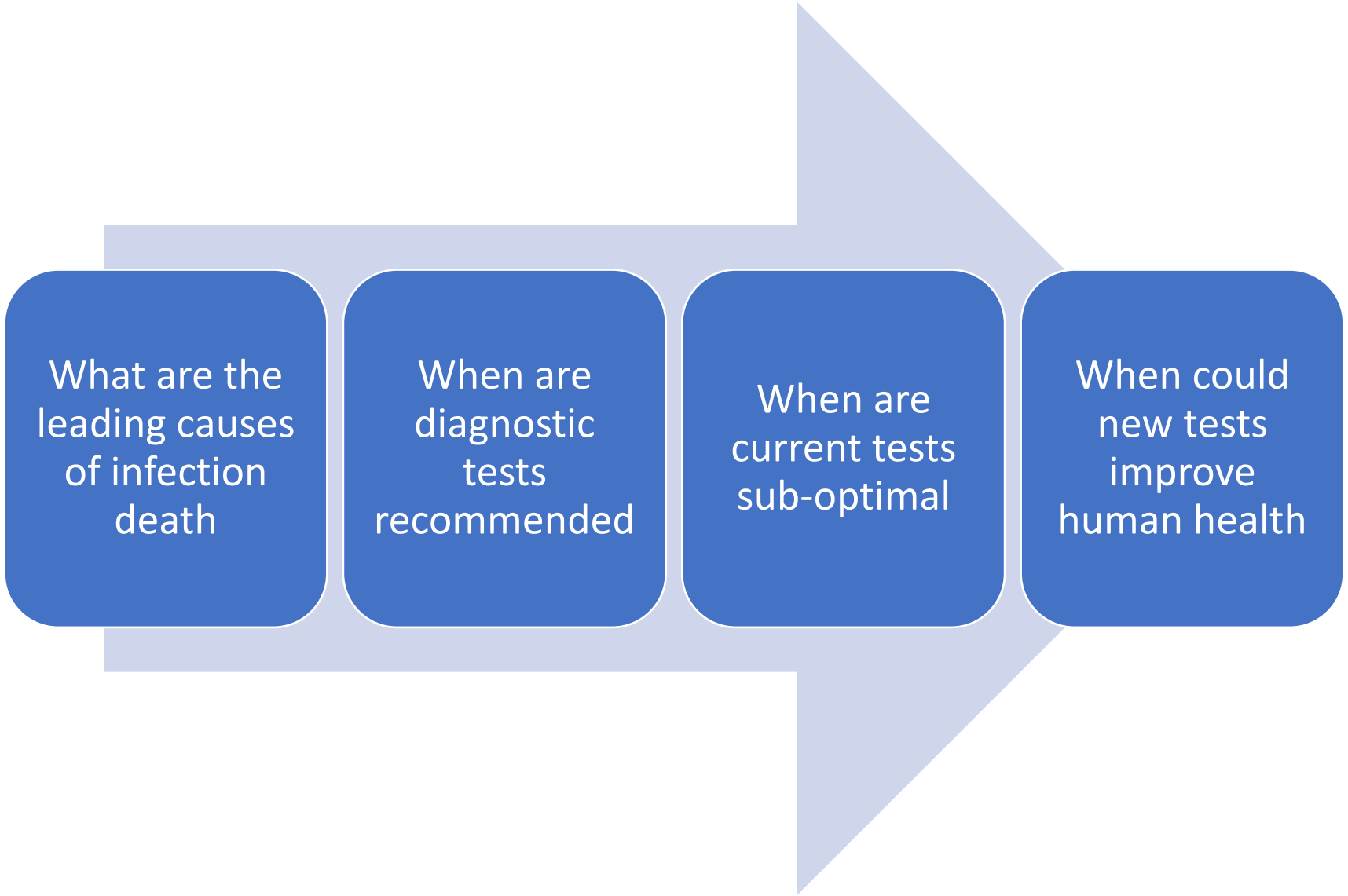
Diagnostic innovation to improve patient outcomes from global infectious diseases, including AMR infection

Sharon Peacock, University of Cambridge

Panel 2: Catalyzing innovation and access to AMR diagnostics for humans and animals, 14th April 2023

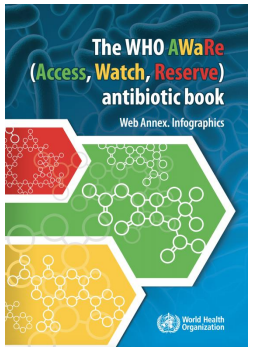
Defining areas for diagnostic innovation to improve global outcomes from infectious diseases, including AMR infection

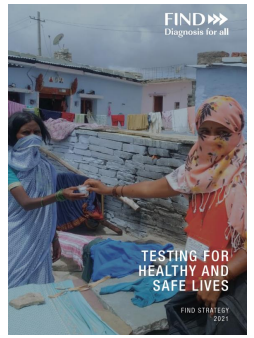


Defining areas for diagnostic innovation to improve global outcomes from infectious diseases

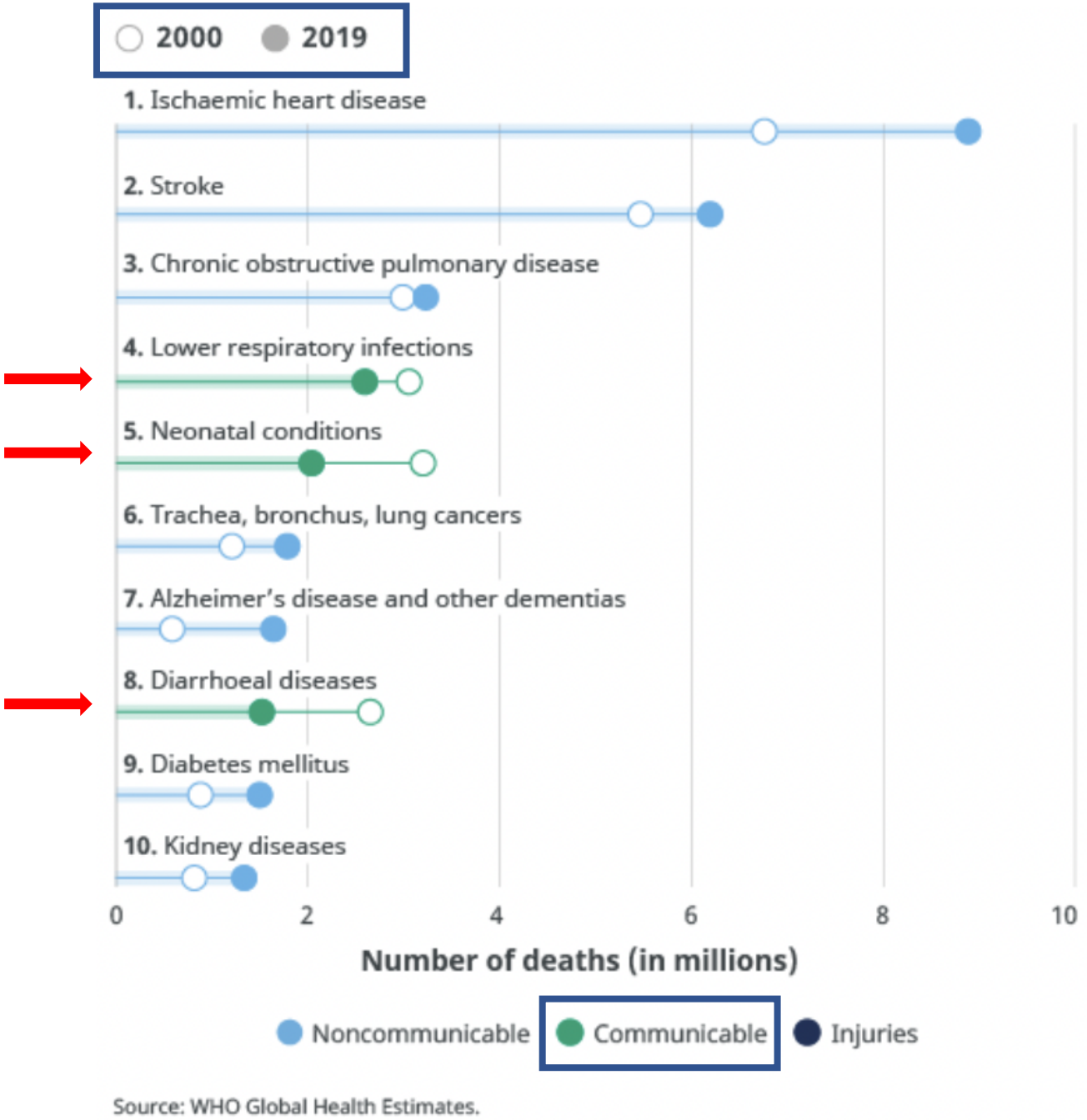
- What are the leading causes of infection death
- When are diagnostic tests recommended
- When are current tests sub-optimal
- When could new tests improve human health

World Health Organization





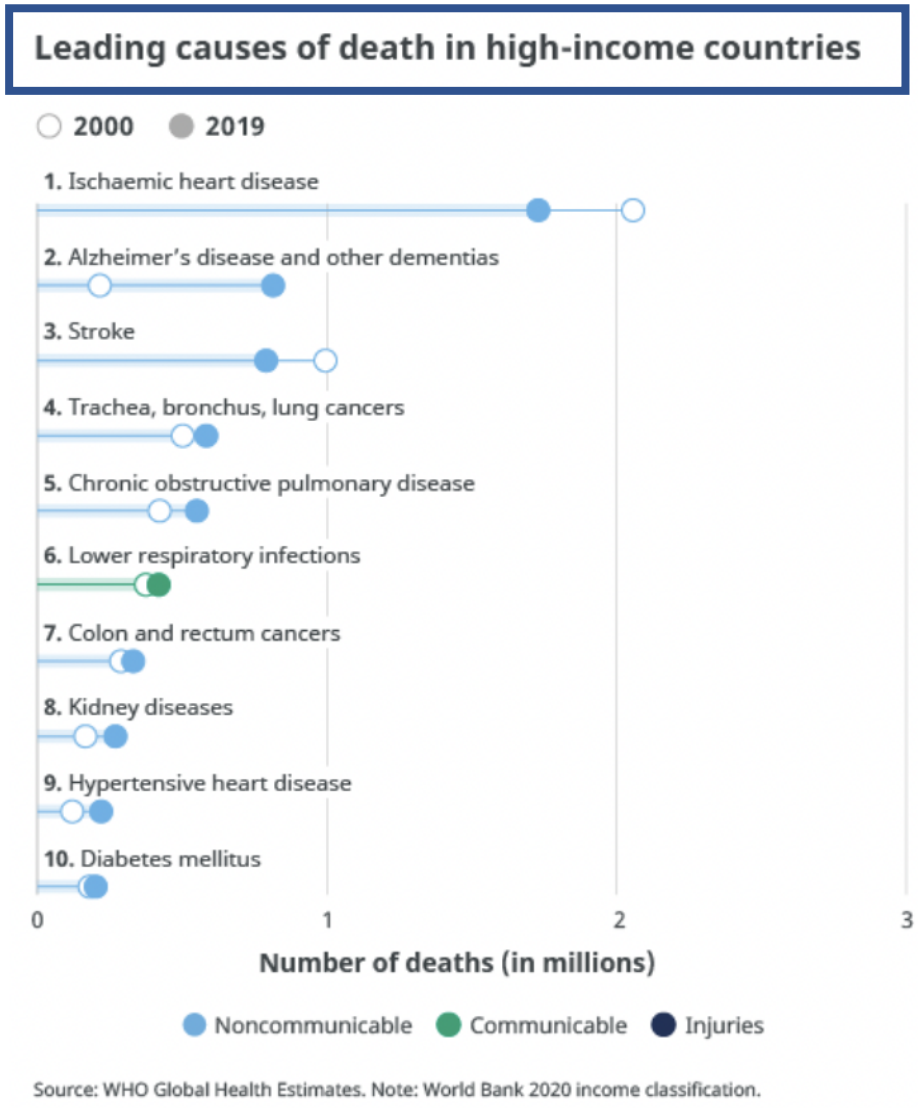
Top 10 causes of death globally, overall

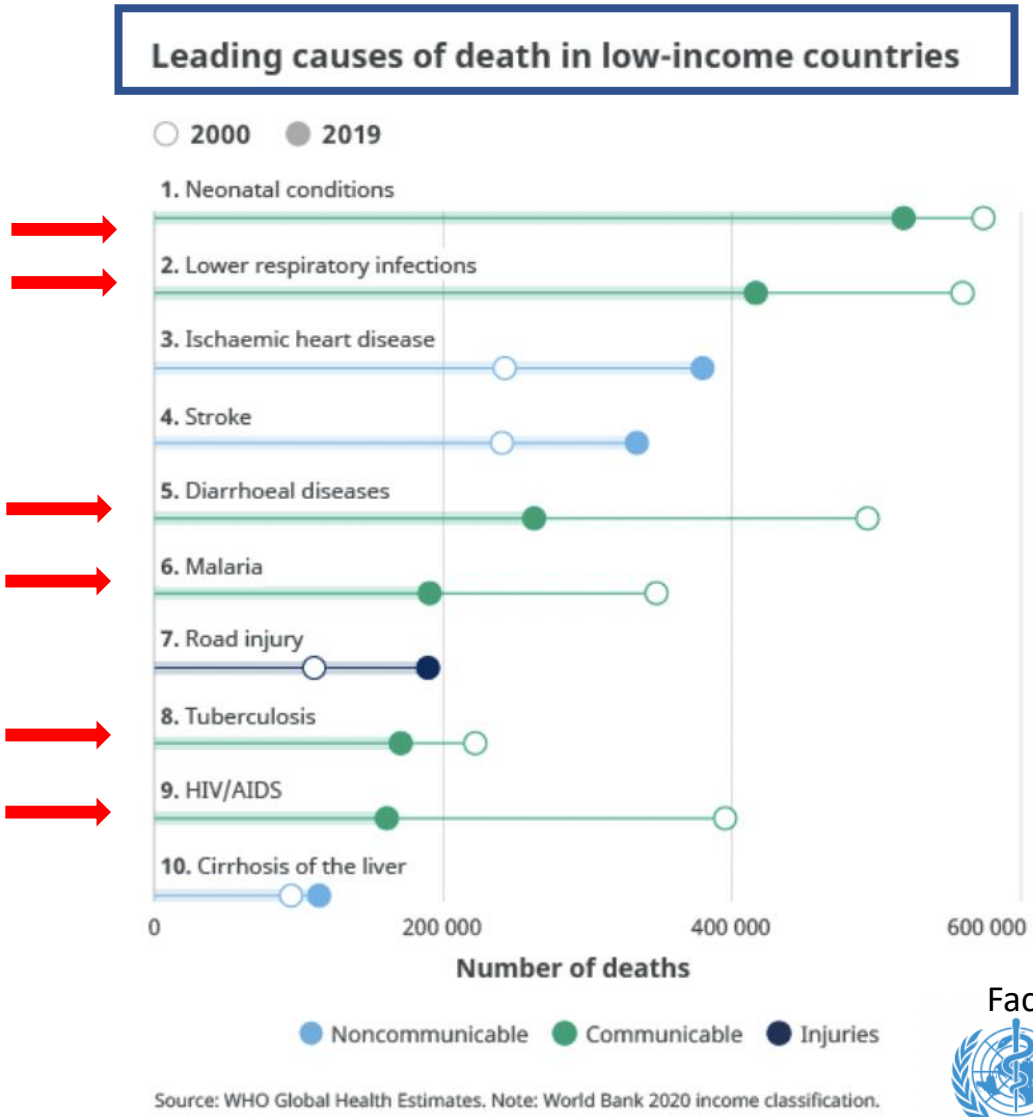


World Health Organization

Fact sheet 9 Dec 2020

Top 10 causes of death

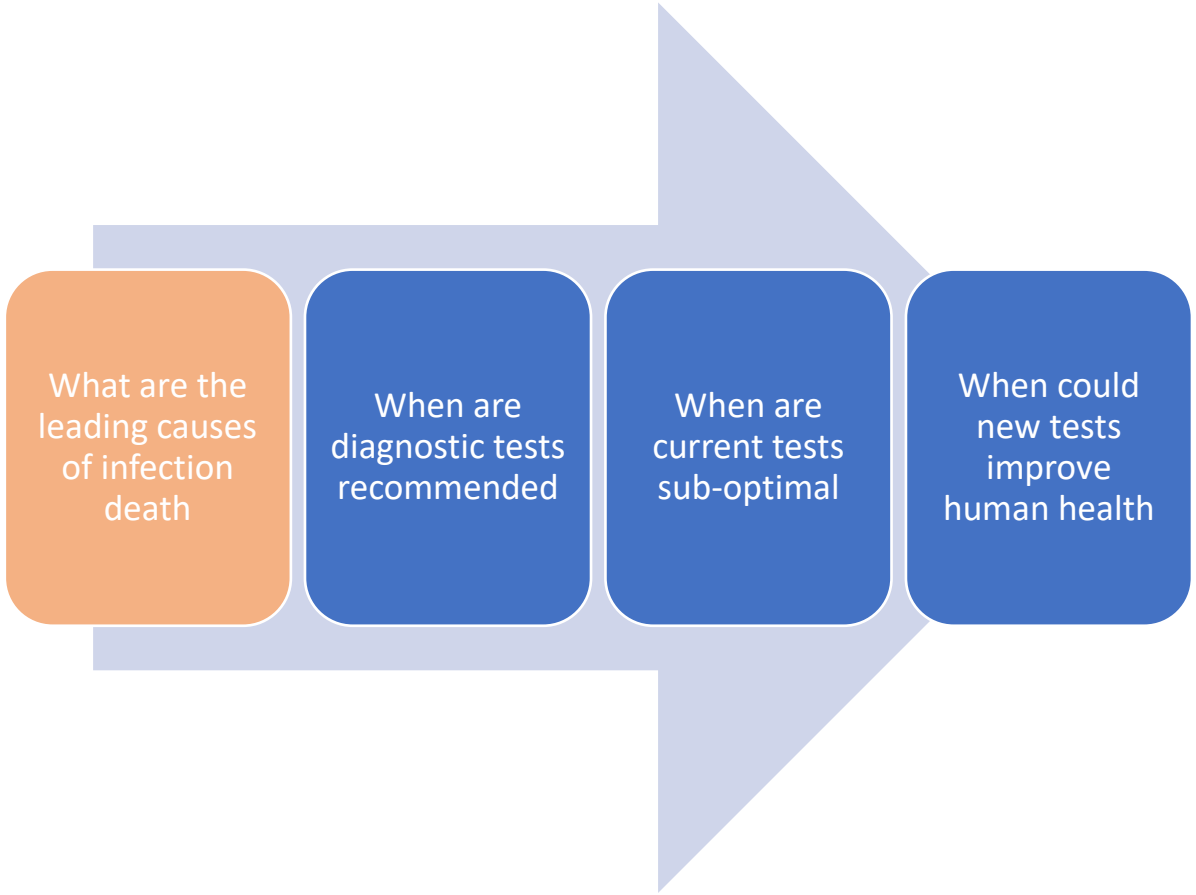




Fact sheet 9 Dec 2020

World Health Organization

Focus on diagnostic areas for health outcomes



<u>3 syndromes and 3 specific conditions</u>:

- Neonatal conditions
- Lower respiratory tract infections
- Diarrhoeal diseases

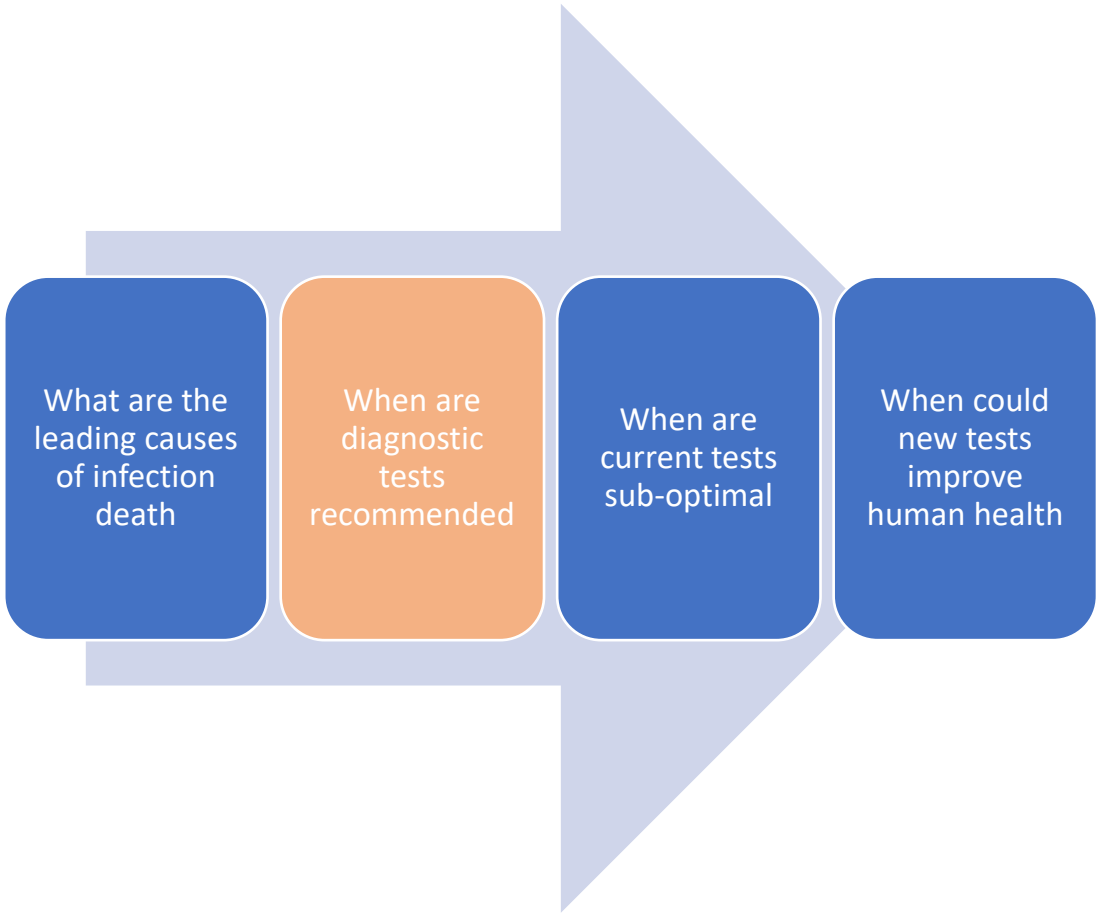
- TB
- HIV
- Malaria

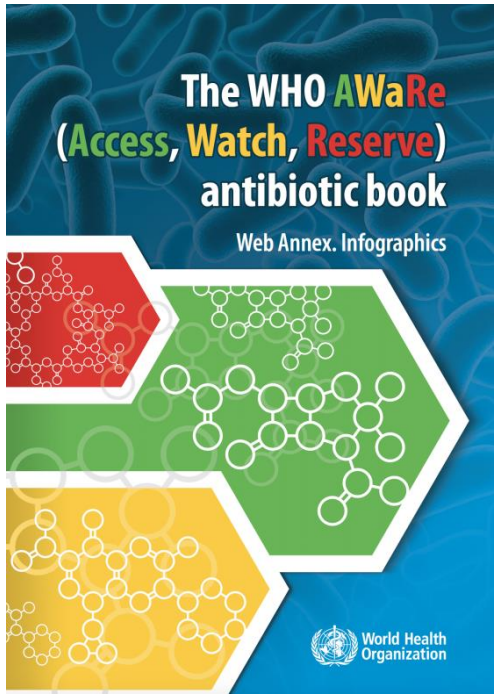
Table 1. **Recent large-scale, multicentre observational studies of the pathogens causing neonatal sepsis and their findings**

Author, year	Country(ies)	Setting	Population	Dates of recruitment	Incidence of culture-positive sepsis, %	Most frequent pathogen causing neonatal sepsis (from neonates with culture-positive sepsis)	Proportion that were MDR or resistance to key antibiotics
DeNIS collaboration, 2016[30]	India	Three urban tertiary hospitals	• 13 530 neonates admitted to intensive care units • 840 developed culture-positive sepsis • Followed daily until discharge or death	2011–2014	6.2% (840/13 530)	*Acinetobacter* spp. (22.1%; 222/1005) *Klebsiella* spp. (16.8%;169/1005) *Escherichia coli* (13.6%; 137/1005) *Staphylococcus aureus* (12.1%; 122/1005)	81.5% (181/222) 53.8% (91/169) 38.0% (52/137) 37.7% (43/114) of *S. aureus* isolates resistant to methicillin
Saha et al. (The ANISA Study), 2018[29]	Bangladesh, India, Pakistan	Community settings across five sites	• 63 114 infants visited at home by community health workers up to 10 times between ages 0 and 59 days • 6022 identified as having possible serious bacterial infections • 4859 had blood taken for culture	2011–2014	2.7% (132/4859), excluding contaminants; incidence of culture-confirmed infection = 1.6 per 1 000 live births	• *E. coli* (20.6%; 21/102) • *Klebsiella* spp. (16.7%; 17/102) • *S. aureus* (11.8%; 12/102) • Group A *streptococcus* (10.8%; 11/102)	• 25.0% of all 50 tested pathogenic gram-negative isolates not susceptible to penicillin, ampicillin or gentamicin • Incidence of gram-negative organisms higher among hospital-born than community-born infants (1.3/1000 live births vs 0.7/1000 live births)
Sands et al. (BARNARDS network), 2021[18]	Bangladesh, Ethiopia, India, Nigeria, Pakistan, Rwanda, South Africa	Network of 12 urban hospitals	• 36 285 neonates prospectively recruited in the peripartum period • 2483 developed culture-confirmed sepsis • Followed up until day 60, study withdrawal or death	2015–2017	6.8% (2 483/36 285)	• *K. pneumoniae* (10.4%; 258/2483) • *Serratia marcescens* (6.1%; 151/2483) • *K. michiganesis* (4.7%; 117/2483) • *E. coli* (3.0%; 75/2483) • *Enterobacter cloacae* complex (3.2%; 80/2482) • Gram-positive bacteria constituted 48.3% (1266/2620)	• Of 885 gram-negative pathogens, high levels of resistance found to ampicillin (95.0%), cefotaxime (83.0%), ceftriaxone (80.0%), meropenem (87.0%) and tigecycline (85.0%) • 67.0% (597/885) of gram-negative isolates resistant to at least one β-lactam and one aminoglycoside • Very high rates of class B and class D carbapenemases across gram-negative species • All isolated pathogens resistant to multiple antibiotic classes, including classes recommended as empirical treatment for neonatal sepsis
Huynh et al. (BIRDY Study Group), 2021[31]	Cambodia, Madagascar, Senegal	Nine urban and rural hospitals	• 3688 neonates recruited during pregnancy, followed until day 28	2012–2018	Culture-positive incidence per 1000 live births: Cambodia, 6.5 (95% CI: 2.7–15.6); Madagascar, 15.2 (95% CI: 10.6–21.8); Senegal, 10.2 (95% CI: 4.8–21.3)	• *Klebsiella* spp. (24.4%; 11/45) • *E. coli* (22.2%; 10/45) • *Staphylococcus* spp. (24.4%; 11/45)	• 31.0% (13/42) of *Klebsiella* spp. resistant to both ampicillin and gentamicin • 48.0% (12/25) gram-negative isolates resistant to cefotaxime • 46.4% (13/28) gram-negative isolates resistant to gentamicin
Russell et al. (NeoOBS network), 2022[7]	Bangladesh, Brazil, China, Greece, India, Italy, Kenya, South Africa, Thailand, Uganda, Viet Nam	19 urban and rural hospitals	• 3204 infants < 60 days presenting to hospital with > 2 sepsis criteria, followed for 28 days	2018–2020	17.6% (564/3204)	• *K. pneumoniae* (23.4%; 132/564) • *Acinetobacter* spp. (12.8%; 72/564) •*S. aureus* (9.6%; 54/564) • *E. coli* (8.3%; 47/564)	• 57.7% (75/130 tested) of *K. pneumoniae* isolates resistant to gentamicin, 75.0% (96/128) resistant to commonly used third-generation cephalosporins and 32.6% (43/132) resistant to meropenem • 71.4% (50/70) *Acinetobacter* spp. resistant to meropenem • 35.6% (16/45) *E. coli* isolates resistant to third-generation cephalosporins

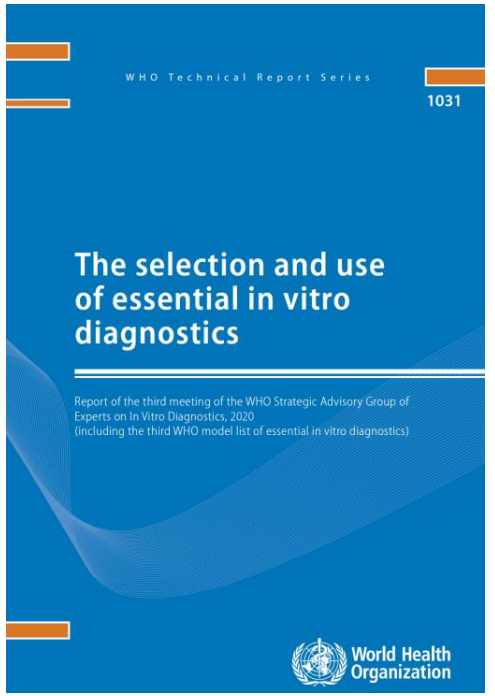
Phoebe Williams et al. Antibiotics needed to treat MDR infections in neonates. Bull World Health Organ 2022;100:797–807

WHO Guidelines on testing



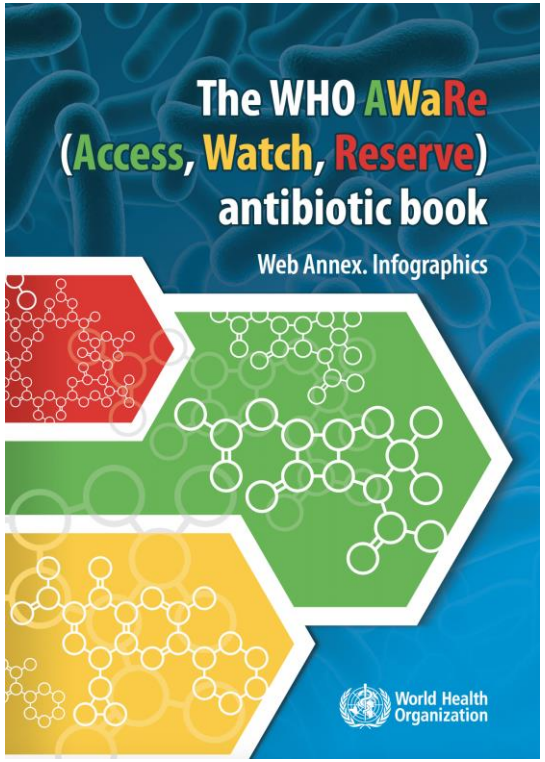


https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2022.02



https://www.who.int/publications/i/item/9789240019102

WHO AWaRe antibiotic book: management of infection



- Evidence-based guidance on antibiotic dose, route and duration for 34 common clinical infections in children and adults in primary health care and hospitals
- Complements the *WHO Model list of essential medicines* and *WHO Model list of essential medicines for children*
- A book in three sections: Primary healthcare, Hospital facility, Reserve antibiotics

https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2022.02

WHO AWaRe antibiotic book: management of infection

PRIMARY HEALTH CARE 1
Bronchitis 3
Acute otitis media 5
Pharyngitis 8
Acute sinusitis 12
Oral and dental infections 16
Localized acute bacterial lymphadenitis 22
Conjunctivitis 26
Endophthalmitis 29
Keratitis 31
Periorbital cellulitis 33
Trachoma 36
Community-acquired pneumonia 38
Exacerbation of chronic obstructive pulmonary disease 42
Acute infectious diarrhoea/gastroenteritis 44
Enteric fever 48
Impetigo / Erysipelas / Cellulitis 50
Burn wound-related infections 53
Wound and bite-related infections 56
Chlamydial urogenital infection 60
Gonococcal infection 62
Syphilis 65
Trichomoniasis 67
Lower urinary tract infection 68

When to do a diagnostic test

- Severe pneumonia*
- Suspected TB*
- Sexually transmitted diseases*
- Symptomatic urinary infection*
- Pharyngitis if high risk of Group A strep infection
- Selected gastroenteritis (eg. suspected cholera, bloody diarrhoea)
- Some eye diseases

* Risk of AMR

WHO AWaRe antibiotic book: management of infection

HOSPITAL FACILITY 73
Sepsis & septic shock 75
Sepsis in children 79
Sepsis in neonates 82
Bacterial meningitis 85
Community-acquired pneumonia 89
Hospital-acquired pneumonia 93
Acute cholecystitis & cholangitis 97
Pyogenic liver abscess 102
Acute appendicitis 107
Acute diverticulitis 112
Clostridioides difficile infection (CDI) 114
Upper urinary tract infection 117
Acute bacterial osteomyelitis 121
Septic arthritis 125
Necrotizing fasciitis 129
Pyomyositis 133
Febrile neutropenia 136
Surgical prophylaxis 140

When to do a diagnostic test

- Most acute conditions*
- These conditions require patients to have blood culture

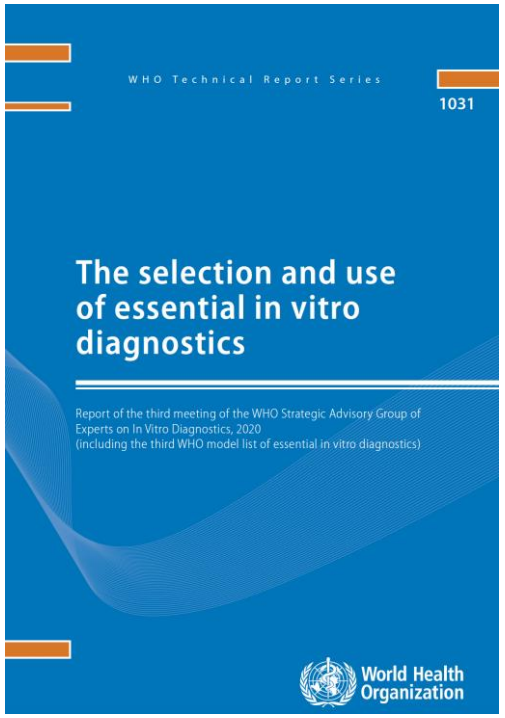
* Risk of AMR

WHO AWaRe antibiotic book: management of infection

Last-resort reserve antibiotics. Restricted to very selected cases of confirmed or suspected infection with multidrug-resistant pathogen

RESERVE ANTIBIOTICS 145
Cefiderocol 147
Ceftazidime+avibactam 148
Fosfomycin 149
Linezolid 150
Meropenem+vaborbactam 151
Plazomicin 152
Polymyxin B and colistin (polymyxin E) 153

What tests to perform? WHO essential tests



https://www.who.int/publications/i/item/9789240019102

1. Disease-specific diagnostics in community health facilities without labs (point of care tests)

2. Health care facilities with clinical labs:
   - Clinical microbiology (staining, culture, blood culture, identification, susceptibility testing)
   - Viral tests (eg HIV, hepatitis, flu, measles)
   - Sexually transmitted diseases
   - Neglected tropical diseases
   - Malaria
   - TB

Mind the gap: lack of utilization of tests that work

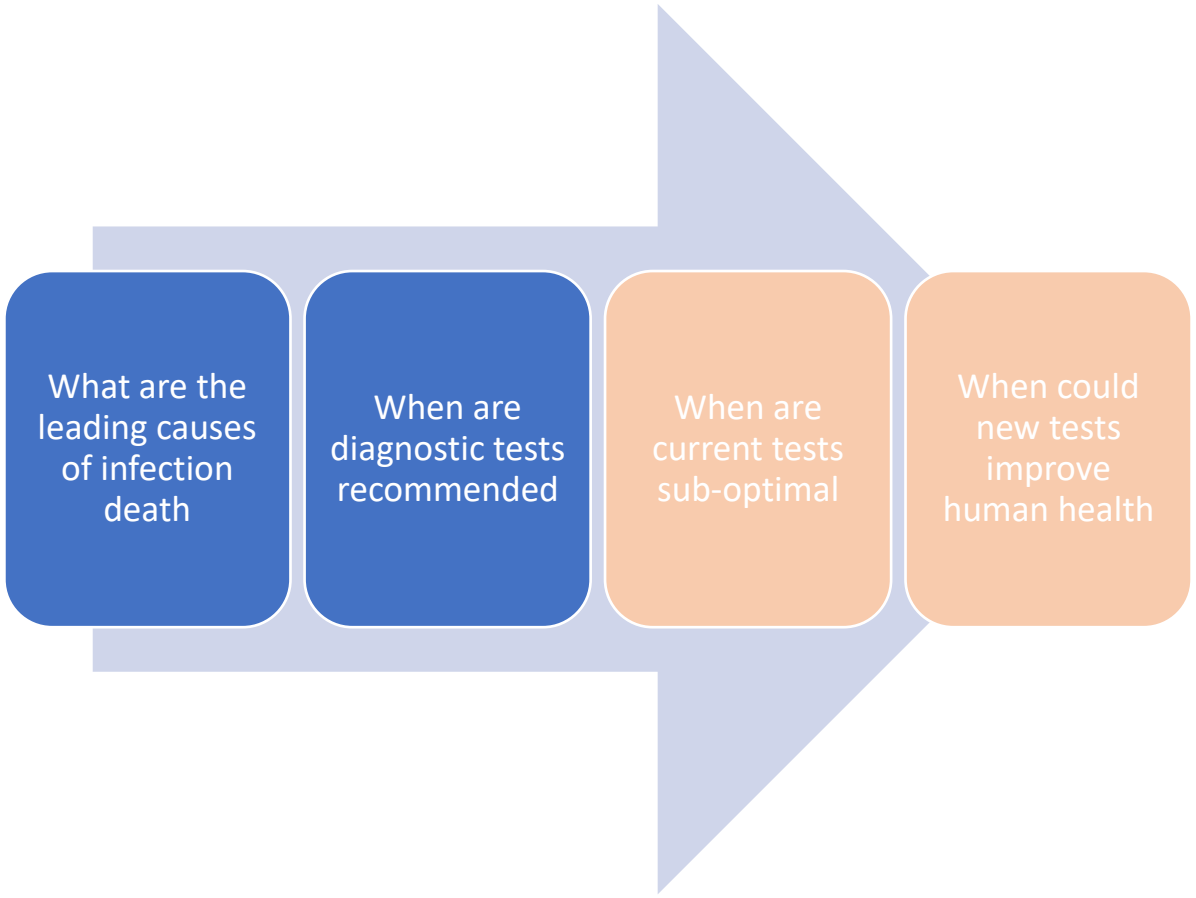
- Many diagnostic tests have already been described but are not used, or not used effectively to guide antibiotic use (e.g. blood culture, susceptibility testing):
  - Lack of sustainable lab capacity, funding, training

- How can diagnostic innovation be directed to improve uptake of existing tests – which would then inform personalized prescribing and improve antibiotic use and stewardship?

Mind the gap – importance of surveillance

- Most prescribing in the community for bacterial infections is based on surveillance data rather than diagnostic testing
- Prescribing in hospitals for bacterial infections also depends on surveillance data combined with a variable amount of testing depending on availability
- How can innovation create stronger diagnostic surveillance networks for empiric prescribing and better patient outcome from all infection, including AMR infection?

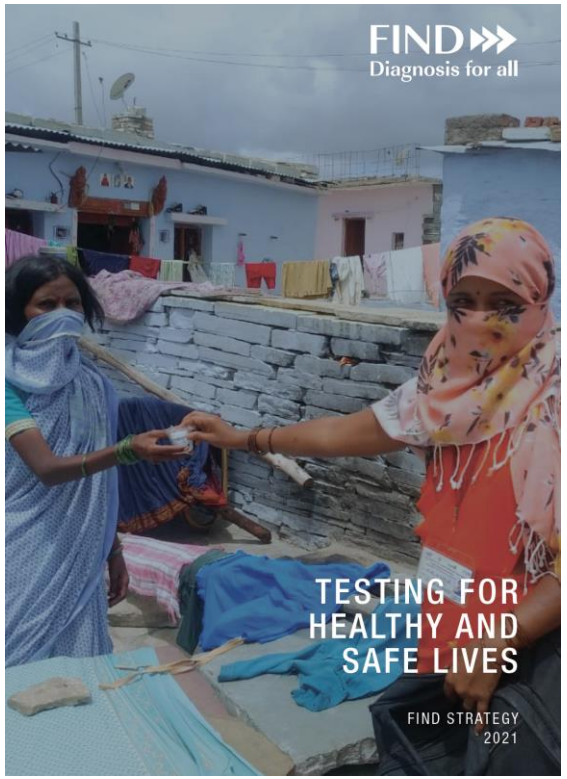
When current tests are sub-optimal



1. When tests are not available to direct antimicrobial prescribing
2. When tests are available but are not performed (or do not perform) correctly and lead to sub-optimal prescribing
3. When tests are performed but the data is not used again to inform empiric prescribing and provide population-based AMR data

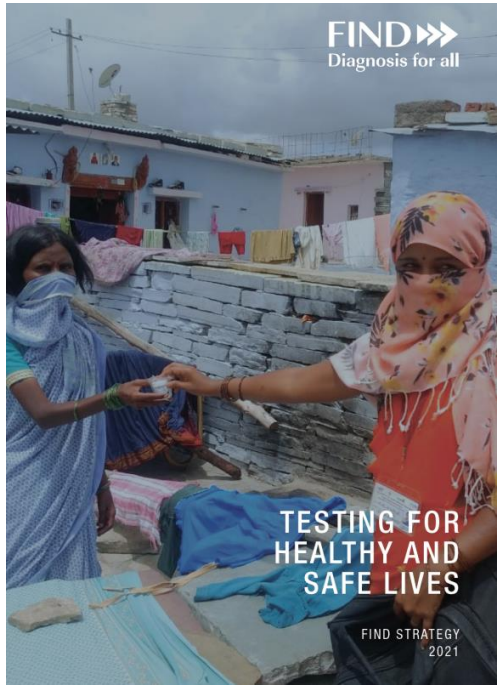
Innovation focused on appropriate prescribing through stronger diagnostics systems

1. Strengthen diagnostics ecosystems in the community to preserve existing and new antibiotics (e.g. point of care tests for STIs)
2. Strengthen diagnostics ecosystems in hospitals (introducing essential tests, improved diagnostics systems) to reduce death from severe infections (including neonatal and respiratory)
3. Empower on the ground diagnostic surveillance to improve empiric prescribing and use of local data (networks, digital tools, etc)
4. Improving ease of accurate susceptibility testing for the reserve antibiotic list
5. Focus on TB to find the missing millions



Innovation focused on local empowerment of test manufacture

1. Bringing local innovation in diagnostic test manufacturing at scale
2. Sustainable, local markets for quality assured and affordable diagnostics
3. Taming the testing ‘wild west’[see FIND Strategy] associated with the use of poor-quality assays



Summary highlights for diagnostic innovations

- Innovation that strengthens diagnostics ecosystems in the community e.g. POC tests
- Innovation that strengthens diagnostic test utilization and data networks in the hospitals
- Innovation that strengthens on the ground surveillance and use of data for empiric prescribing
- Diagnostic innovation in local test manufacturing to provide affordable high-quality tests