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Global Antibiotic Research & Development Partnership

Typhoid fever - priorities for research and development of new treatments

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World Health Organization

DNDi
Drugs for Neglected Diseases *initiative*

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

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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

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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: Enterobacteriacae (gram negative, facultative anaerobic, nonmotile, rod-shaped bacteria)

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Epidemiology

Table 2. Total cases and incidence for the Global Burden of Disease regions and subregions made up of low- and middle-income countries. Total cases are shown in millions and incidence is per 100,000 person-years.

	Cases	Incidence
All LMICs	**17.8 (6.9, 48.4)**	**293 (111, 794)**
Central Europe, Eastern Europe, and Central Asia	**0.1 (0.02, 0.6)**	**28 (7, 166)**
Central Asia	0.05 (0.01, 0.5)	55 (12, 541)
Central Europe	0.01 (0.003, 0.06)	21 (4, 100)
Eastern Europe	0.03 (0.01, 0.13)	16 (4, 65)
Latin America and Caribbean	**1.0 (0.2, 3.9)**	**169 (32, 642)**
Andean Latin America	0.4 (0.04, 2.1)	704(80, 3751)
Caribbean	0.02 (0.004, 0.05)	47(12, 166)
Central Latin America	0.3 (0.07, 1.3)	120 (30, 512)
Southern Latin America	0.04 (0.01, 0.2)	61 (15, 276)
Tropical Latin America	0.2 (0.04, 1.1)	89 (18, 517)
North Africa and Middle East	**2.6 (0.5, 5.7)**	**557 (100, 1208)**
Sub-Saharan Africa	**7.2 (2.2, 30.2)**	**762 (230, 3208)**
Central Sub-Saharan Africa	1.7 (0.4, 8.4)	1459 (371, 6984)
Eastern Sub-Saharan Africa	2.4 (0.8, 11.3)	620(213, 2921)
Southern Sub-Saharan Africa	0.1 (0.04, 0.4)	149 (57, 571)
Western Sub-Saharan Africa	2.8 (0.7, 11.2)	753 (198, 3075)
Southeast Asia, East Asia, and Oceania	**2.21 (0.7, 6.8)**	**108 (36, 334)**
Southeast Asia	1.3 (0.4, 5.3)	217 (88, 571)
East Asia	0.5 (0.1, 1.7)	33 (9, 122)
Oceania	0.4 (0.03, 0.5)	5454 (397, 6576)
South Asia	**3.6 (1.5, 9.4)**	**204 (64, 851)**

doi:10.1371/journal.pntd.0005376.t002

Antillón et al, Plos NTD 2017

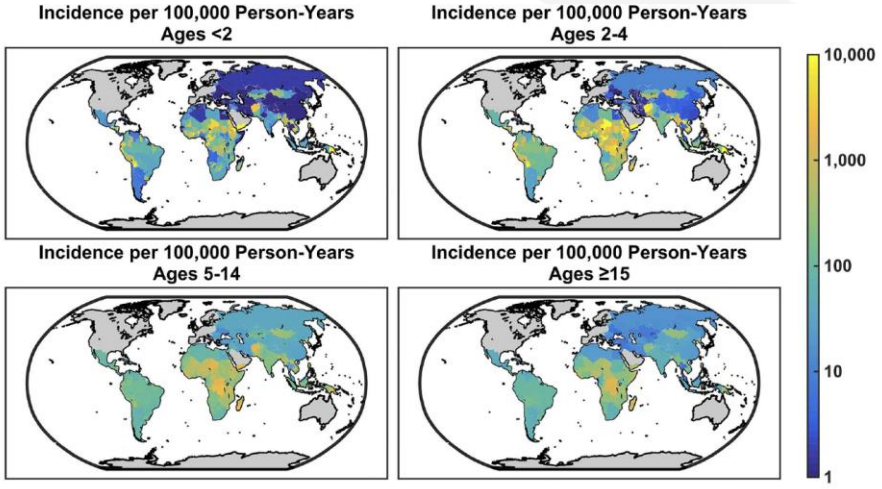

Fig 7. Model-predicted age-specific incidence per 100,000 person-years. The median posterior predicted incidence per 100,000 person-years in each of the age groups (<2 years, 2–4 years, 5–14 years, and ≥15 years) is mapped for all low- and middle-income countries (LMICs) with a resolution of 0.1 degrees.

- 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

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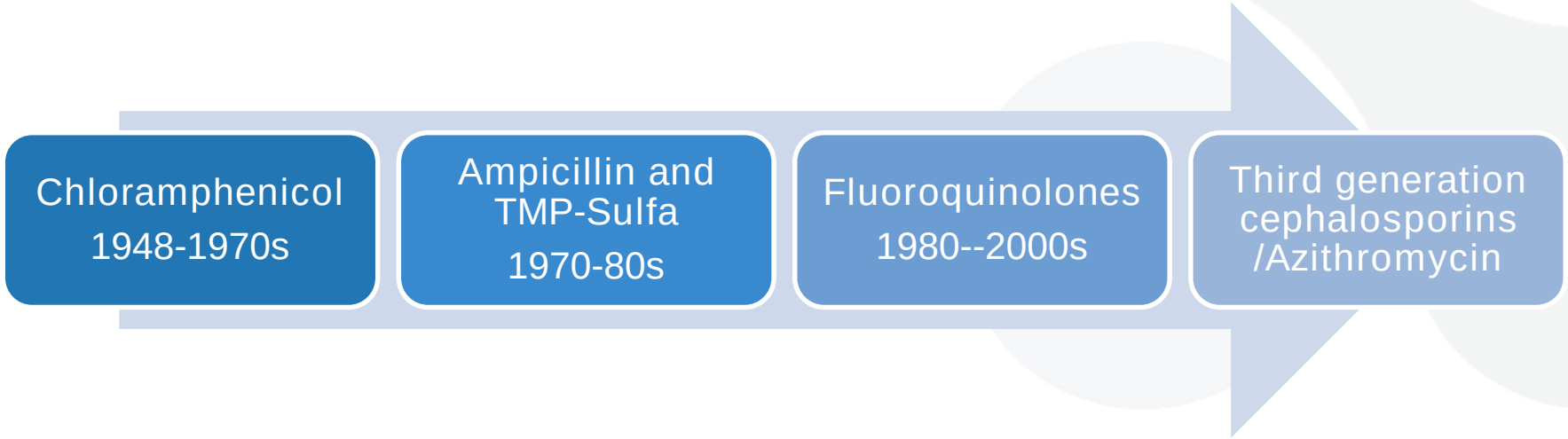
History of treatment and acquisition of resistance



- 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

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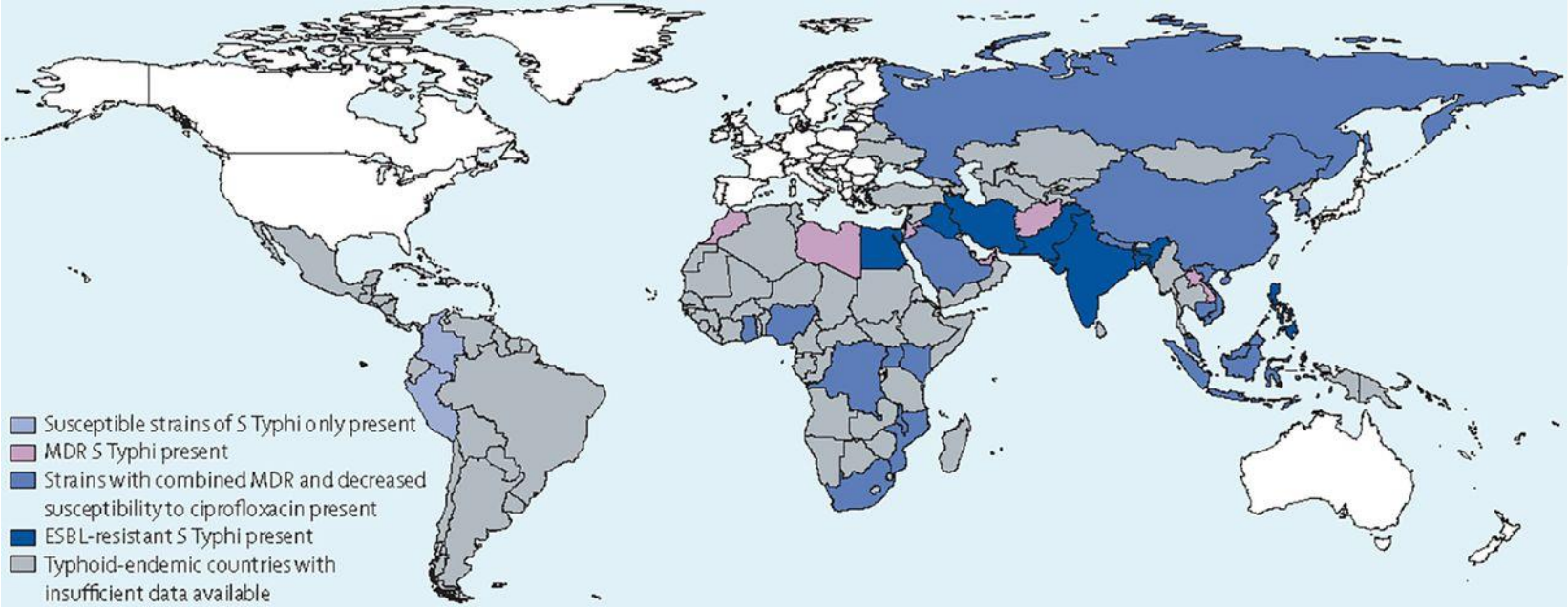
Antibiotic resistance

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

Worldwide distribution of antimicrobial drug resistance in Salmonella enterica serovar Typhi.



John A. Crump et al. Clin. Microbiol. Rev. 2015;28:901-937

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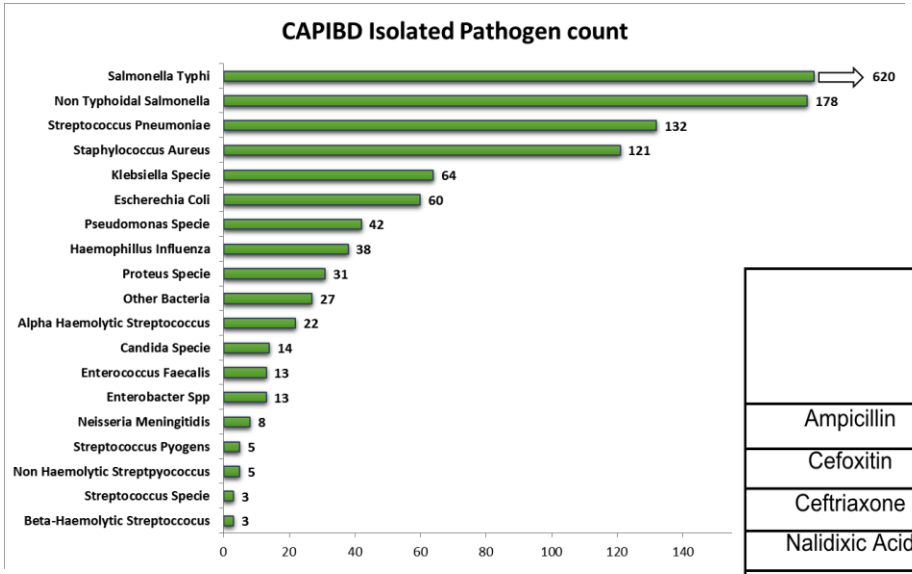
Nigeria - invasive bacterial isolates



Resistance by location

	location					
	Abuja (N=78)		Kano (N=165)			
	% Res	n	% Res	n	Difference	P
Ampicillin	55.13%	43	69.88%	115	14.57%	0.024
Cefoxitin	5.13%	4	1.81%	3	3.32%	0.148
Ceftriaxone	0.00%	0	2.41%	4	2.41%	0.168
Nalidixic Acid	3.85%	3	4.22%	7	0.37%	0.892
Gentamicin	0.00%	0	1.20%	2	1.20%	0.332
Kanamycin	0.00%	0	0.6%	1	0.60%	0.494
Streptomycin	24.36%	19	56.02%	92	31.67%	.000
Trimethoprim/Sulfa	58.97%	46	74.1%	122	15.12%	0.017
Sulfamethoxazole	92.31%	72	92.17%	152	0.15%	0.97
Tetracycline	47.44%	37	62.65%	103	15.21%	0.025
Chloramphenicol	61.54%	48	35.54%	59	26%	.000
Azrithromycin	2.63%	2	22.42%	37	19.79%	.000

Obaro SK et al, CID 2015

400 km distance between sites
Rural versus Urban

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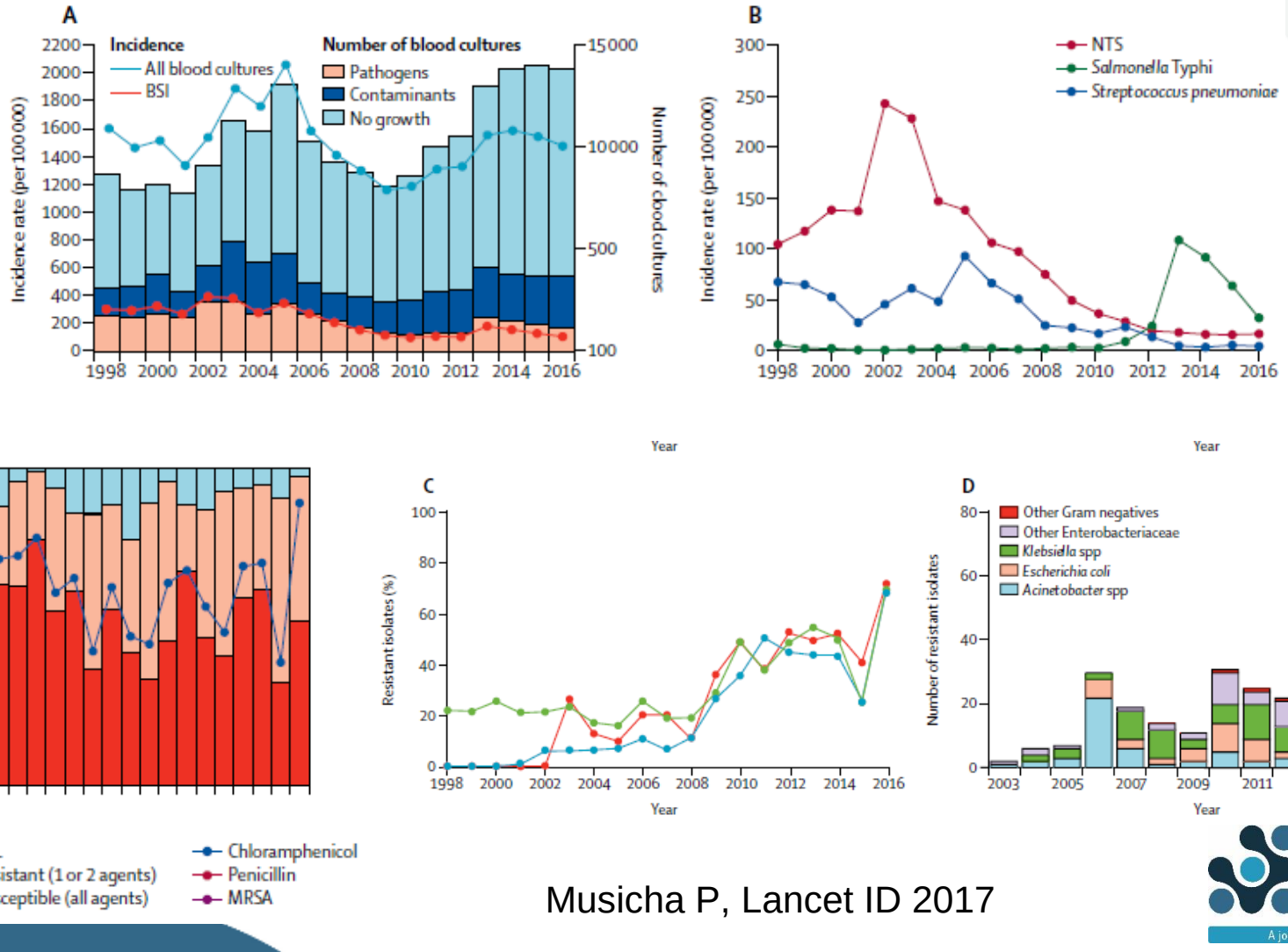
Malawi – antimicrobial resistance trends in bloodstream infections



Musicha P, Lancet ID 2017

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WHO Priority Pathogen for R&D

World Health Organization

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

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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

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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

3. Clinical trials of antimicrobial combinations for: 1. Fever with suspected typhoid and 2. Fever with confirmed typhoid

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 Enterobacteriacae infections.

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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.

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Thank You

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