

Developing antibiotics for children – medical need and regulatory challenges

Guest speakers: Phoebe Williams, Irja Lutsar
Moderator: Sally Ellis (GARDP)
Host: Astrid Pentz-Murr (GARDP)

28 October 2020



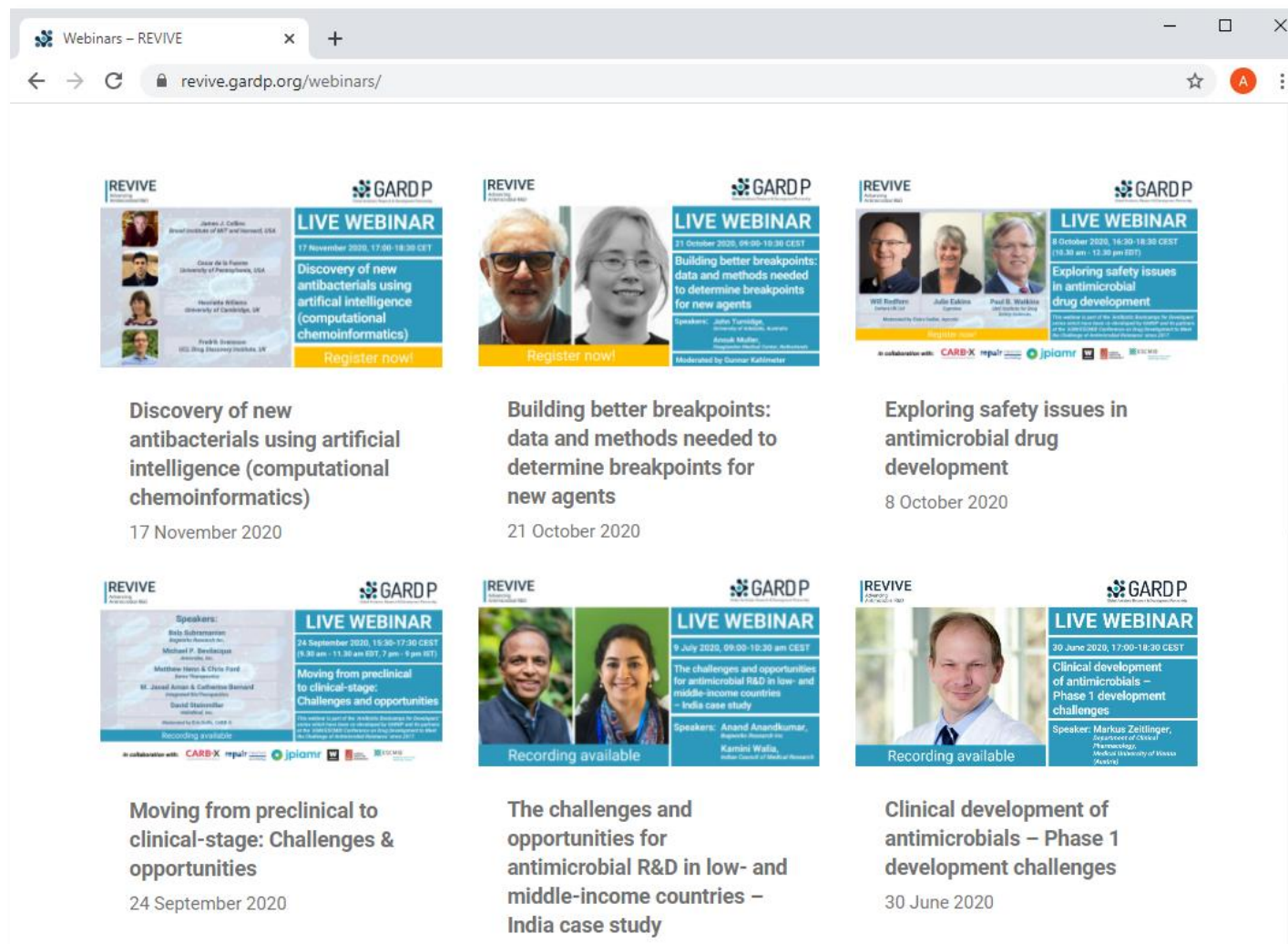
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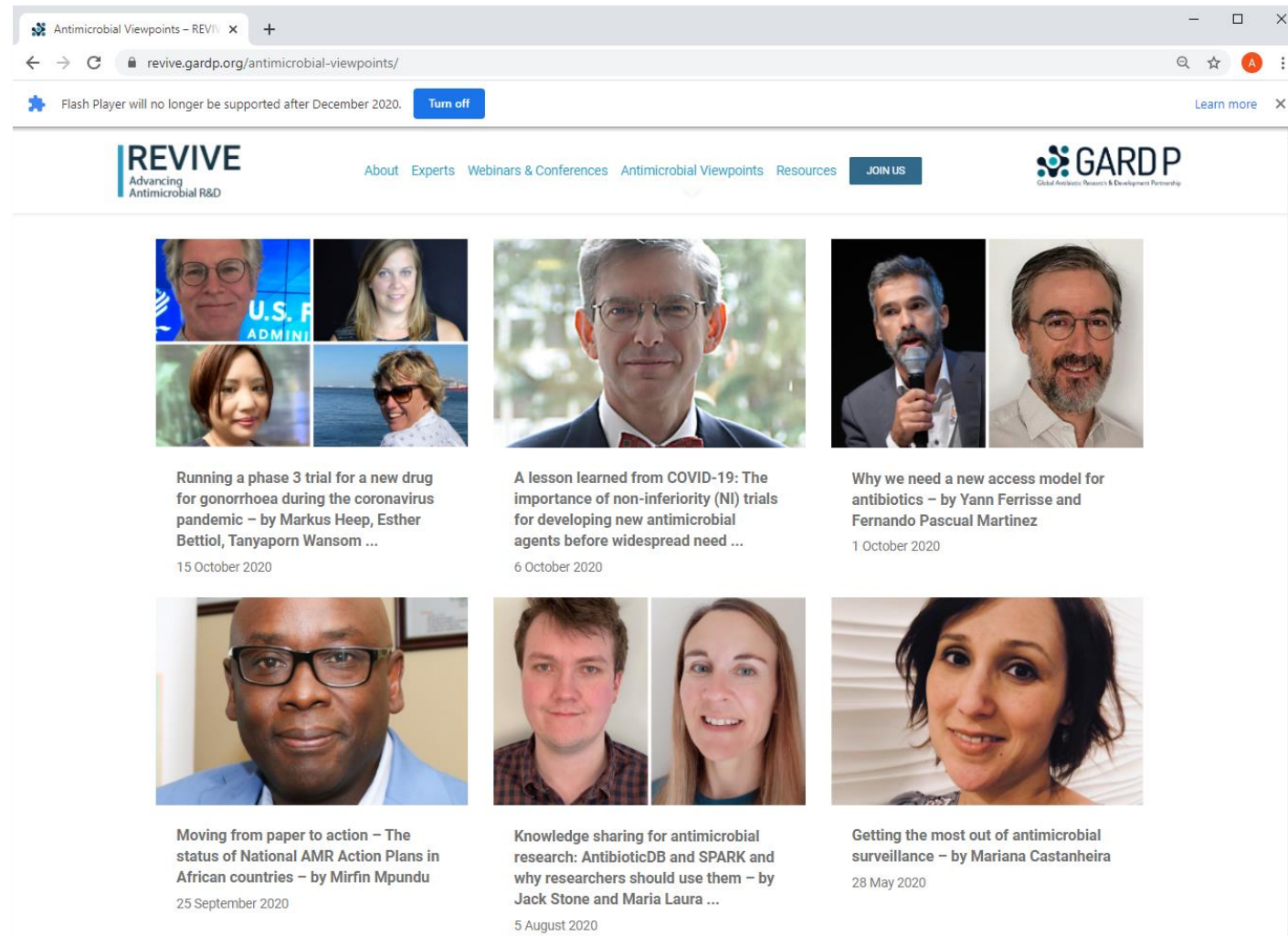


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Clinical development of antimicrobials – Phase 1 development challenges	30 June 2020	Recording available

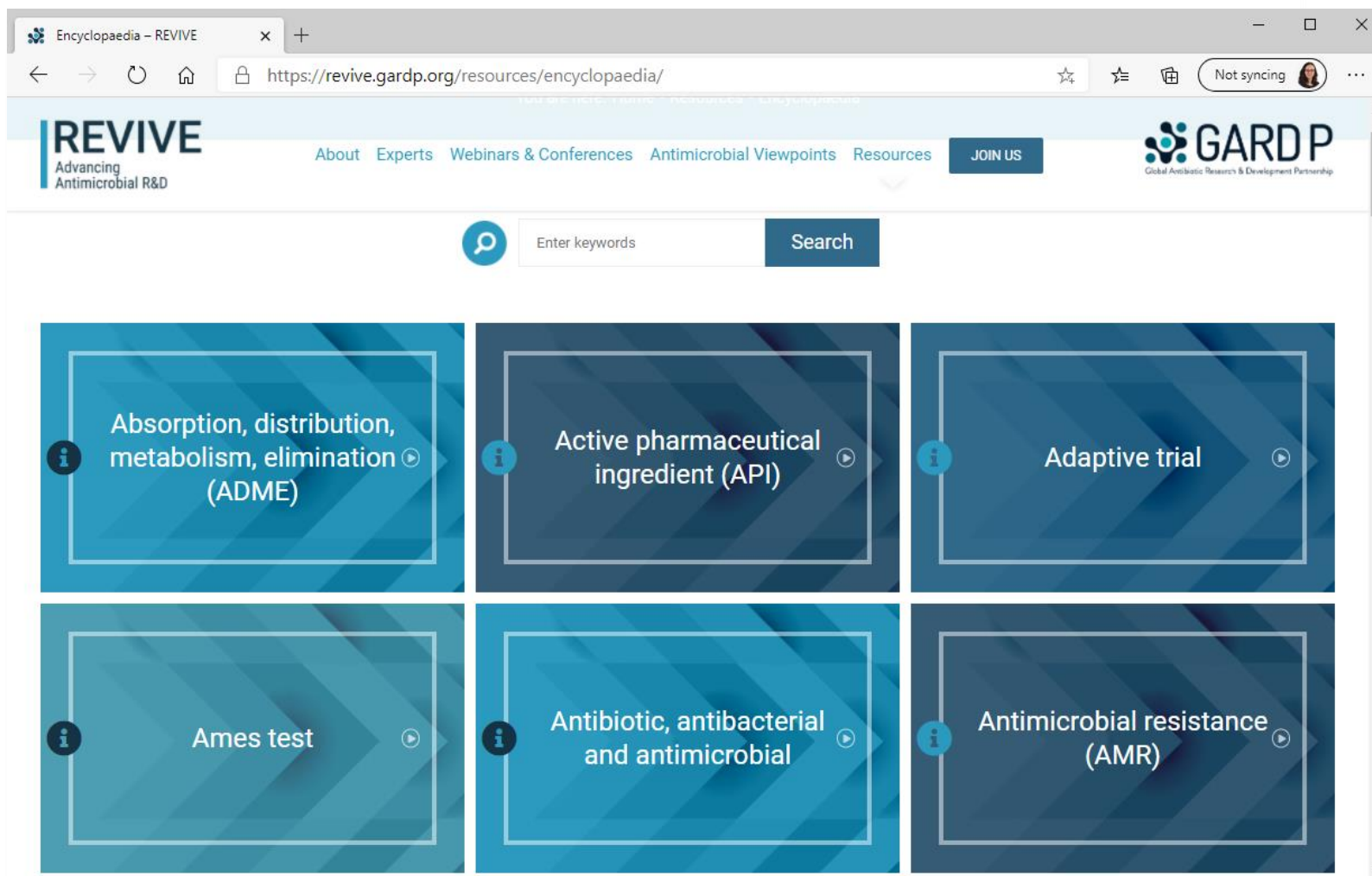
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Today's speakers

Developing antibiotics for children – medical need and regulatory challenges



Phoebe Williams

Consultant Paediatrician, Infectious Diseases Fellow, NHMRC Fellow
University of Sydney & Sydney Children's Hospital (Australia)



Irja Lutsar

Professor in Clinical Microbiology and head of department
University of Tartu (Estonia)



Moderator:

Sally Ellis

Children's Antibiotics Project Leader
GARDP (Switzerland)

Phoebe Williams



Phoebe Williams is a Consultant Paediatrician who completed her medical training at The University of Sydney and Sydney Children's Hospital, as well as undertaking further subspecialty training in Infectious Diseases following the completion of undergraduate studies in development economics. Phoebe subsequently completed a Diploma of Child Health, Masters of Global Health Science and a PhD with the Nuffield Department of Medicine at The University of Oxford (UK). Her PhD was on the topic of paediatric clinical infectious diseases and was undertaken at The University of Oxford's Tropical Medicine Network Unit in Kilifi, rural Kenya.

Phoebe has worked as a Paediatrician in urban and rural health settings throughout Australia, as well as frequently working in East Africa. She continues to work closely with a number of hospitals in low-income countries and is passionate about global health issues. In 2021, Phoebe will commence an NHMRC Fellowship aimed at addressing antimicrobial resistance in neonates in low- and middle-income settings, with a particular focus on the South East Asian region.



Developing Antibiotics for Children

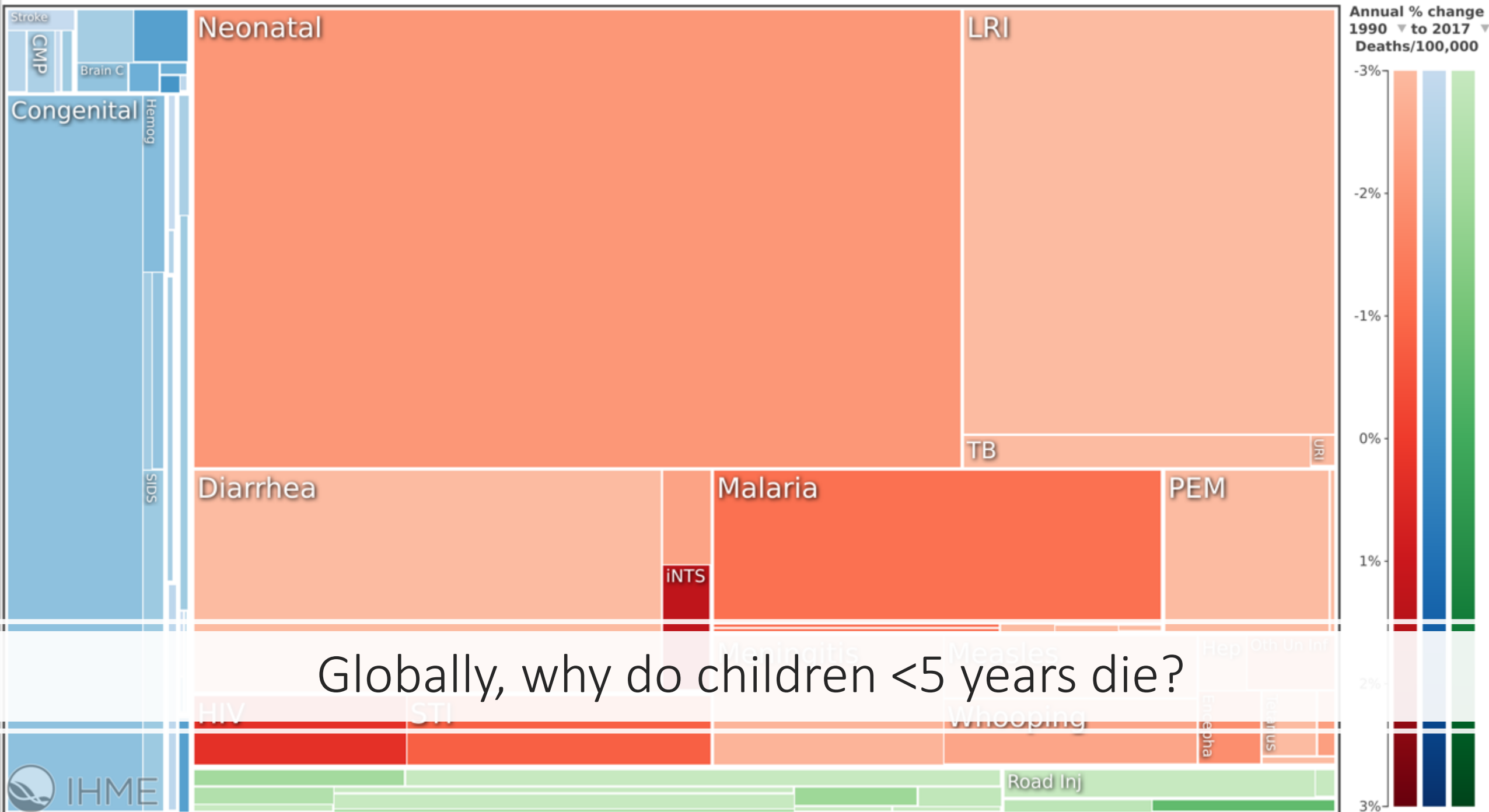
Dr Phoebe Williams

BSc BCom MBBS (Hons.) MSc DCH DPhil FRACP

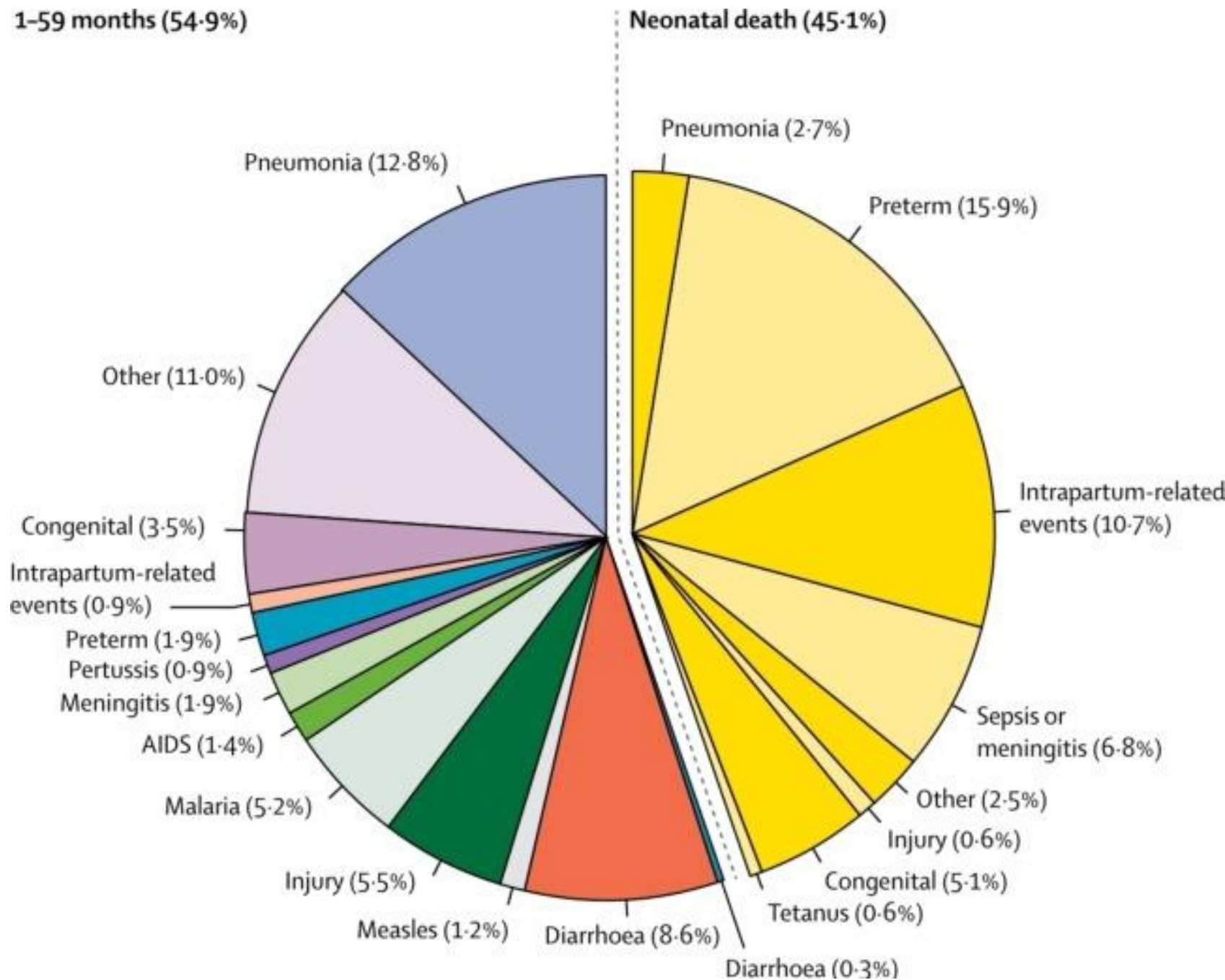
The University of Sydney

Sydney Children's Hospital Network

Both sexes, <5 years, 2017, Deaths



Global Causes of Under-5 Deaths

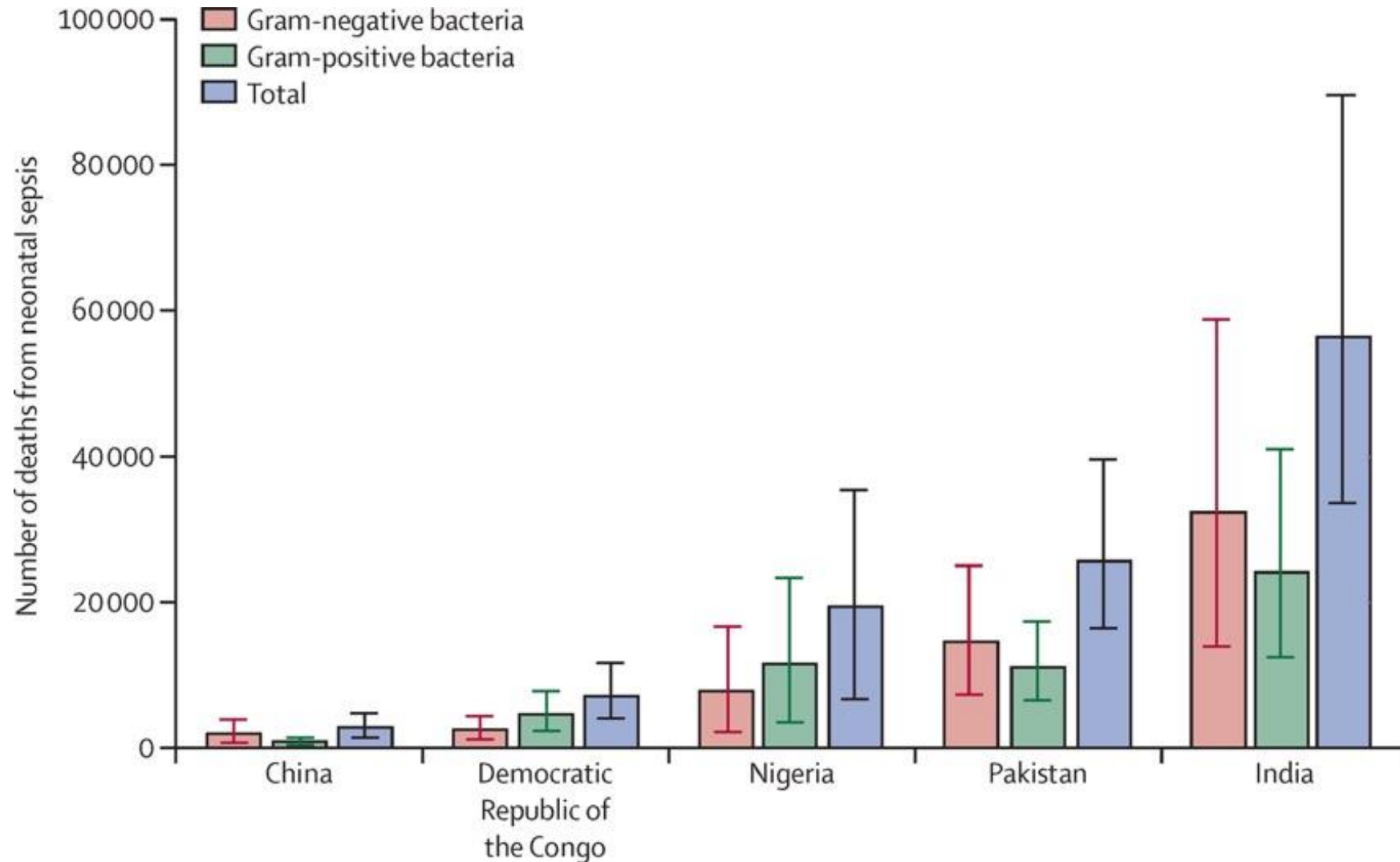




Antimicrobial Resistance (AMR) and Neonatal Mortality

- Multidrug-resistant (MDR) pathogens (harbouring extended-spectrum beta-lactamases, ESBLs & carbapenemases) account for 30% of all **global** neonatal sepsis mortality
- Low- and middle-income countries are most significantly affected by increasing AMR:
 - Higher burden of infectious diseases
 - Weaker health-care systems, over-crowding
 - Insufficient access to effective antibiotics

Estimated annual neonatal sepsis deaths caused by bacteria resistant to first-line antibiotics in 5 high-burden countries



Characterisation and antimicrobial resistance of sepsis pathogens in neonates born in tertiary care centres in Delhi, India: A cohort study

DeNIS Collaboration
The Lancet, 2016.

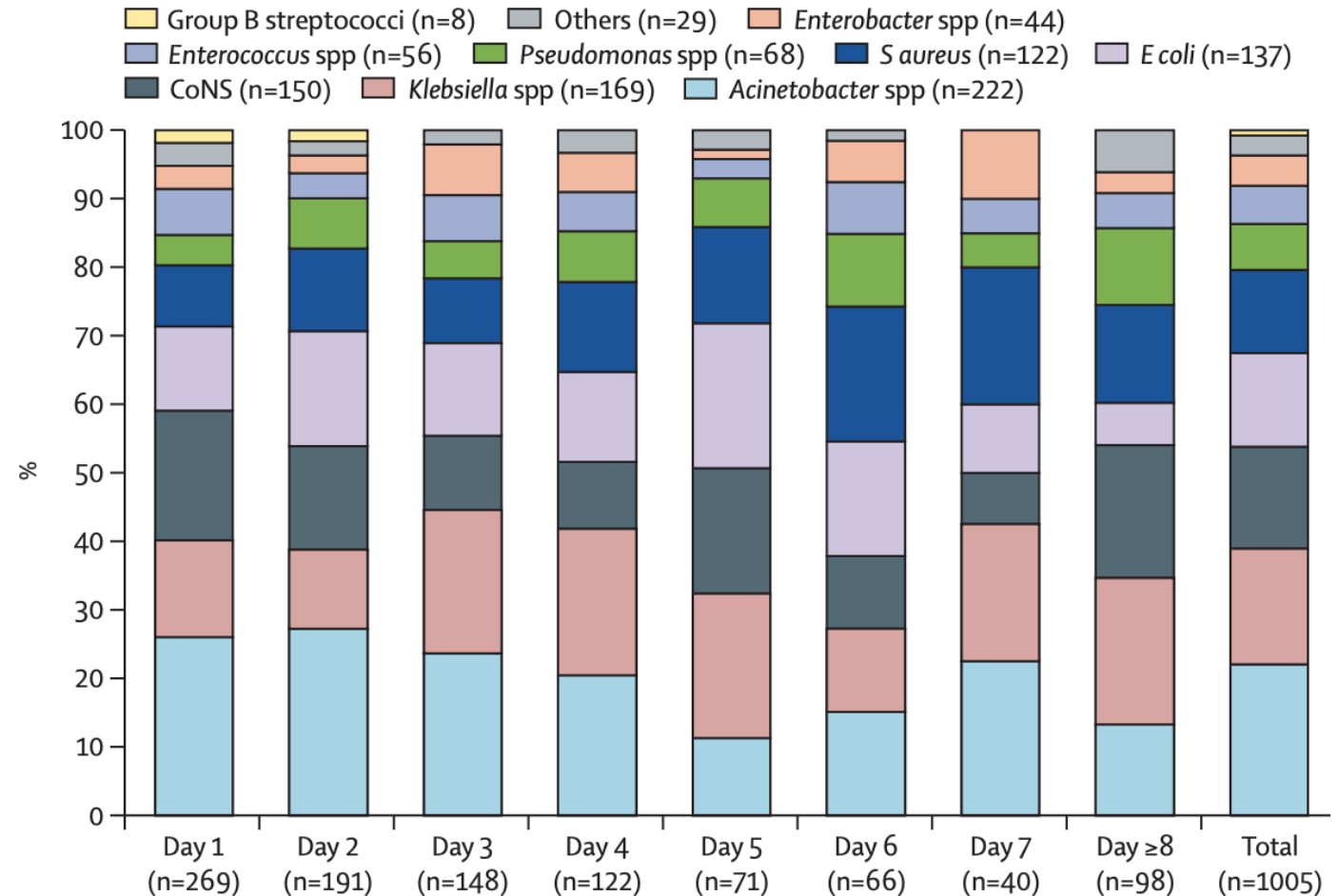


Figure 2: Profile of pathogens isolated on different days of life
CoNS=coagulase-negative staphylococci.

There are high rates of resistance to first-line antibiotics (amp/gent/ceftriaxone) amongst many pathogens causing sepsis in neonates and children

Reported non-susceptibility

Sepsis in a child aged <2 months^{8,23-25}

Klebsiella spp

Ampicillin	100% (71–100) ^{14,26-29}
Gentamicin	49% (48–58) ^{14,26,27,29,30}
Ceftriaxone	43% (NA); ²⁶ 50% (NA) ²⁷

Staphylococcus aureus

Ampicillin	90% (85–100) ^{14,27,28,31,32}
Gentamicin	29% (10–60) ^{14,32-34}
Cloxacillin	20% (10–55) ^{14,27,28}

Streptococcus agalactiae

Ampicillin	0% (NA) ^{31,35}
Gentamicin	Not reported
Ceftriaxone	0% (NA) ³⁵

Escherichia coli

Ampicillin	93% (78–96) ^{14,26-29,36}
Gentamicin	29% (20–46) ^{14,26-29,31}
Ceftriaxone	16% (12–34) ²⁶⁻²⁹



Meningitis in a child aged <28 days

Klebsiella spp

Ampicillin	100% (71–100) ^{14,26-29}
Gentamicin	49% (48–58) ^{14,26,27,29,30}
Ceftriaxone	43% (NA); ²⁶ 50% (NA) ²⁷

Sagalactiae

Ampicillin	0% (NA) ^{31,35}
Gentamicin	Not reported
Ceftriaxone	0% (NA) ³⁵

E coli

Ampicillin	93% (78–96) ^{14,26-29,36}
Gentamicin	29% (20–46) ^{14,26-29,31}
Ceftriaxone	16% (12–34) ²⁶⁻²⁹

Haemophilus influenzae type b

Penicillin and ampicillin	5–100%*
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S pneumoniae

Ampicillin	20% (NA) ³⁸ or 22% (NA) ³²
Gentamicin	77% (NA) ³² or 78% (NA) ³⁸
Ceftriaxone	0% (NA) ³⁸

Table 3 Antimicrobial resistance patterns in the NeoAMR network

	Gram-negative cultures resistant to at least one third-generation cephalosporin, n (%)	Gram-negative cultures resistant to a carbapenem, n (%)	% of Gram-positive cultures resistant to a glycopeptide
Bangladesh	49/58 (84)	47/58 (81)	0/1 (0)
Brazil	17/57 (30)	5/57 (9)	0/12 (0)
Cambodia	6/9 (67)	0/9 (0)	0/2 (0)
China	78/185 (42)	13/185 (7)	0/84 (0)
Colombia	25/42 (60)	1/42 (2)	0/50 (0)
Greece	8/13 (62)	0/13 (0)	0/1 (0)
India	286/562 (51)	154/562 (27)	35/265 (13)
Nigeria	26/36 (72)	7/36 (19)	5/11 (45)
South Africa	427/627 (68)	245/627 (39)	0/394 (0)
Thailand	12/46 (26)	10/46 (22)	0/11 (0)

NeoAMR, Neonatal AMR research network.

AMR is a Risk Factor for Neonatal Mortality

Table 3. Hospital-acquired infections with, and antibiotic resistance in *Acinetobacter baumannii*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* in relation to treatment outcomes.

	Acinetobacter baumannii			Klebsiella pneumoniae			Pseudomonas aeruginosa		
	% (n)	LOS	CFR (n)	% (n)	LOS	CFR (n)	% (n)	LOS	CFR (n)
Hospital-acquired infections (HAI)									
Sepsis	41.0 (66)	27.7	67.7 (44)	45.3 (73)	27.8	58.2 (39)	31.8 (50)	31.5	58.3 (28)
Pneumonia	44.0 (117)	29.3	60.2 (65)	39.8 (106)	32.3	51.0 (49)	33.8 (90)	33.2	54.4 (43)
Other HAI	37.5 (3)	39.0	33.3 (2)	37.5 (3)	38.3	50.0 (3)	16.7 (3)	44.0	40.0 (2)
Antibiotic resistance (ABR)									
Cephalosporins	97.2 (139)	30.0	59.7 (77)	93.1 (121)	30.8	51.9 (56)	89.4 (93)	32.6	53.7 (44)
Penicillins	92.3 (132)	31.1	60.7 (74)	90.0 (117)	31.4	51.9 (54)	91.3 (95)	33.8	48.8 (40)
Carbapenems	88.1 (126)	31.8	62.9 (73)	81.5 (106)	32.5	53.8 (50)	88.5 (92)	33.2	54.4 (43)
Fluoroquinolones	77.6 (111)	32.9	64.1 (66)	71.5 (93)	33.9	54.3 (44)	81.7 (85)	34.9	52.1 (38)
Aminoglycosides	92.3 (132)	31.2	61.5 (65)	93.1 (121)	30.4	52.8 (57)	89.4 (93)	33.0	53.1 (43)
Monobactams	25.9 (37)	33.1	61.8 (21)	58.5 (76)	32.5	56.7 (38)	39.4 (41)	34.9	52.8 (19)
Colistin	10.5 (15)	31.2	64.3 (9)	16.9 (22)	39.2	61.1 (11)	17.3 (18)	39.5	53.3 (8)
Trimethoprim/ Sulfamethoxazole	69.2 (99)	34.4	61.1 (55)	73.1 (95)	33.5	52.4 (44)	90.4 (94)	34.1	48.1 (39)

LOS = length of stay in days, here after infection; CFR = case fatality rate in percentage and in absolute numbers (n)

The first section displays the proportion of sepsis, pneumonia and other HAI caused by *Acinetobacter baumannii*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* respectively. The sum exceeds 100% since pneumonia and sepsis were often concurrent conditions and hospital-acquired infections (HAI) were frequently caused by more than one pathogen. The second section describes the proportion of antibiotic resistance (ABR) to the respective antibiotic class in the isolated bacteria. HAI and ABR are additionally displayed by treatment outcomes—the mean length of hospital stay (LOS) after infection and the case fatality rate (CFR)—for each of the bacterial species separately.

- First line antibiotics were often ineffective in patients with healthcare-associated infections (HAIs) caused by MDR pathogens → Delayed appropriate treatment
- "The absence of effective drugs in cases resistant to all tested substances contribute to the increased mortality in our cohort, since empiric treatment might fail due to antibiotic resistance".

AMR is Increasingly Affecting High-Income Health Settings

European AMR Surveillance network:

- Burden of infections due to multidrug-resistant organisms (MROs) has increased significantly in the past decade
 - **Carbapenem-resistance:**
18% in 2007 → 28% in 2015
- Each year: ~700,000 infections with MROs; ~33,000 deaths
- DALYs* for infections with MROs (170 per 100,000 population) = **the combined burden of influenza, tuberculosis and HIV (in Europe)**

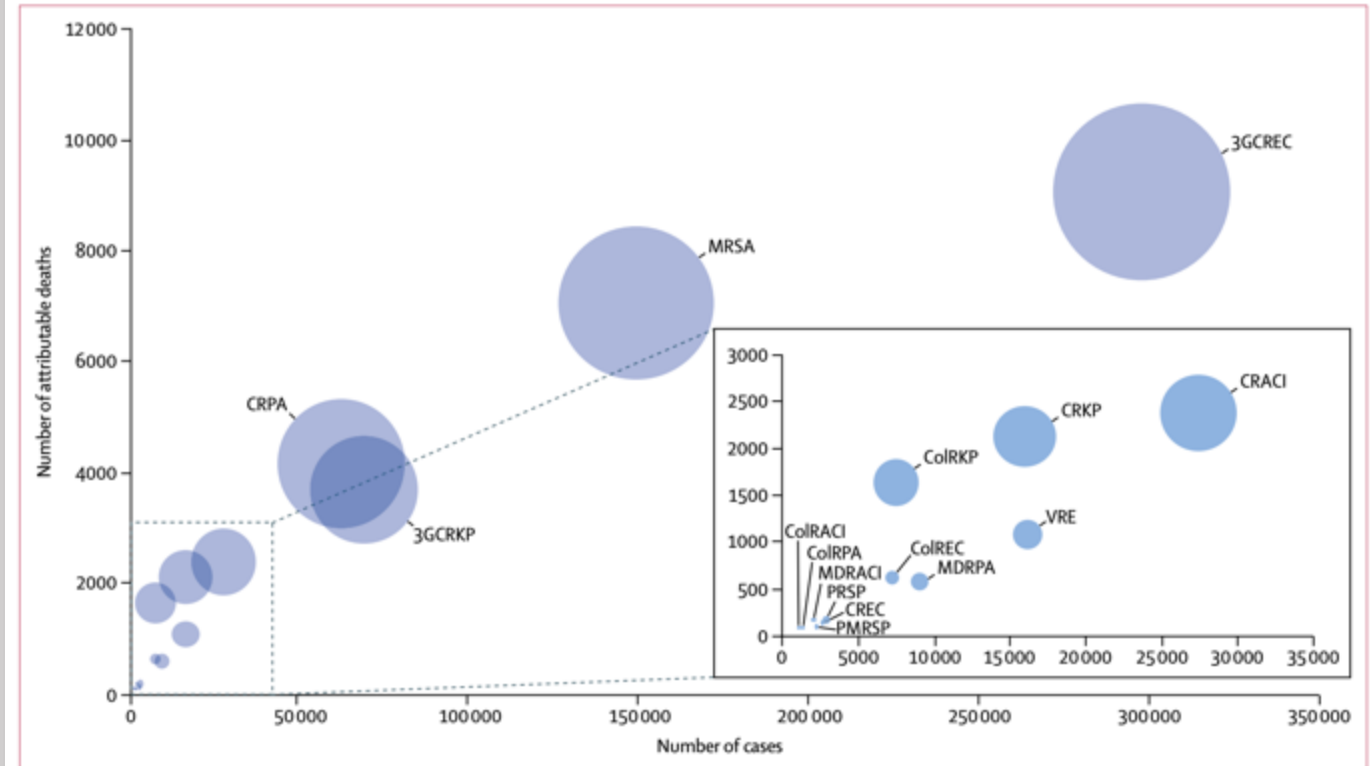
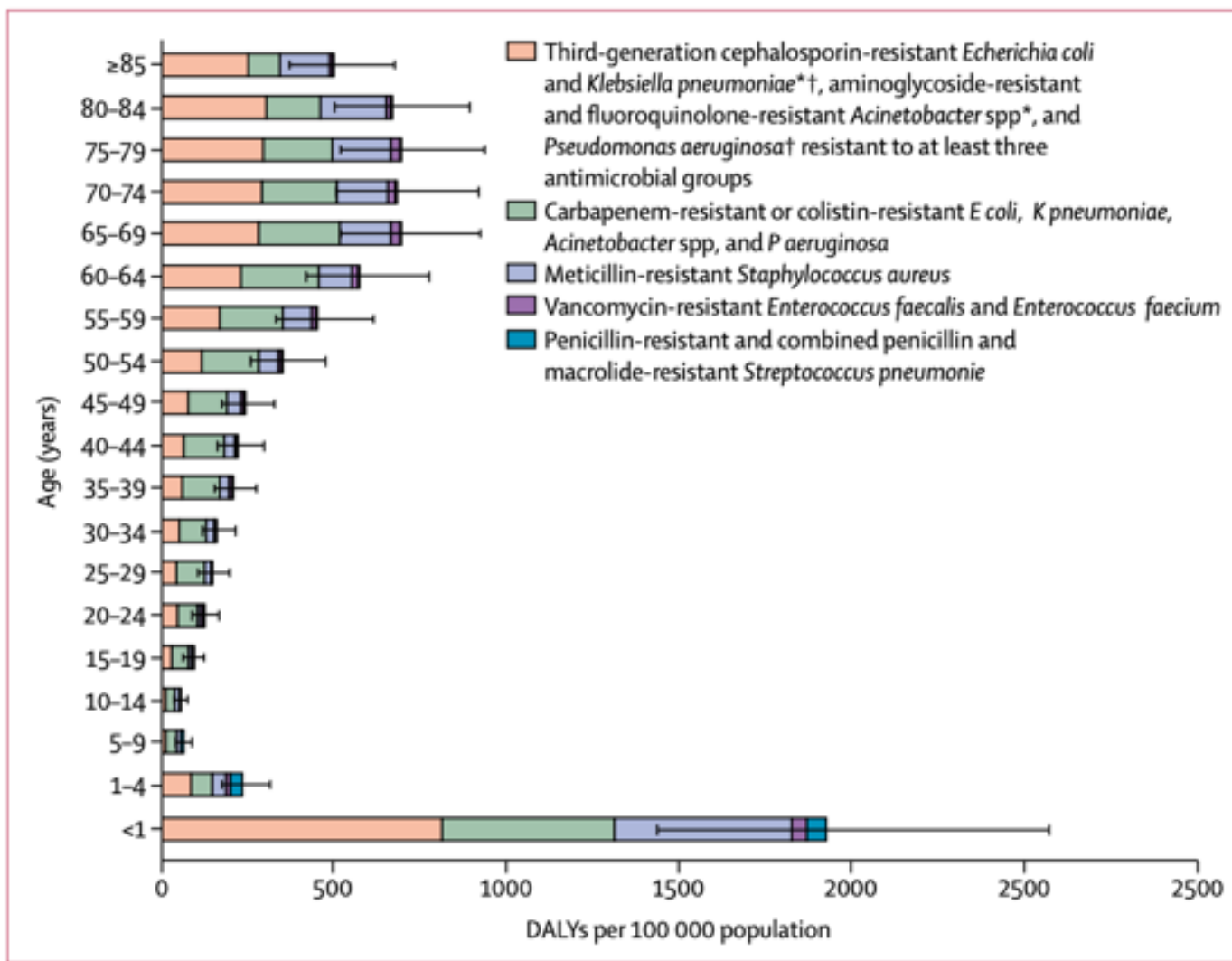


Figure 1: Infections with antibiotic-resistant bacteria, EU and European Economic Area, 2015

Diameter of bubbles represents the number of disability-adjusted life-years. ColRACI=colistin-resistant *Acinetobacter* spp. CRACI=carbapenem-resistant *Acinetobacter* spp. MDRACI=multidrug-resistant *Acinetobacter* spp. VRE=vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium*. ColREC=colistin-resistant *Escherichia coli*. CREC=carbapenem-resistant *E. coli*. 3GCREC=third-generation cephalosporin-resistant *E. coli*. ColRKP=colistin-resistant *Klebsiella pneumoniae*. CRKP=carbapenem-resistant *K. pneumoniae*. 3GCRKP=third-generation cephalosporin-resistant *K. pneumoniae*. ColRPA=colistin-resistant *Pseudomonas aeruginosa*. CRPA=carbapenem-resistant *P. aeruginosa*. MDRPA=multidrug-resistant *P. aeruginosa*. MRSA=meticillin-resistant *Staphylococcus aureus*. PRSP=penicillin-resistant *Streptococcus pneumoniae*. PMRSP=penicillin-resistant and macrolide-resistant *S. pneumoniae*.



Even in High-Income Health Settings, the AMR Burden is Highest in Infants

Figure 2: Model estimates of the burden of infections with antibiotic-resistant bacteria of public health importance in DALYs, by age group, EU and European Economic Area, 2015

Error bars are 95% uncertainty intervals. DALYs=disability-adjusted life-years. *Excludes those resistant to carbapenem or colistin. †In 2015, most of the third-generation cephalosporin-resistant *E. coli* (88.6%) and *K. pneumoniae* (85.3%) isolates reported to the European Antimicrobial Resistance Surveillance Network produced an extended-spectrum *B-lactamase* ⁹

A newborn baby with dark skin and hair is lying on its back on a colorful, patterned blanket. The baby is looking up towards the camera with a curious expression. The blanket features large, stylized floral and leaf patterns in shades of orange, yellow, and green. The baby is wearing a light-colored, possibly pink, garment. The overall lighting is soft and natural.

Rates of neonatal sepsis remain largely unchanged,
and AMR is an additional challenge that is associated
with increased mortality...

In the context of a limited development pipeline for new antibiotics in children.

What Antibiotics Are Available for Treating Children and Babies?



Adopt AWaRe:
Handle antibiotics
with care.

Adopt AWaRe classification

Access	
Amoxicillin	Azithromycin
Amoxicillin and clavulanic acid	Cefixime
Ampicillin	Cefotaxime
Benzathine benzylpenicillin	Ceftriaxone
Benzylpenicillin	Ciprofloxacin
Cefalexin or cefazolin	Clarithromycin
Chloramphenicol	Piperacillin and tazobactam
Clindamycin	Meropenem
Cloxacillin	Vancomycin
Doxycycline	
Gentamicin or amikacin	* Antibiotics that are also in the Watch group
Metronidazole	
Nitrofurantoin	
Phenoxyethylpenicillin	
Procaine benzylpenicillin	
Spectinomycin	
Sulfamethoxazole and trimethoprim	
Core access antibiotics	
Watch	
Anti-pseudomonal penicillins with beta-lactamase inhibitor (eg, piperacillin and tazobactam)	
Carbapenems or penems (eg, faropenem, imipenem and cilastatin, meropenem)	
Cephalosporins, third generation (with or without beta-lactamase inhibitor; eg, cefixime, cefotaxime, ceftazidime, ceftriaxone)	
Glycopeptides (eg, teicoplanin, vancomycin)	
Macrolides (eg, azithromycin, clarithromycin, erythromycin)	
Quinolones and fluoroquinolones (eg, ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin)	
Reserve	
Aztreonam	
Cephalosporins, fourth generation (eg, cefepime)	
Cephalosporins, fifth generation (eg, ceftaroline)	
Daptomycin	
Fosfomycin (intravenous)	
Oxazolidinones (eg, linezolid)	
Polymyxins (eg, colistin, polymyxin B)	
Tigecycline	

Figure: List of antibiotics, classified into Access, Watch, and Reserve groups, to improve prescribing decisions

ACCESS ANTIBIOTICS:

-Narrow-spectrum

-Low toxicity risk

-Should account for
60% of total
antibiotic
consumption

WHO Model List of Essential Medicines for Children

6th edition

6.2 Antibacterials

To assist in the development of tools for antibiotic stewardship at local, national and global levels and to reduce antimicrobial resistance, three different categories were developed – ACCESS, WATCH and RESERVE groups.

Group 1 - KEY ACCESS ANTIBIOTICS

To improve both access and clinical outcomes antibiotics that were first or second choice antibiotics in at least one of the reviewed syndromes are designated as key ACCESS antibiotics, emphasizing their role as the antibiotics that should be widely available, affordable and quality-assured. ACCESS antibiotics are listed below. Selected ACCESS antibiotics may also be included in the WATCH group.

6.2.1 Beta-lactam medicines		6.2.2 Other antibacterials	
amoxicillin	cefotaxime*	amikacin	gentamicin
amoxicillin + clavulanic acid	ceftriaxone*	azithromycin*	metronidazole
ampicillin	cloxacillin	chloramphenicol	nitrofurantoin
benzathine benzylpenicillin	phenoxymethylpenicillin	ciprofloxacin*	spectinomycin (EML only)
benzylpenicillin	piperacillin + tazobactam*	clarithromycin*	sulfamethoxazole + trimethoprim
cefalexin	procaine benzyl penicillin	clindamycin	vancomycin (oral)*
cefazolin	<i>meropenem</i> *	doxycycline	<i>vancomycin (parenteral)*</i>
cefixime*			

Italics = complementary list

*Watch group antibiotics included in the EML/EMLc only for specific, limited indications

WATCH ANTIBIOTICS:

-Increased toxicity
concerns and
resistance potential

Group 2 - WATCH GROUP ANTIBIOTICS

This group includes antibiotic classes that have higher resistance potential and so are recommended as first or second choice treatments only for a specific, limited number of indications. These medicines should be prioritized as key targets of stewardship programs and monitoring.

This group includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine¹ and/or antibiotics that are at relatively high risk of selection of bacterial resistance.

Watch group antibiotics
Quinolones and fluoroquinolones e.g. ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin
3rd-generation cephalosporins (with or without beta-lactamase inhibitor) e.g. cefixime, ceftriaxone, cefotaxime, ceftazidime
Macrolides e.g. azithromycin, clarithromycin, erythromycin
Glycopeptides e.g. teicoplanin, vancomycin
Antipseudomonal penicillins + beta-lactamase inhibitor e.g. piperacillin-tazobactam
Carbapenems e.g. meropenem, imipenem + cilastatin
Penems e.g. faropenem

RESERVE ANTIBIOTICS:

-Last-resort options

-For life-threatening
infections due to
multidrug-resistant
organisms

Group 3 - RESERVE GROUP ANTIBIOTICS

This group includes antibiotics that should be treated as “last resort” options that should be accessible, but whose use should be tailored to highly specific patients and settings, when all alternatives have failed (e.g., serious, life-threatening infections due to multi-drug resistant bacteria). These medicines could be protected and prioritized as key targets of national and international stewardship programs involving monitoring and utilization reporting, to preserve their effectiveness.

Reserve group antibiotics	
Aztreonam	Fosfomycin (IV)
4th generation cephalosporins e.g. cefepime	Oxazolidinones e.g. linezolid
5th generation cephalosporins e.g. ceftaroline	Tigecycline
Polymyxins e.g. polymyxin B, colistin	Daptomycin

2019 EMLc

Access	
• Amikacin	• Cloxacillin
• Amoxicillin	• Doxycycline
• Ampicillin	• Gentamicin
• Amoxicillin–clavulanic acid	• Metronidazole
• Benzathine benzylpenicillin	• Nitrofurantoin
• Benzylpenicillin	• Phenoxymethyl penicillin
• Cefazolin	• Procaine penicillin
• Chloramphenicol	• Spectinomycin
• Clindamycin	• Sulfamethoxazole–trimethoprim
Watch	
• Azithromycin	• Vancomycin (intravenous* and oral)
• Cefixime	• Ciprofloxacin
• Ceftriaxone	• Clarithromycin
• Cefotaxime	• Meropenem*
• Ceftazidime*	• Piperacillin–tazobactam
• Cefuroxime	
Reserve*	
• Fosfomycin (intravenous)	• Ceftazidime–avibactam
• Linezolid	• Meropenem–vaborbactam
• Colistin	• Plazomicin
• Polymyxin B	

Figure: Antibiotics included in 2019 WHO Essential Medicines List by AWaRe group

*Antibiotics listed in the complementary list of the 2019 WHO Essential Medicines List, indicating the need for specialist supervision.

- 3 new antibiotics included in Reserve group, some removed
- All antibiotics classified into AWaRe groups to encourage optimal use:
 - 37 essential antibiotics
 - 180 total antibiotics

Overuse of
'Watch' and
'Reserve'
antibiotics will
exacerbate
antimicrobial
resistance

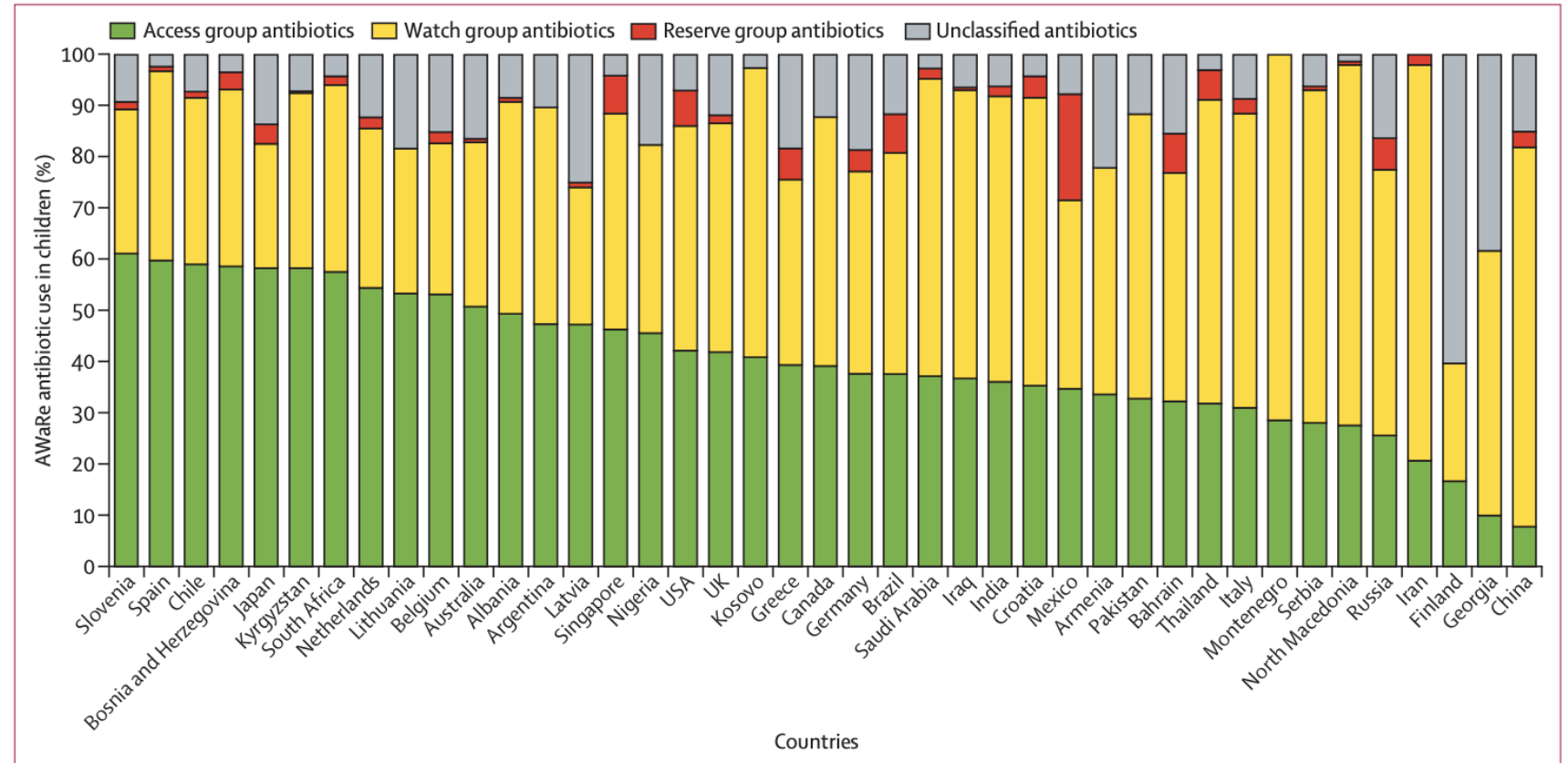


Figure 3: Percentage of total antibiotic use in children by WHO AWaRe classification by country
Only countries with prescriptions >25th percentile are included. AWaRe=Access, Watch, and Reserve.

The Antibiotic Development Pipeline: 2014-2018

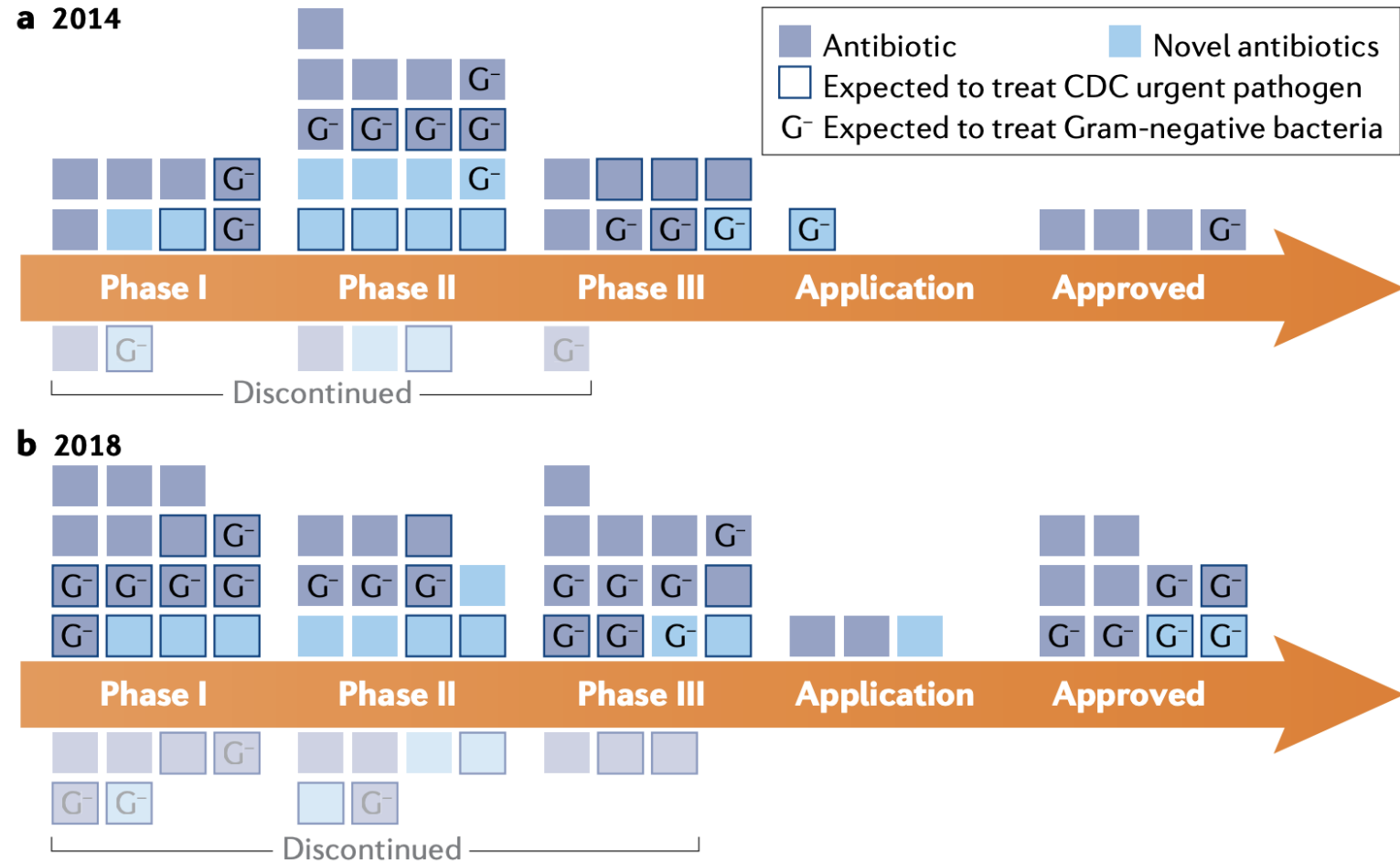


Fig. 1 | **Changes in the antibiotic development pipeline from 2014–2018.** The snapshot for 2014 (a) provides the baseline for the analysis, with changes to the overall pipeline in the following 5 years added to the snapshot for 2018 (b). The year-over-year changes for this 5-year period can be seen in the associated visualization (see Related links).

What are the Barriers to Paediatric Drug Development?

- Paediatric drug development is particularly slow: **on average, the licensing of medications for use in children typically lags adult licensing by one decade**, due to:
 - Poor financial incentives from the market → less trials overall
 - Greater liability risk → deters industry from sponsoring trials
 - Higher risk of experiencing adverse events
 - Complex regulatory frameworks:

Table 1

Similarities and differences in the pediatric legislation in the United States and European Union. Table provided by European Medicines Agency (EMA) and/or US Food and Drug Administration (FDA).

	US Best Pharmaceuticals for Children Act	US Pharmaceutical Research Equity Act	European Union
Development Instrument	Optional Written Request	Mandatory Pediatric Study Plan	Mandatory* Paediatric Investigation Plan
Waiver	N/A	3 grounds	3 grounds
Timing	Any time adequate information available	End of Phase II	> End of Phase I
Reward	6-mo exclusivity	–	Main: 6-month SPC extension (patent)
Orphan products	Included	Excluded	Included
Decision	FDA	FDA	EMA [not European Commission (EC)] Opinion: Paediatric Committee
Scope of pediatric development	Not limited to adult indication	= adult indication	= adult indication
Scientific advice	Normally in global fee	Normally in global fee	Free for paediatrics

* Optional for off-patent.

What are the Barriers to Paediatric Drug Development?

- Ethical challenges:
 - Inherently vulnerable population
 - High risk of mortality and morbidity
 - Difficulties in obtaining parental consent
- Technical challenges:
 - Blood volume collection, including impact on blood volume
 - Monitoring required
- Divergent physiology
 - Children possess a unique and constantly evolving set of physiological characteristics
 - Affects drug absorption, volume of distribution, serum concentrations (due to protein binding ability and the impact of immature elimination pathways)

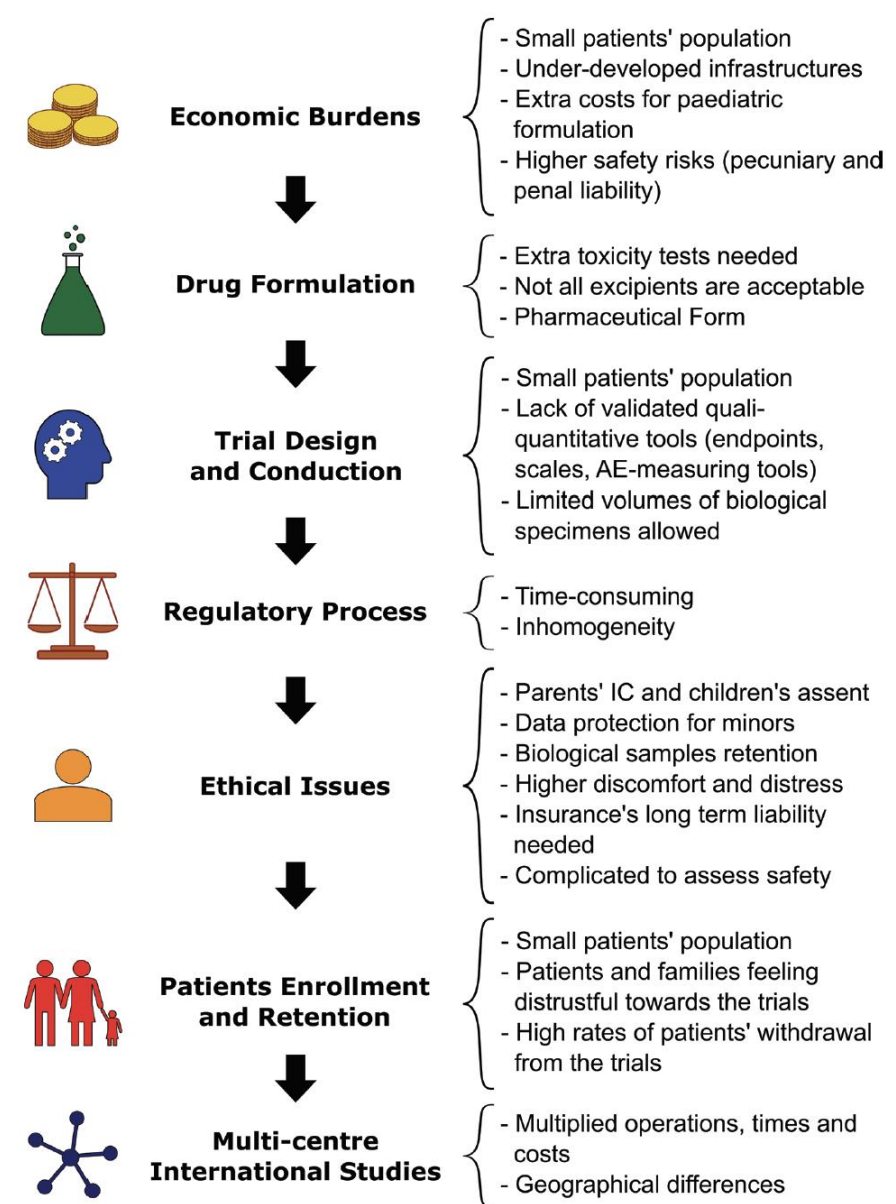


Figure 1. Aspects to consider for trial design. The flowchart summarises the most common drawbacks that can be encountered during the conduct of a paediatric clinical trial.

The use of off-label (unlicensed) prescribing in children is therefore widespread

- Nearly half of all paediatric medicines in Europe are prescribed off-label
 - Prescribing in a manner different to that recommended in the product license (different dose, different frequency, different route, different age group)
 - Due to minimal efficacy and safety data in children
- Particularly a problem in neonates
 - However, there is a growing necessity to conduct all stages of drug development trials in neonates, as many disease conditions are specific to this population and drugs have variable pharmacokinetic/pharmacodynamic (PK/PD) and safety profiles

Off-label drug use is common

TABLE 1 Prevalence Rates of Off-Label Systemic Drug Orders in Ambulatory Pediatric Visits in the United States (2006–2015)

Off-Label Characteristic	Sample, <i>n</i>	% of Total Visits (95% CI)	% of Visits With Systemic Drugs (95% CI)	% of Off-Label or Possibly Off-Label Drugs (95% CI)	Estimated Orders, Millions per Year (95% CI)
Off label for any reason	17 064	18.5 (17.7–19.3)	44.5 (43.3–45.8)	90.6 (89.8–91.4)	41.2 (39.9–42.4)
Possibly off label for any reason	1801	1.6 (1.5–1.8)	3.9 (3.5–4.4)	9.4 (8.6–10.2)	4.3 (3.9–4.7)
Off label by indication	13 914	15.6 (15.0–16.3)	37.6 (36.4–38.8)	74.6 (73.2–75.9)	33.9 (32.7–35.1)
Possibly off label by indication	2079	1.8 (1.7–2.0)	4.4 (4.0–4.9)	10.2 (9.5–11.1)	4.6 (4.3–5.1)
Off label by age	3501	4.3 (3.9–4.6)	10.3 (9.6–11.0)	17.6 (16.5–18.7)	8.0 (7.4–8.6)
Off label by wt	131	0.2 (0.2–0.3)	0.6 (0.4–0.8)	0.6 (0.4–0.8)	0.4 (0.3–0.6)
Possibly off label by wt	419	0.5 (0.4–0.6)	1.2 (1.0–1.5)	1.2 (0.9–1.5)	0.9 (0.7–1.1)
Off label by combination of age, indication, and (when applicable) wt ^a	893	1.2 (1.0–1.4)	2.8 (2.5–3.3)	4.6 (4.1–5.3)	2.1 (1.8–2.4)

All rates account for sampling, clustering, and strata, reflecting nationally representative estimates.

^a Drugs that were ordered for an approved indication and an approved age (and, when applicable, wt) for a different indication but an unapproved age or wt for the documented diagnoses and symptoms.

TABLE 4 Absolute Prevalence of Off-Label Systemic Drug Orders by Drug Class and Age for Children in US Ambulatory Settings (2006–2015)

Drug Class ^a	Off-Label Orders per 1000 Ambulatory Visits (95% CIs)					
	Age <1 mo	Age 1 mo to <2 y	Age 2–5 y	Age 6–11 y	Age 12–17 y	All Children
Anti-infective	13.7 ^b (6.8–20.5)	60.1 (52.9–67.2)	88.6 (80.7–96.6)	78.3 (70.3–86.2)	79.8 (70.1–89.5)	74.8 (69.6–79.9)
Respiratory	0.5 ^b (0–1.6)	48.0 (40.6–55.4)	63.5 (56.5–70.6)	61.0 (53.8–68.2)	50.1 (43.8–56.5)	53.8 (49.8–57.9)
Nervous	9.0 ^b (1.2–16.7)	8.6 (4.3–12.9)	16.0 (12.8–19.1)	62.6 (54.2–71.0)	123.0 (108.9–137.2)	53.7 (47.8–59.5)
Alimentary	27.5 (15.8–39.2)	26.3 (21.9–30.8)	26.9 (22.1–31.8)	27.8 (23.5–32.1)	22.1 (18.8–25.5)	25.8 (23.2–28.4)
Hormonal	ND ^b	13.4 (10.5–16.3)	15.8 (12.8–18.7)	12.2 (9.1–15.2)	10.3 (7.8–12.9)	12.4 (10.9–13.9)
Cardiovascular	0 ^b (0–0.1)	1.6 ^b (0.8–2.4)	3.4 (2.2–4.6)	6.4 (4.5–8.4)	8.3 (6.2–10.4)	4.9 (4.0–5.9)
Musculoskeletal	1.3 ^b (0–3.4)	3.8 (2.5–5.1)	3.3 (1.8–4.8)	3.4 (2.2–4.5)	8.5 (6.4–10.5)	4.7 (3.9–5.6)
Genitourinary	ND ^b	0.2 ^b (0–0.5)	0.3 ^b (0–0.5)	0.6 ^b (0.1–1.2)	15.7 (12.8–18.6)	4.4 (3.6–5.2)

ND, not defined.

^a Drug class according to ATC level 1 classification.

^b Values are based on <30 observations.

TABLE 6 Proposed dosing for the drugs most frequently used against carbapenem-resistant Gram-negative bacterial infections in children^a

Drug	Dose	Age group with regulatory approval	Comments
Meropenem	40 mg/kg/dose i.v. over 3 h q8h (max, 2 g/dose); for neonates with <32 wk gestation and <2 wk old, the same dose q12h	EMA, children >3 mo old; FDA, all ages (age <3 mo only for IAI)	
Ertapenem	For children ≥13 yr old and adults, 1 g q24h; for children <13 yr old, 30 mg/kg/day q12h (max, 1 g/day)	EMA and FDA, >3 mo	Combined ertapenem-meropenem regimen for extensive drug-resistant isolates (consider a higher dose [max, 2 g/day])
Gentamicin	5–7.5 mg/kg q24h; for neonates, dose by gestational and postnatal age (153)	FDA and EMA, all ages (use caution in premature infants)	Desired serum levels are a peak of 6–12 µg/ml and a trough of <2 µg/ml; consider higher doses (7.5–10 mg/kg/day) for patients with shock, lung infections, and cystic fibrosis
Amikacin	15–20 mg/kg q24h; for neonates, dose by gestational and postnatal age (153)	FDA and EMA, all ages (use caution in premature infants)	Desired serum levels are a peak of 20–35 µg/ml and a trough of <5 µg/ml; higher doses (25–30 mg/kg/day) might be considered in patients with shock, lung infections, and cystic fibrosis
Colistin (colistimethate sodium)	Maintenance dose of 75,000–150,000 IU/kg/day q8h to q12h; a loading dose of 75,000–150,000 IU/kg is recommended in critically ill patients (max daily dose, 10,800,000 IU)	FDA and EMA, all ages for the treatment of serious infections due to Gram-negative pathogens in patients with limited treatment options	Higher maintenance doses (150,000–250,000 IU/kg/day) should be considered in patients with shock, lung infections, and cystic fibrosis
Polymyxin B	Maintenance dose of 15,000–25,000 IU/kg/day q12h for those ≥2 yr old and 25,000–40,000 IU/kg/day q12h for those <2 yr old; consider a loading dose of 25,000/kg in critically ill patients (max daily dose, 2,000,000 IU)	FDA, all ages for the treatment of serious infections due to Gram-negative pathogens in patients with limited treatment options; EMA, not available in Europe	
Tigecycline	A 100-mg loading dose and then 50 mg q12h for those ≥12 yr old; a 2-mg/kg loading dose and then 1.2 mg/kg/dose q12h (max, 50 mg/dose) for those 8 to 11 yr old	EMA, restricted to children >8 yr of age with infections without alternative antibacterial therapy available; FDA, not recommended unless alternative treatment is not suitable	Consider a higher dose for patients with lung infections, cUTIs, BSIs, or shock: for those 8 to 11 yr of age, a 3-mg/kg loading dose (max, 200 mg) and then a 2-mg/kg/dose (max, 100 mg) q12h; for those ≥12 yr of age, a 200-mg loading dose and then 100 mg q12h
Fosfomycin	12–24 g/day i.v. q6h to q8h for those >12 yr old (wt, >40 kg); 200–400 mg/kg/day q6h to q8h for those 1–12 yr old (wt, 10–40 kg); 200–300 mg/kg/day q8h for those 1–12 mo old (wt, ≤10 kg); 200 mg/kg/day q8h for neonates (postnatal age, 40–44 wk); 100 mg/kg/day q12h for premature neonates (postnatal age, <40 wk)	EMA, all ages; FDA, not available in USA (i.v. formulation)	Consider a higher dose (400 mg/kg/day q6h to q8h in patients >12 mo old [max, 8 g q8h]) for severe infections, in particular when caused by organisms with moderate susceptibility; serum electrolyte levels and water balance must be monitored during therapy
Aztreonam	120–150 mg/kg/day q8h (max, 8 g/day); for neonates, dose by gestational and postnatal age (153)	FDA and EMA, all ages	The highest dose might be considered in severe infections
Ceftazidime-avibactam	A 2-h i.v. infusion q8h; for those 6 mo to <18 yr old, 50-mg/kg ceftazidime (max, 2 g/dose) and 12.5-mg/kg avibactam (max, 0.5 g/dose); for those 3 to <6 mo old, 40-mg/kg ceftazidime and 10-mg/kg avibactam	FDA, >3 mo; EMA, not approved for use in those <18 yr old	Consider a 3-h infusion for severe infections
Ceftolozane-tazobactam	A 1-h i.v. infusion q8h of ceftolozane at 20 mg/kg/dose (max, 1 g/dose) and tazobactam at 10 mg/kg/dose (max, 0.5 g/dose)	FDA and EMA, not approved for use in those <18 yr old	For severe lung infections, consider ceftolozane at 40 mg/kg/dose and tazobactam at 20 mg/kg/dose (max, ceftolozane at 2 g/dose and tazobactam at 1 g/dose) q8h; the pediatric dose is from a phase I clinical trial (87) and two phase II clinical trials (88)
Meropenem-vaborbactam	A 3-h i.v. infusion q8h of meropenem at 40 mg/kg/dose (max, 2 g/dose) and vaborbactam at 40 mg/kg/dose (max, 2 g/dose)	FDA and EMA, not approved for use in those <18 yr old	Dose from an ongoing phase I clinical trial in children <18 yr of age (https://clinicaltrials.gov/ct2/show/NCT02687906)
Imipenem-cilastatin-relebactam	For those 1 mo to <18 years old, imipenem at 15 mg/kg/dose (max, 500 mg/dose) with cilastatin at 15 mg/kg/dose (max, 500 mg/dose) and relebactam at 7.5 mg/kg/dose i.v. q6h	FDA and EMA, not approved for use in those <18 yr old	Dose from a phase I clinical trial in children <18 yr of age (128)
Ampicillin-sulbactam	Ampicillin at 400 mg/kg/day q6h (max, ampicillin 8 g/day).	FDA and EMA, >12 mo	

^aBSI, bloodstream infection; cUTI, complicated urinary tract infection; EMA, European Medicines Agency; FDA, U.S. Food and Drug Administration; q6h, every 6 h; q8h, every 8 h; q12h, every 12 h; q24h, every 24 h; i.v., intravenous; max, maximum. Colistin may be labeled as international units (IU) of colistimethate sodium (CMS), milligrams of CMS, or milligrams of colistin base activity (CBA). The conversion is as follows: 1,000,000 IU of CMS = 80 mg of CMS = 30 mg of CBA. Polymyxin B may be labeled as international units or milligrams. The conversion is as follows: 10,000 IU = 1 mg. Children with cystic fibrosis, in general, require higher dosages to achieve therapeutic serum concentrations equivalent to those in children without cystic fibrosis due to enhanced clearance (154).

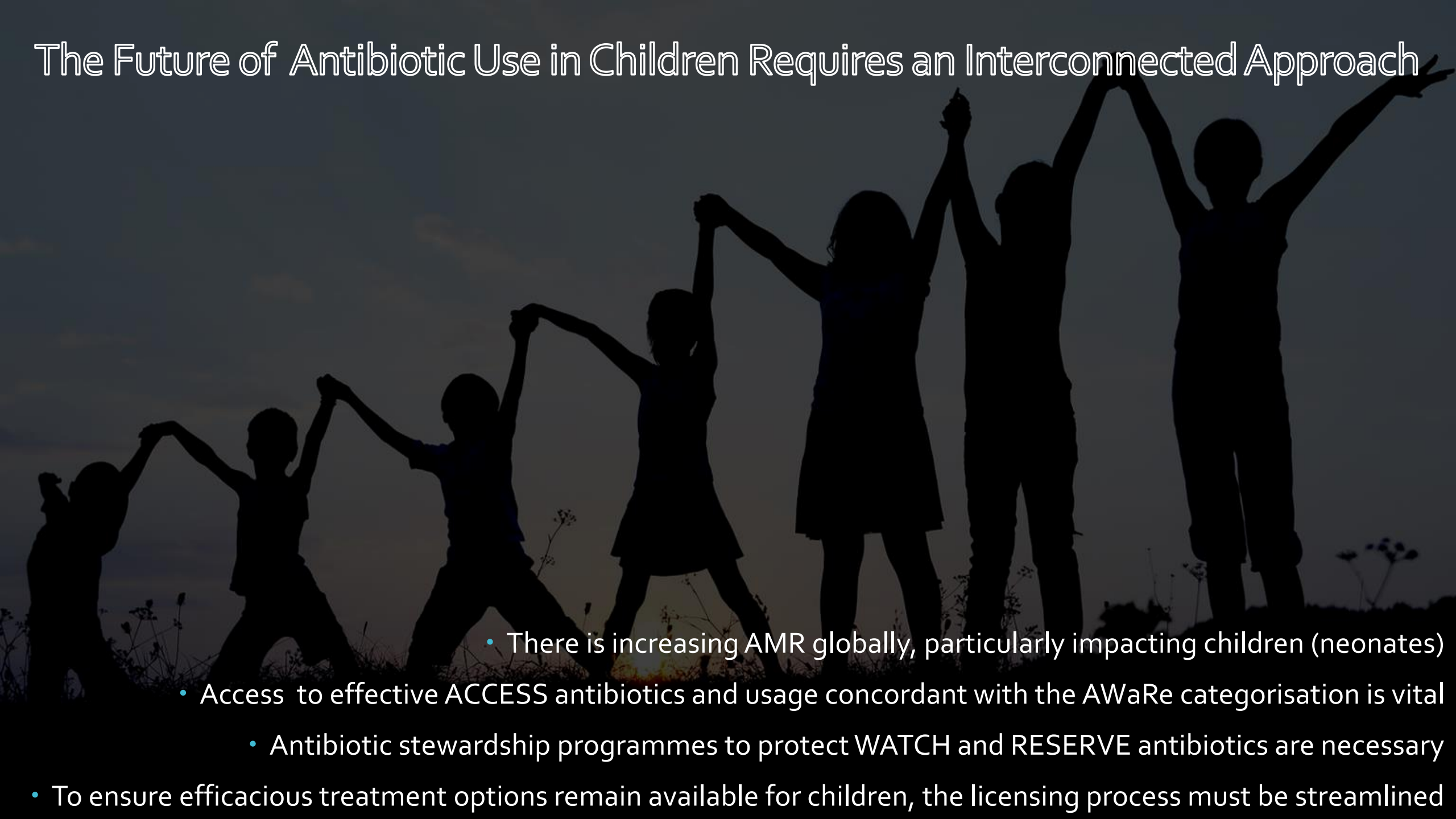
What legacy agents are available for treating Gram-negative MRO infections in children?

- Polymixins (polymyxin B, colistin [polymyxin E])
 - Many reports of efficacy when used to treat MRO infections in children
 - Limited by their high rates of adverse effects (nephrotoxicity in 22%)
 - Unclear dosing regimens: divergent case reports in the literature
 - Resistance is increasing (linked to animal sources – high usage in agriculture and veterinary sciences)
- Fosfomycin
 - Phosphonic acid derivative
 - Best used in combination for invasive infections, due to concerns regarding resistance emerging
- Aminoglycosides, Fluoroquinolones
 - In many health settings, MRO infections in children retain amikacin and/or fluoroquinolone susceptibility
- Aztreonam, Tigecycline:
 - Recently removed from the essentials medicines list

What newer agents are available for treating Gram-negative MRO infections in children?

- Carbapenems
 - Particularly for ESBL-producing organisms; and some carbapenem-resistant Enterobacteriaceae (CREs)
 - Monte Carlo simulations suggest high doses as extended-infusions most helpful
- Ceftazidime-avibactam (BL/BLI)
 - Approved by FDA for children >3/12 with complicated intra-abdominal infections (with anaerobic cover) and UTIs
- Meropenem-vaborbactam (BL/BLI)
 - Phase I trial underway
- Imipenem-cilastatin-relebactam
 - Clinical trials underway; may be a potential treatment option for MDR *Pseudomonas aeruginosa* infections
- Ceftolozane-tazobactam (BL/BLI)
 - Helpful in drug-resistant *Pseudomonas aeruginosa* infections
 - Pharmacokinetics and safety analysis currently underway in children
- Cefiderocol
 - Novel siderophore cephalosporin
 - Phase 2 trial for children >3mo recruiting

The Future of Antibiotic Use in Children Requires an Interconnected Approach

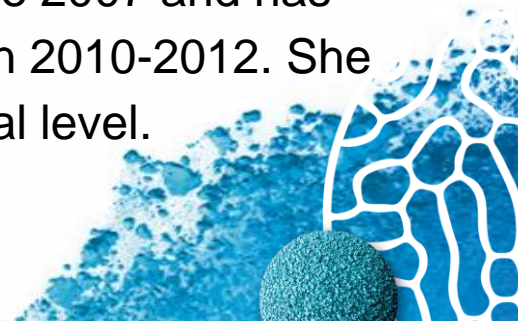
- 
- A silhouette of a group of children of various ages holding hands in a line, standing on a grassy field. They are positioned against a bright sunset or sunrise sky, which creates a strong backlighting effect. The children's arms are raised, and they are holding hands, symbolizing unity and interconnectedness. The overall mood is hopeful and positive.
- There is increasing AMR globally, particularly impacting children (neonates)
 - Access to effective ACCESS antibiotics and usage concordant with the AWaRe categorisation is vital
 - Antibiotic stewardship programmes to protect WATCH and RESERVE antibiotics are necessary
 - To ensure efficacious treatment options remain available for children, the licensing process must be streamlined

Irja Lutsar



Irja Lutsar is a Professor in Clinical Microbiology and head of department at the University of Tartu, Estonia. She gained her medical and PhD degree at the University of Tartu and is a qualified pediatric infectious diseases specialist. Between 1995 and 1998 she was a research fellow in paediatric infectious diseases at the Southwestern Medical School in Dallas, USA and from 1999 to 2004 she worked as a director in clinical development at Pfizer Ltd, UK.

Her research interests include antibiotic pharmacokinetics/dynamics, neonatal infections, fungal infections and antibiotic resistance. She has been leading investigator in more than 20 clinical trials in children including studies evaluating pharmacokinetic properties of antibiotics in premature neonates. Irja has published more than 150 publications in peer reviewed international journals and about 10 book chapters in various areas of the pediatric infectious diseases. She is a member of the Pediatric Committee at the European Medicines Agency since 2007 and has been active member of ESPID since 1993 being a board member in 2010-2012. She has received numerous research grants at national and international level.





UNIVERSITY OF TARTU



Clinical development of antibiotics in paediatrics



Irja Lutsar MD, PhD

UNIVERSITY OF TARTU
ESTONIA

28 October 2020

How to start paediatric drug development?

- **FIRST STEPS**

Is the new agent/antibiotic needed in paediatrics?

Is the indication in adults also a paediatric indication?

Is the new treatment „me too“ or unmet medical need?

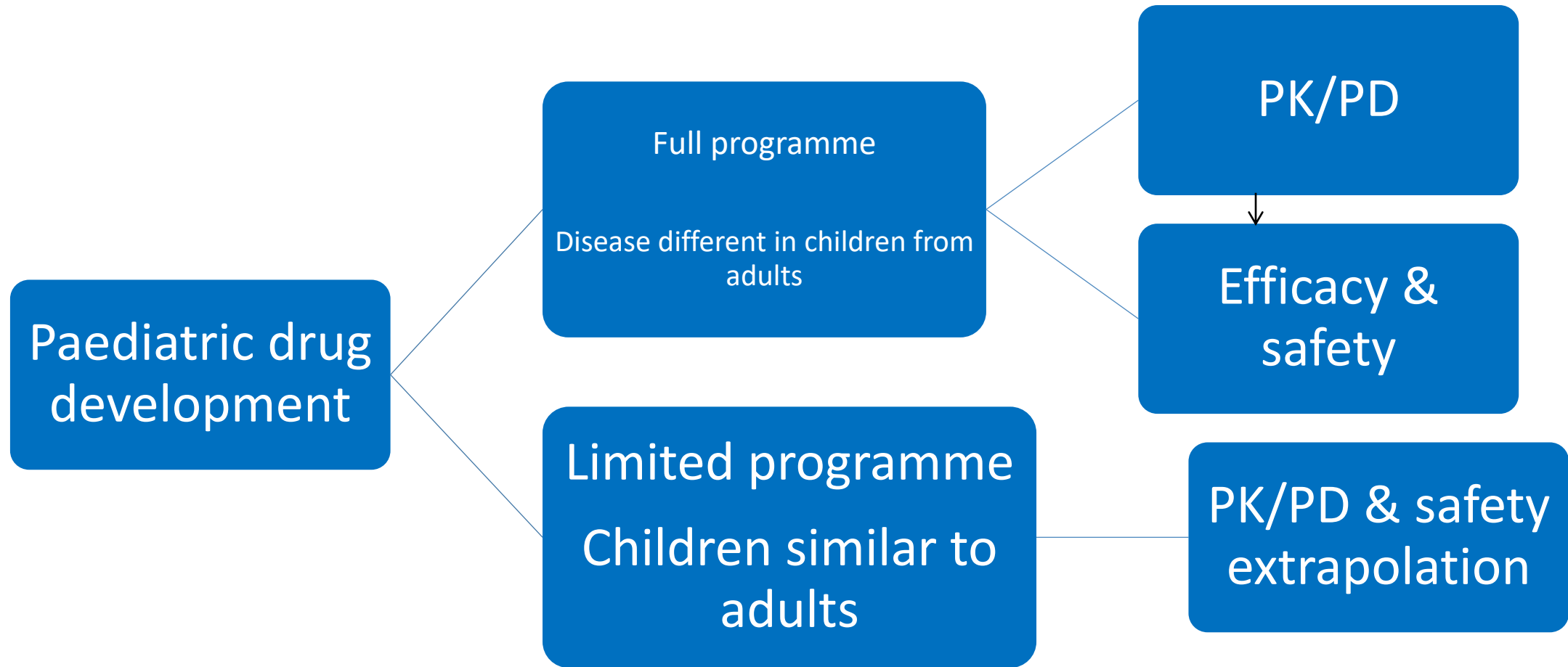
Is the new antibiotic needed in all age groups or only in some?

- **NEXT STEPS**

Has the PK/PD target been characterised and defined?

Do we need to know the efficacy and safety in adults?

Paediatric drug development: antiinfectives



Full programme: only or predominantly for childhood infections

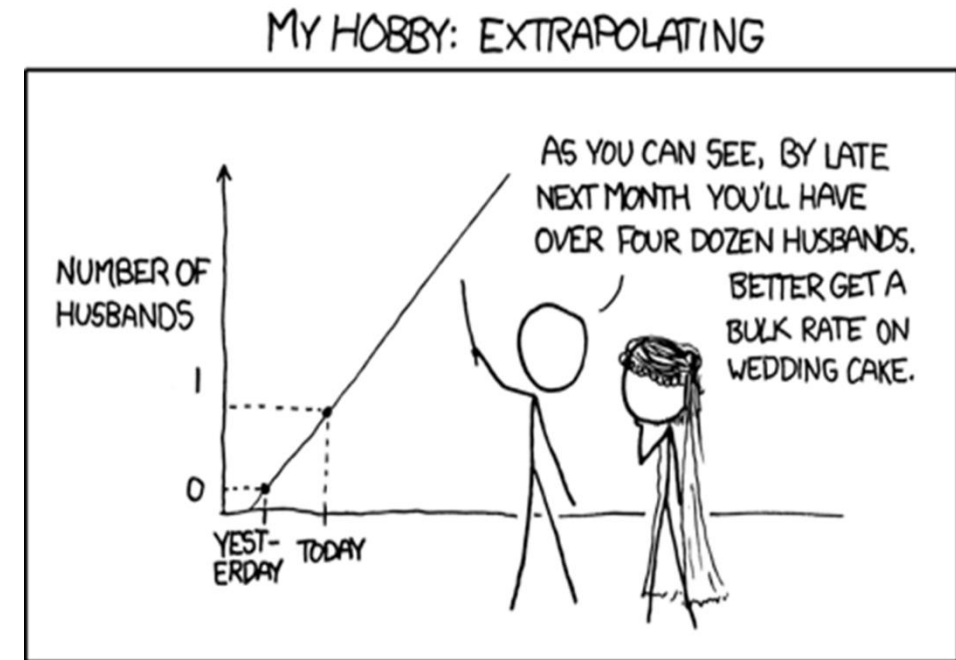
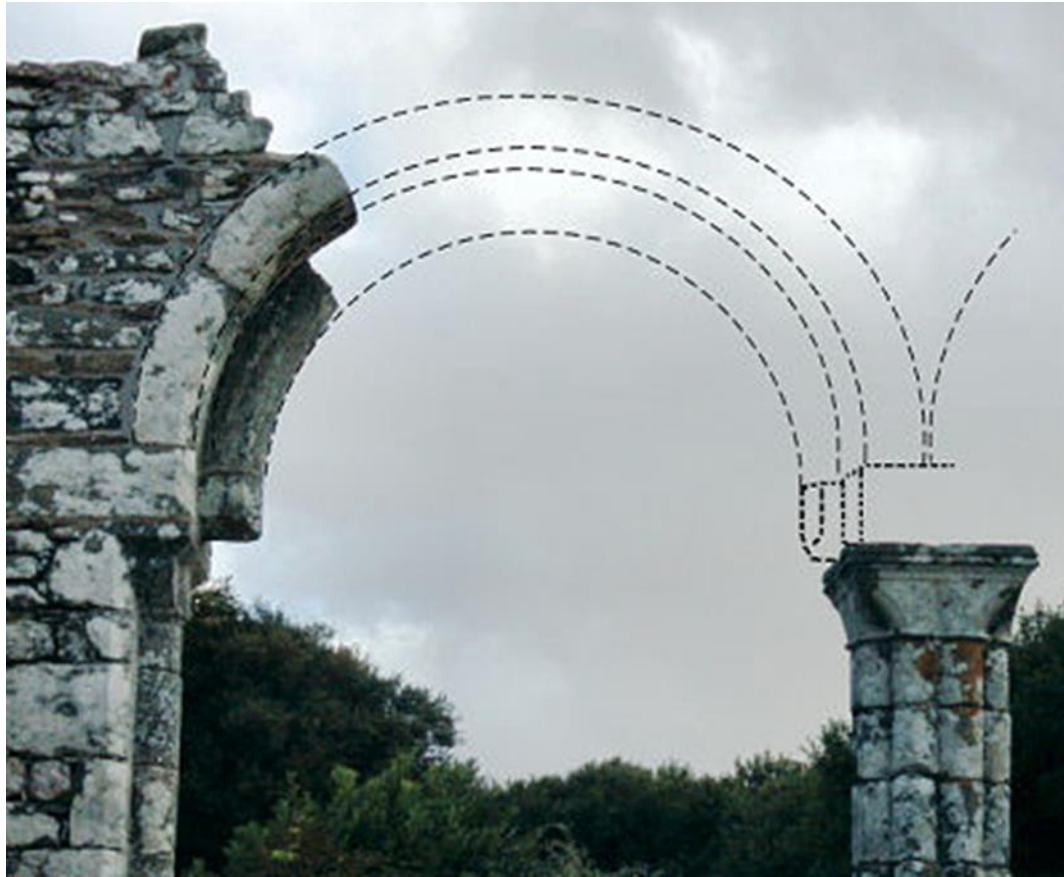
- Full development requested in (target) paediatric population
 - PK studies should be conducted first
 - Efficacy & safety studies with adequate power
- Tolerability studies in adults before embarking to paediatric development
- Parallel development to adults may be accepted
- Staggered approach not always justified

Examples for full development

- CAP (community-acquired pneumonia) – 15% of cases caused by bacteria or virus+bacteria, remaining by viruses (N Engl J Med 2015;372:835-845)
- VAP (ventilator-associated pneumonia) – mostly caused by *S.aureus*, *P.aeruginosa* but is very rare
- AOM (acute otitis media) – is not an adult disease
- GABHS (group A beta-haemolytic *streptococcus*) tonsillitis – efficacy in children is worse than in adults
- Neonates –
 - mainly infection without source (neonatal sepsis)
 - are immunotolerant and require higher antibiotic exposure than adults

PK/PD based extrapolation or extrapolation of efficacy is not feasible

Extrapolation



Extrapolation of efficacy

Concept Paper on extrapolation of efficacy and safety in medicine development (EMA/129698/2012)

Rationale of extrapolation:

- To avoid unnecessary studies
- To allocate resources to areas where studies are the most needed
- To conduct studies in situations where the feasibility of studies is restricted

Possibilities for extrapolation

- **Extrapolation efficacy from studies conducted in adults**
 - Adult drug exposure = paediatric drug exposure
- **PK/PD-based extrapolation**
 - Probability of target attainment (PTA) modelled in paediatric patients

Extrapolation efficacy from studies conducted in adults

- **Assumptions**
 - Infecting organisms in adults and children are the same
 - Disease process in adults and children is the same
- **Extrapolation**
 - PK studies should be conducted
 - Efficacy will be extrapolated from adult studies provided that the exposure is the same (AUC)
 - Safety studies should be conducted
 - Is the safety in children different of that in adults?
- **Problem**
 - Paediatric and adult indications for antimicrobial use might be different

PK/PD based extrapolation: PTA modelled in paediatric patients

- **Assumption**

- Infecting organisms are different or have different resistance
- The minimum inhibitory concentrations (MICs) of paediatric microorganisms are known
- Disease process is different
- PD targets of studied population are defined (e.g. AUC/MIC)

- **Extrapolation studies**

- PK studies in target population
- MCS* using the most likely microorganism with the highest susceptible MIC value and maximal PD index

- **Problem**

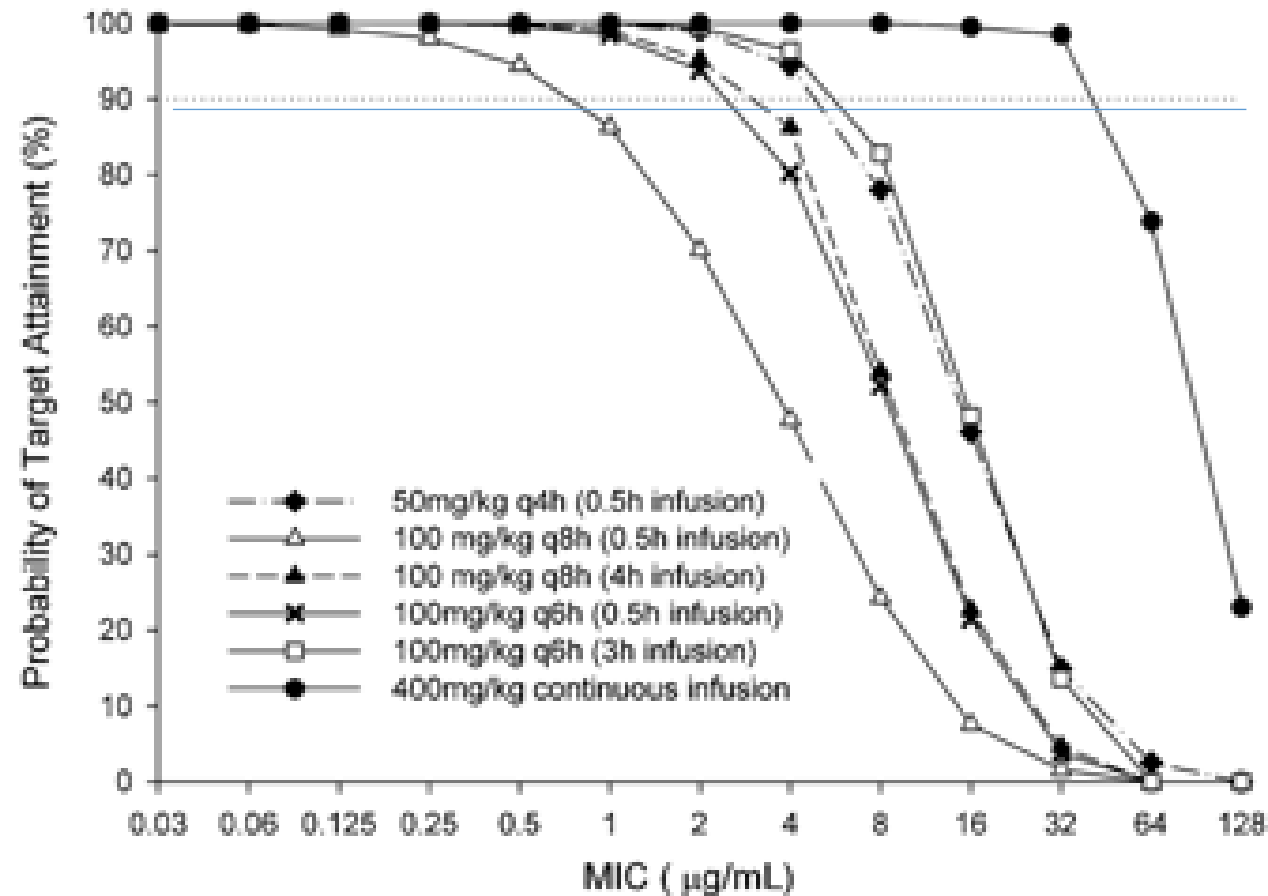
- Do all patients need so high doses?
- Safety is of concern and should be tested

Children may require different PK/PD targets

- Immune system is underdeveloped
 - Neonates are immunotolerant
 - Genetic syndromes often associated with immune function deficiencies
- PK parameters in children are different from adults
 - Prolonged vs short infusions of beta-lactams

Higher antibiotic exposure has been more effective in adults requiring intensive care

Population pharmacokinetics of the piperacillin component of piperacillin/tazobactam in paediatric oncology patients with fever and neutropenia



Paediatric development in cases of limited development in adults

- Antimicrobials that cover multi-resistant organisms or are for rare infections
- PK and limited safety data is required for children
- Efficacy can be extrapolated from adults

Establishing safety

- Safety cannot always be extrapolated from adults
 - Overall safety of antibiotics is predictable (*Drugs* 2018; **78**: 231–244)
- Studies are requested by FDA and EMA
- Comparative studies are preferred (not necessarily 1:1)
- Still under discussion
 - a single comparator (ideal)
 - several predefined comparators
 - site/country/ investigator's selection?
- What is sufficient number of patients?
- Registries/clinical databases could be used

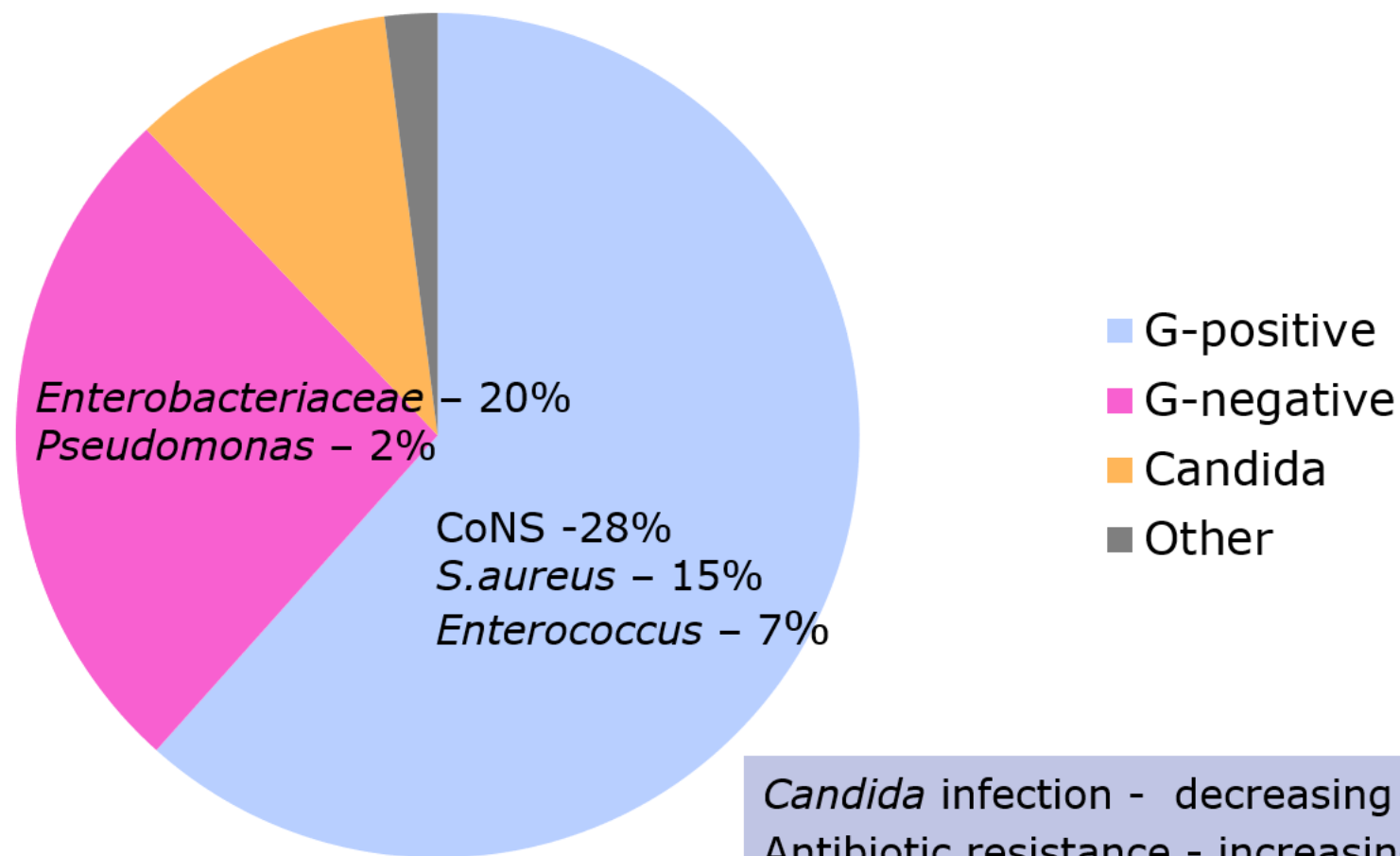
Antiinfectives for neonates:

Neonatal bacterial infections

- **Mostly neonatal sepsis (about 50% of cases)**
 - < 1500 g of all hospitalised babies
 - EOS – 1,5% - 2%
 - LOS – 21% - 25%
 - In patients with risk factors
 - EOS – 4,9%
 - LOS – 26%
- **Other infections**

– Pneumonia	7-32% of HAI
– UTI	29% device related and 77% of unrelated
– Meningitis –	3% of all infections
– Osteomyelitis –	1.5% of all infections
– Endocarditis –	5-12/100,000 newborns
– cSSTI	???

Causative pathogens of LOS (age >72h)



* CoNS – Coagulase-negative *staphylococci*

Characteristics of neonatal development

PK studies are requested

- in term and preterm neonates

Condition for neonatal studies

- suspected or proven late-onset sepsis regardless of adult indication

Characteristics of PK studies

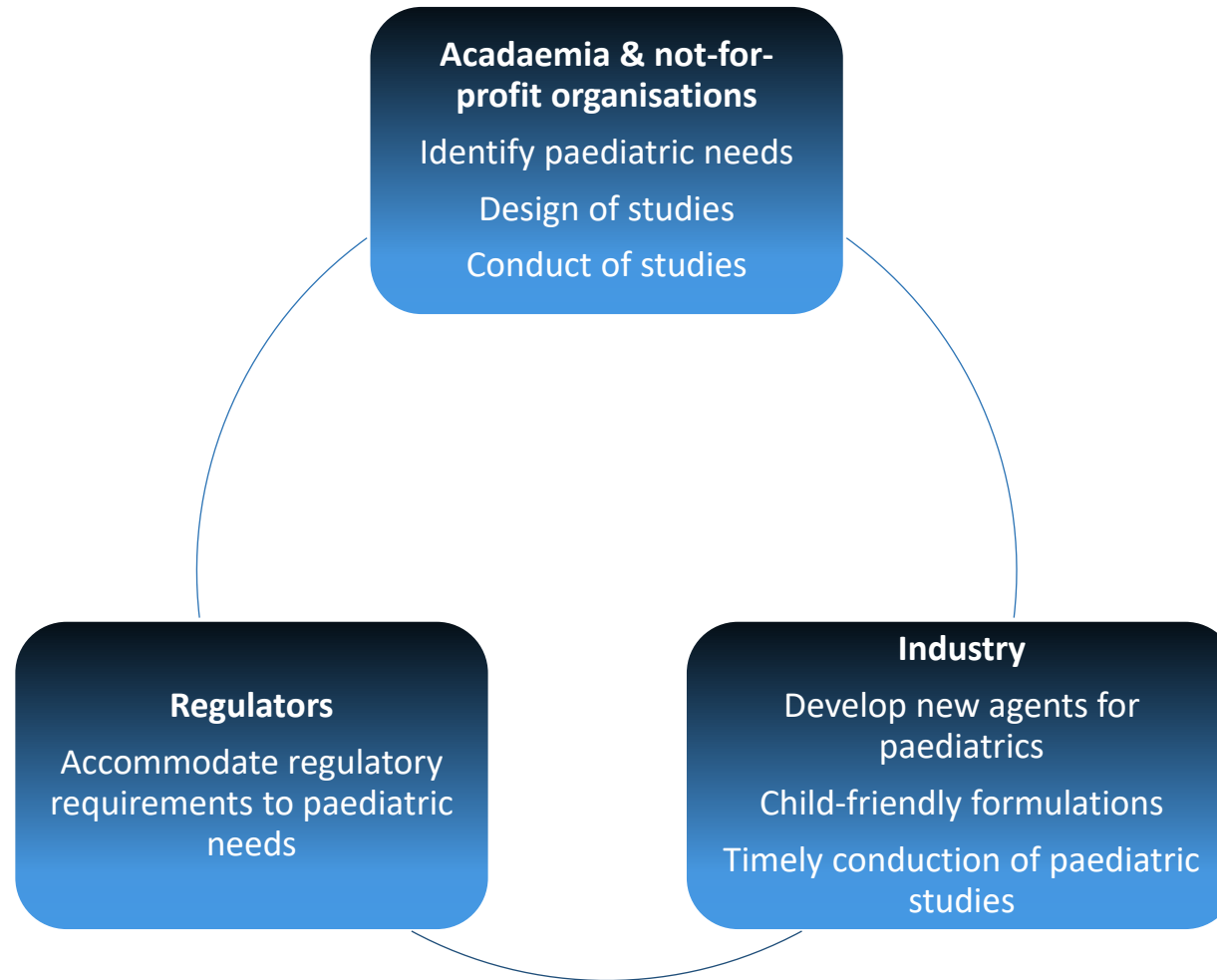
- add-on therapy
- sparse or semirich sampling
- microsampling assays

Staggered approach

- delays availability of new drug to neonates
- in well tolerated agents may not be justified

Safety in limited number of subjects

Stakeholders





Thank you

Today's speakers

Developing antibiotics for children – medical need and regulatory challenges



Phoebe Williams

Consultant Paediatrician, Infectious Diseases Fellow, NHMRC Fellow
University of Sydney & Sydney Children's Hospital (Australia)



Irja Lutsar

Professor in Clinical Microbiology and head of department
University of Tartu (Estonia)



Moderator:

Sally Ellis

Children's Antibiotics Project Leader
GARDP (Switzerland)

Join us for our next webinars

17 November, 17:00-18:30 CET

Discovery of new antibacterials using artificial intelligence (computational chemoinformatics)

Speakers:

James Collins (Broad Institute)
Cesar de la Fuente (University of Pennsylvania)
Henriette Willems (University of Cambridge)
Fredrik Svensson (UCL Drug Discovery Institute)

Moderator: Laura Piddock (GARDP)

20 November, 10:30-12:00 CET

Saving childrens' lives – treating neonatal sepsis

Speakers:

Hanan Balkhy (WHO)
Manica Balasegaram (GARDP)
Dhanya Dharmapalan (Pediatric Infectious Disease Society)
Borna Nyaoke (DNDi/GARDP Kenya)

Moderator: Peter Beyer (WHO)

**Registration links and more
information available on:
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