinetic-pharmacodynamics; and clinical data

2. In-vitro assessments of old and new drugs and drug combinations against a relevant panel isolates


4. Evaluation of salvage regimens for multi-drug resistant typhoid fever

Long Term

5. Development of new chemical entities for the treatment of typhoid fever - R&D agenda that intersects with the broader needs for the treatment of multidrug resistant Enterobacteriacaeae infections.
Combination treatment

- Development of combination regimens for typhoid fever and invasive salmonella infections.
  - Data to suggest that in other diseases combination therapy may reduce the emergence of antibiotic resistance.
  - Evidence of synergy cephalosporins and quinolones in fluoroquinolone resistant strains
  - Potential impact on duration of acute faecal shedding, development of chronic carriers and resultant disease transmission.
  - Potential to shorten the required course of treatment and improve compliance.
Thank You

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