Key Aspects of Epidemiology, Prevention, Diagnosis and Clinical Management of Neonatal and Pediatric Sepsis

WHO Sepsis Technical Expert Meeting 16-17 January 2018

Professor Mike Sharland

Tuesday 16th January

St George's University of London

World Health Organization

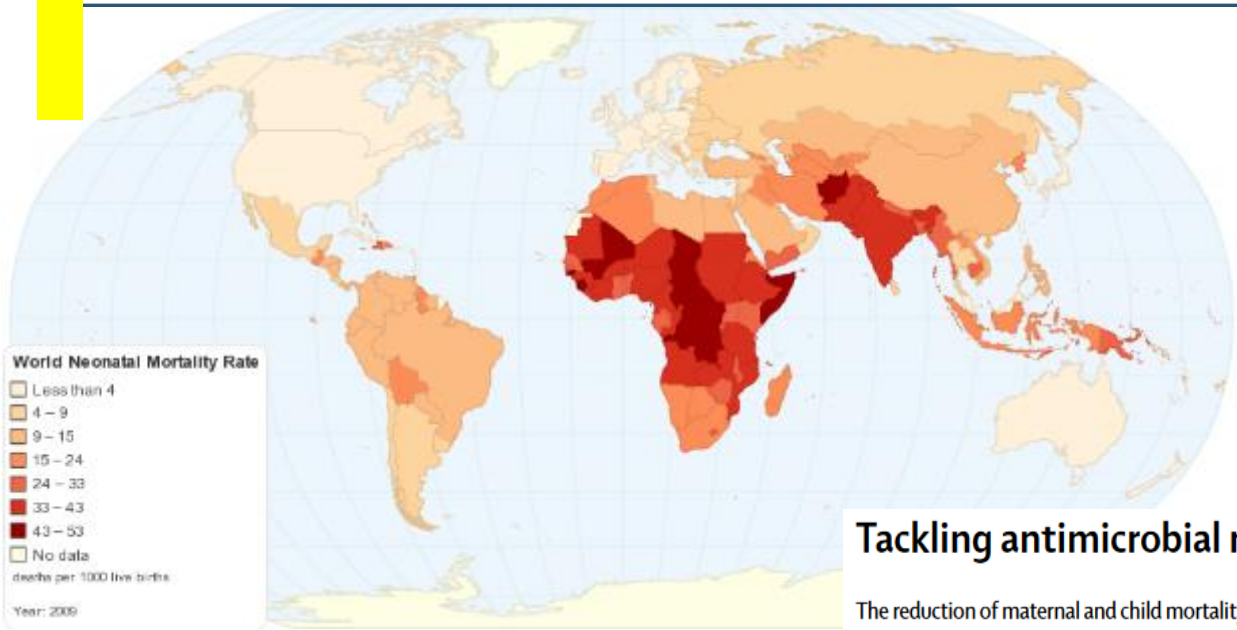
DNDi Drugs for Neglected Diseases initiative

GARDP Global Antibiotic Research & Development Partnership

Epidemiology - factors

- **Community** setting – ANISA/SATT Afrinest
- Classical pathogens – CAI (E coli, MSSA, GBS) Lower rates of MDR
- **Hospital** Setting
- M/XDR Gram Negs/MSSA
- Underling disease (prem/HIV/Malnutrition
- HAI– ESBL/CRO

Global neonatal sepsis mortality



Maternal and child mortality has halved worldwide in the past two decades but the number of neonatal deaths has remained unacceptably high – due to **infections, prematurity and asphyxia**

An estimated 2.9 millions deaths every year (44% of all deaths in children younger than 5 years) worldwide **– one quarter of these are due to neonatal sepsis**

Tackling antimicrobial resistance in neonatal sepsis

The reduction of maternal and child mortality, which has halved worldwide in the past two decades, is considered one of the greatest successes of the Millennium Development Goals programme.[1] However, the number of neonatal deaths has remained unacceptably high, with an estimated 2·9 million deaths every year (44% of all deaths in children younger than 5 years, worldwide).[2] In 2012, the most common causes of neonatal death globally were preterm-birth complications, intrapartum-related conditions, and infections.

Globally, infections cause nearly a quarter (23%) of all neonatal deaths, with neonatal sepsis accounting for 15% of these deaths.[1] Severe bacterial infections in neonates account for about 3% of all disability-adjusted life-years.[3] Prompt diagnosis and appropriate treatment are crucially important in reducing mortality. However, the worldwide spread of antimicrobial resistance represents a major challenge, with nearly half of the pathogens that cause severe neonatal bacterial infections reported to be resistant to the first-line (ampicillin or penicillin, and gentamicin) and second-line (third-generation cephalosporins) WHO-recommended treatments.[4] In 2016, the first estimate of neonatal deaths attributable

Folgori et al Tackling antimicrobial resistance in neonates. Lancet; 2017; 5(11):e1066-8.

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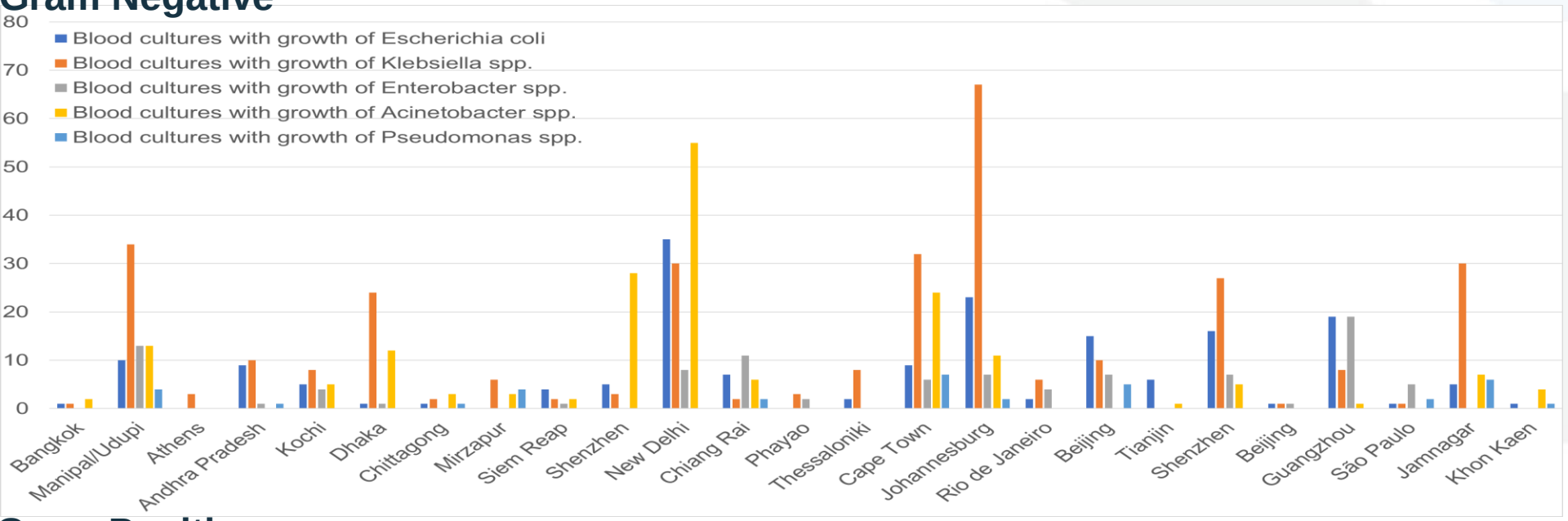
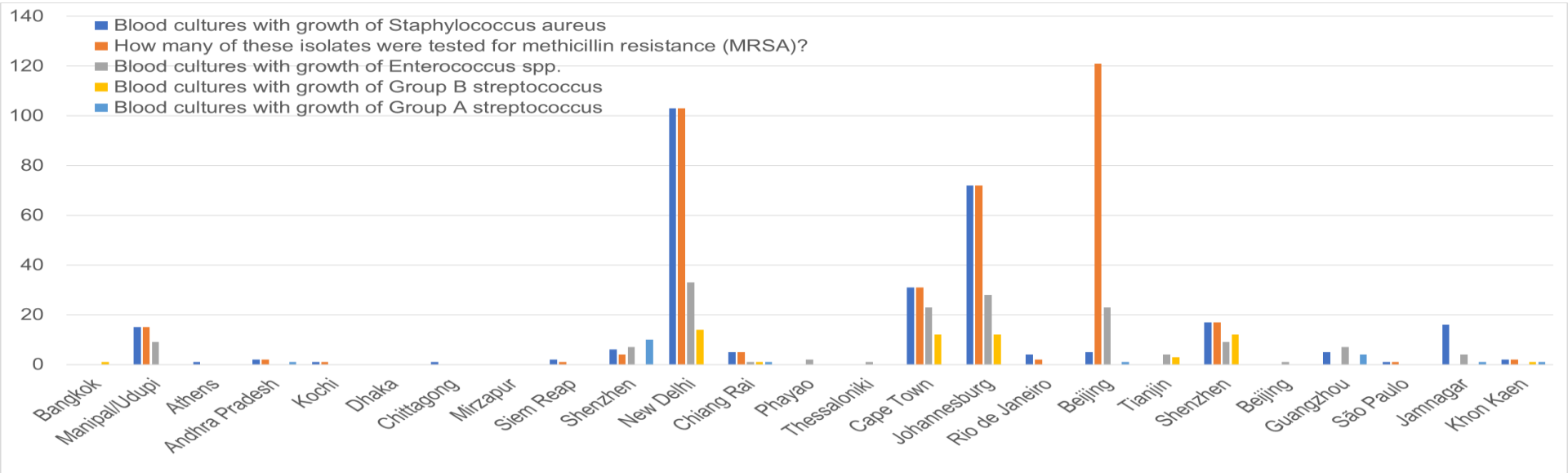
NeoAMR BSI Sepsis in 2016

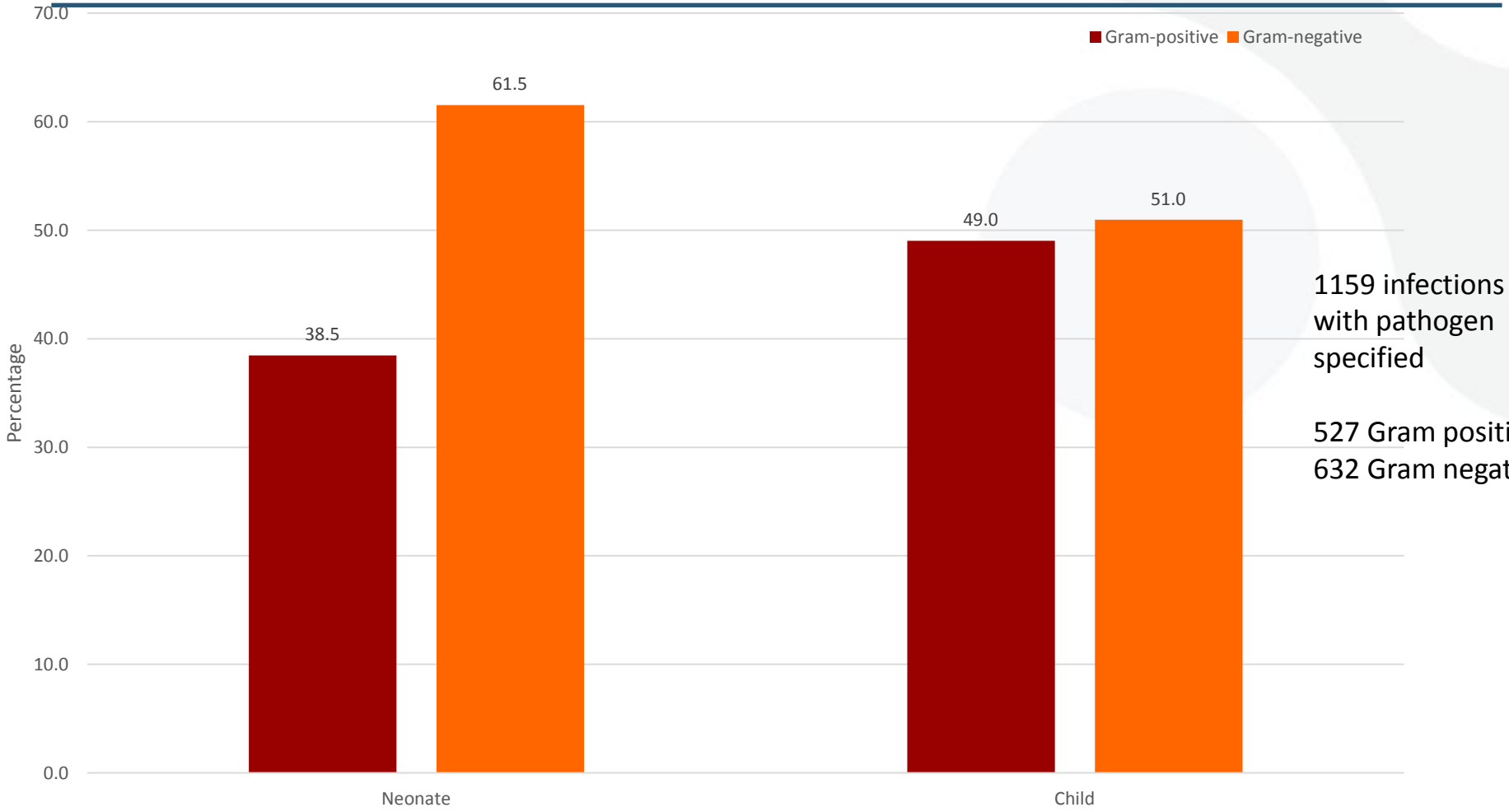
Gram Negative



Gram Positive



GARPEC BSI 2016



1159 infections with pathogen specified

527 Gram positive
632 Gram negative

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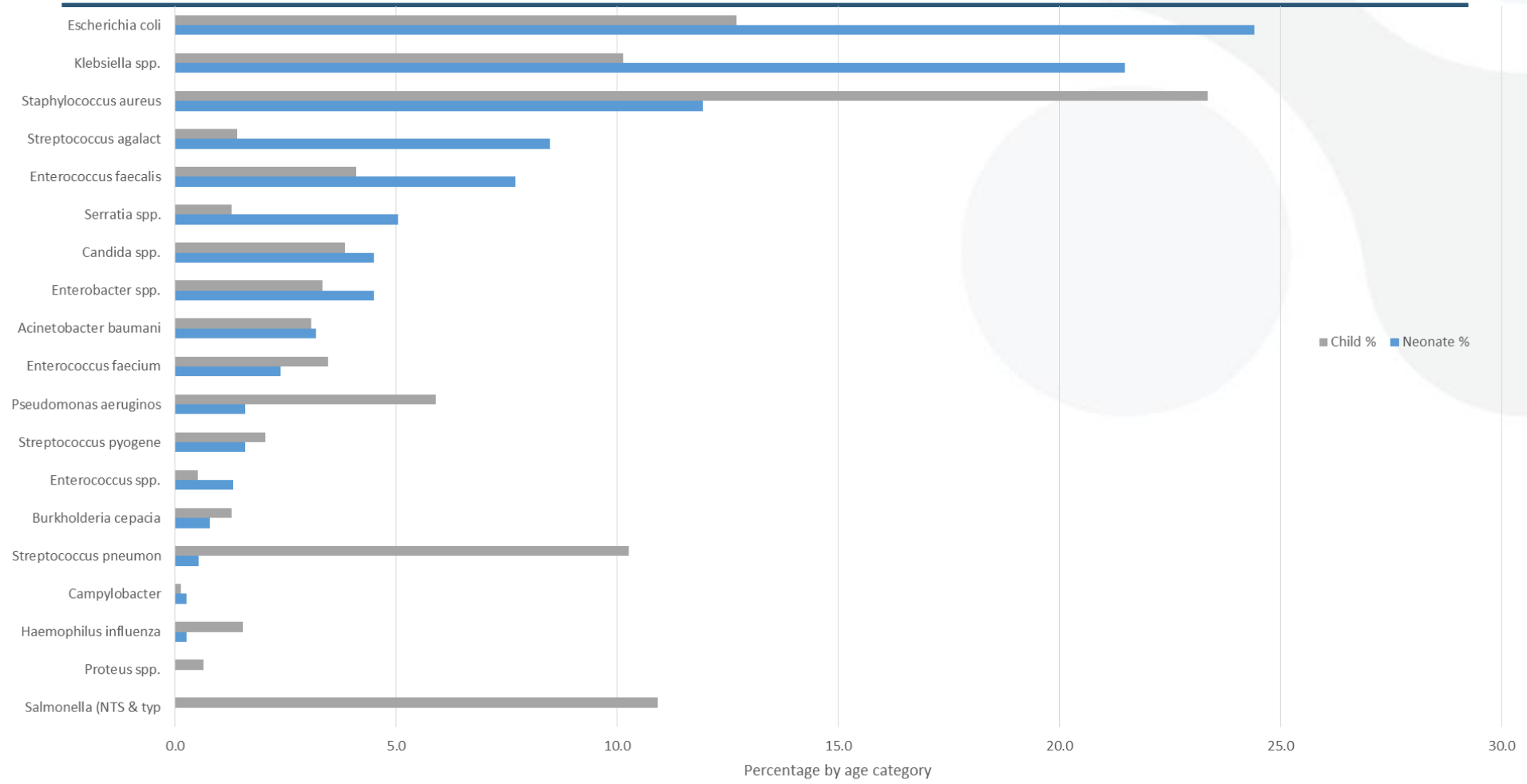
GARPEC BSI 2016 Neonatal/Pediatric



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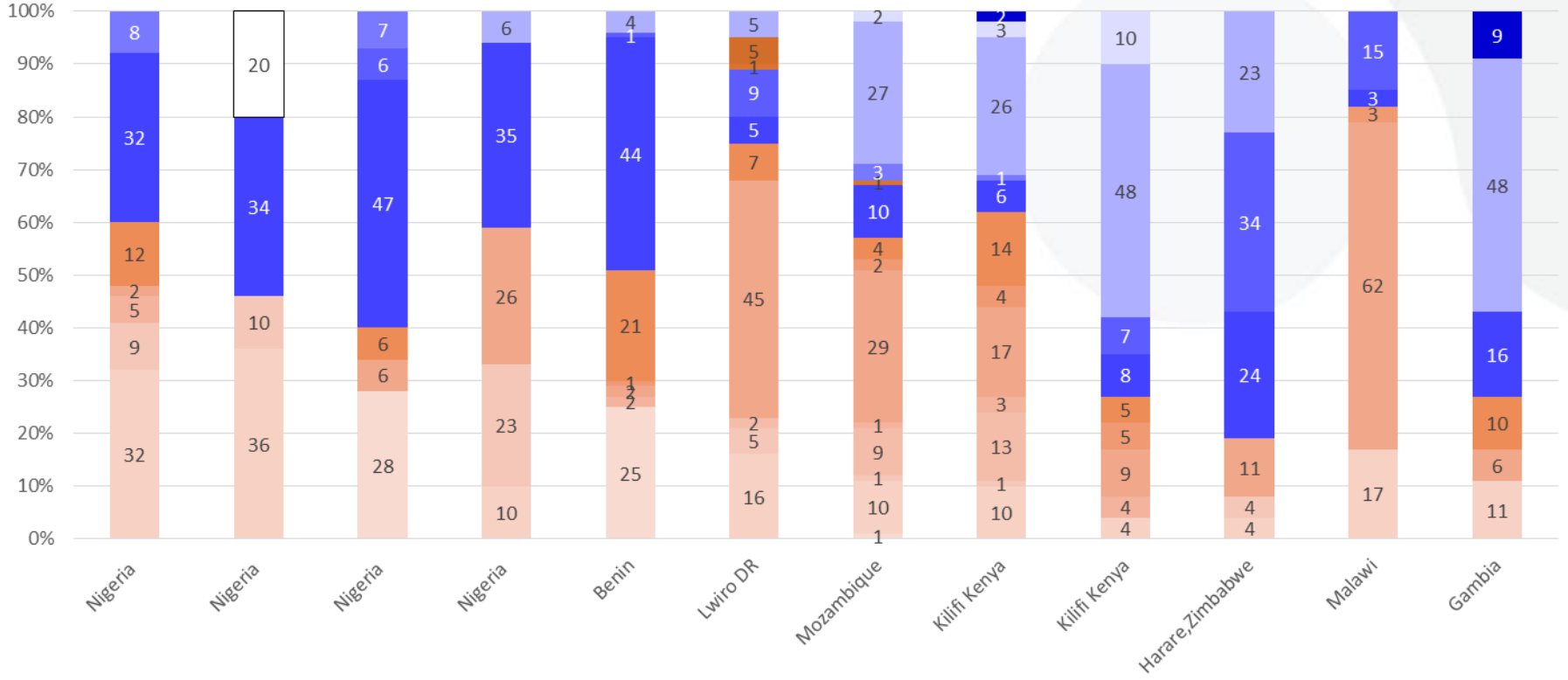
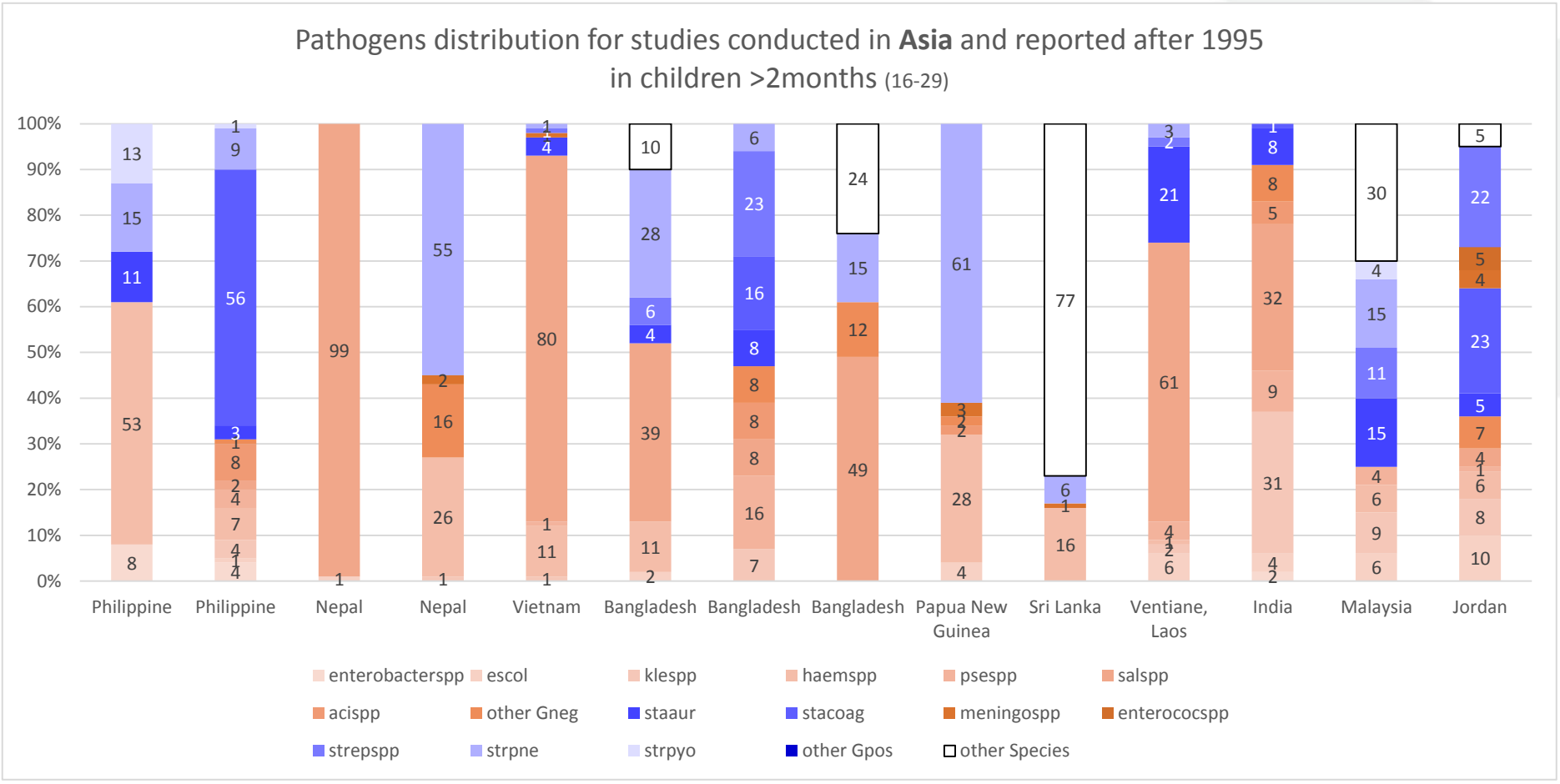
Diagnosis

- Clinical signs – validation/prognosis
- Underlying Disease/ High Risk Setting
- Laboratory
- PPV NPV
- Appropriate specimens; BC rate..
- Microbiology
- Empiric prescribing algorithms

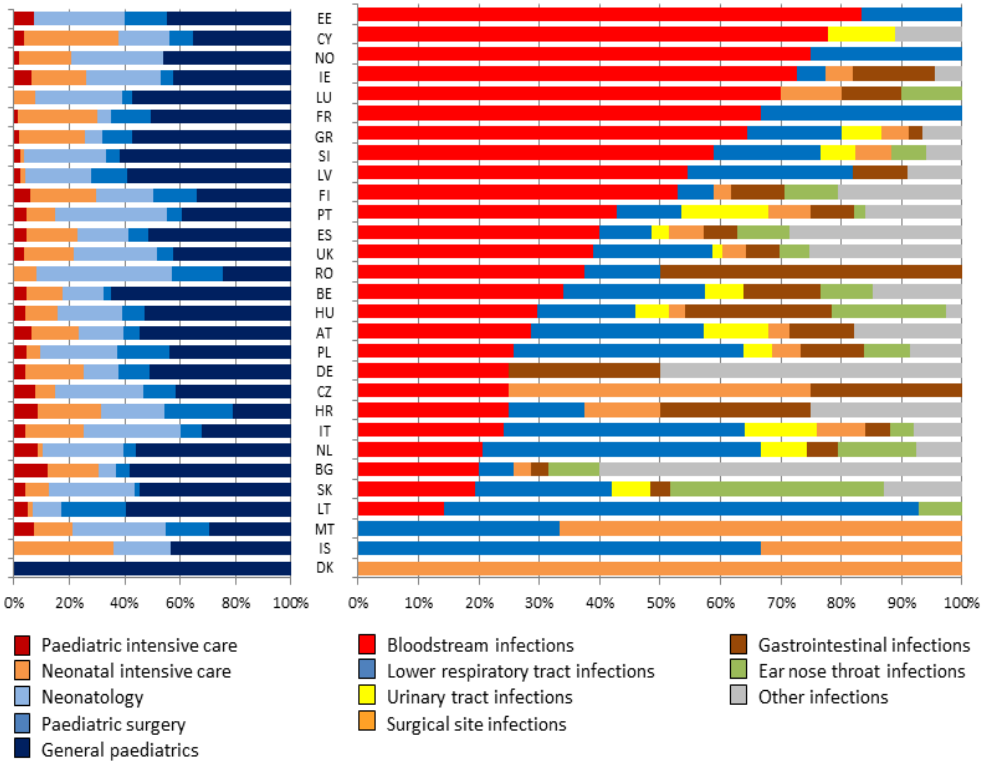
Pathogens distribution for studies conducted in **Africa** and reported after 1995 in children > 2months (4-16)

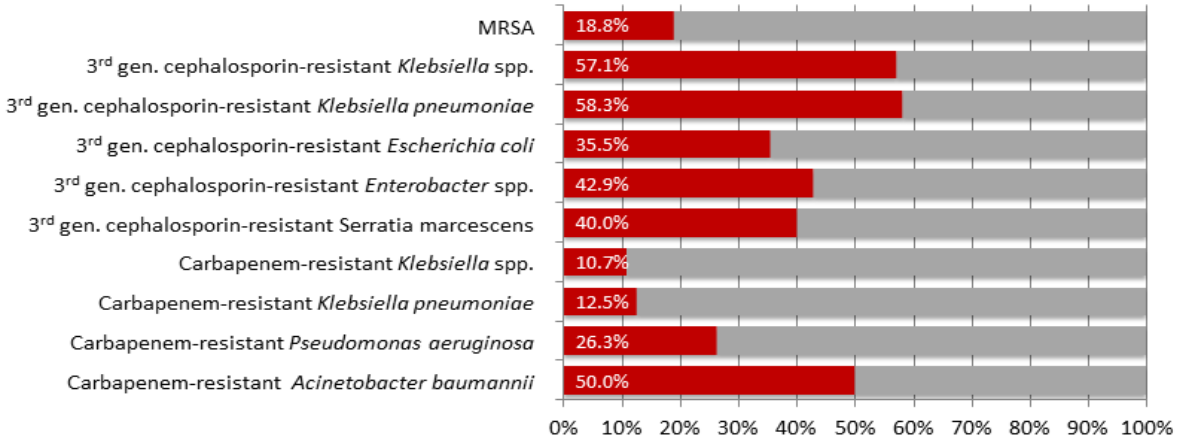



Pathogens distribution for studies conducted in **Asia** and reported after 1995 in children >2months (16-29)
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Philippine
Philippine
Nepal
Nepal
Vietnam
Bangladesh
Bangladesh
Bangladesh
Papua New Guinea
Sri Lanka
Ventiane, Laos
India
Malaysia
Jordan
enterobacterspp
escol
klespp
haemspp
psespp
salspp
acispp
other Gneg
staaur
stacoag
meningospp
enterococspp
strepspp
strpne
strpyo
other Gpos
other Species

HAI In Europe ECDC PPS – children data LID 2016

- Data obtained from 17,273 children
- HAI prevalence of 4.2% (95%CI 3.7-4.8 %)
- Highest prevalence in larger hospitals and in PICU/NICU
- Independent risk factors for HAI:
  - medical devices
  - young age (particularly neonates)
  - prolonged length of stay





- Substantially different pattern of HAIs in children compared to adults - **sepsis**

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Prevention

- Exclusive breast feeding, cord care
- Vaccines - Pneumococcal 15/18, Hib, Men B and C (extending serotypes); Salmonella/Shigella (mortality typhoid)
- GBS (CID SR's) vaccines/intra partum antibiotics. GAS
- RSV/Influenza
- E coli (O antigen); SA
- Monoclonals
- Emollients/ Lactoferrin/synbiotics (Panigrahi Nature 2017)
-

Management

REVIEW

Current challenges in the management of sepsis in ICUs in resource-poor settings and suggestions for the future

Intensive Care Med (2017) 43:612–624
DOI 10.1007/s00134-017-4750-z

Marcus J. Schultz[1,2*], Martin W. Dunser[3], Arjen M. Dondorp[1,2], Neill K. J. Adhikari[4], Shivakumar Iyer[5], Arthur Kwizera[6], Yoel Lubell[2], Alfred Papali[7], Luigi Pisani[1,2], Beth D. Riviello[8], Derek C. Angus[9], Luciano C. Azevedo[10], Tim Baker[11], Janet V. Diaz[12], Emir Festic[13], Rashan Haniffa[1], Randeep Jawa[14], Shevin T. Jacob[15], Niranjan Kissoon[16], Rakesh Lodha[17], Ignacio Martin-Loeches[18], Ganbold Lundeg[19], David Misango[20], Mervyn Mer[21], Sanjib Mohanty[22], Srinivas Murthy[16], Ndidiamaka Musa[23], Jane Nakibuuka[6], Ary Serpa Neto[2,24], Mai Nguyen Thi Hoang[25], Binh Nguyen Thien[26], Rajyabardhan Pattnaik[22], Jason Phua[27], Jacobus Preller[28], Pedro Povoa[29], Suchitra Ranjit[30], Daniel Talmor[8], Jonarthan Thevanayagam[31], C. Louise Thwaites[32] and For the Global Intensive Care Working Group of the European Society of Intensive Care Medicine

WHAT'S NEW IN INTENSIVE CARE

Recommendations for infection management in patients with sepsis and septic shock in resource-limited settings

C. Louise Thwaites[1,2*], Ganbold Lundeg[3], Arjen M. Dondorp[4,5] and For the sepsis in resource-limited settings–expert consensus recommendations group of the European Society of Intensive Care Medicine (ESICM) and the Mahidol-Oxford Research Unit (MORU) in Bangkok, Thailand

Intensive Care Med (2016) 42:2040–2042
DOI 10.1007/s00134-016-4415-3

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Treatment

- **Early appropriate** antibiotics
- Concordant/discordant – ESBL (1); CRO (2)
- Optimal dosing strategies
- High dose, short durations..MIC/RIC
- More frequent dosing/extended infusions
- Risk based approach to empiric regimens

AWaRe Index - EMLc

- Metric for stewardship
- Track progress in ratior antibiotics over time
- Quantify optimal use at and global levels
- Set Quality Goals

ACCESS

amikacin
amoxicillin
amoxicillin + clavulanic acid
ampicillin
benzathine benzylpenicillin
benzylpenicillin
cefalexin
cefazolin
clindamycin
cloxacillin
doxycyline
gentamicin
metronidazole
nitrofurantoin
phenoxymethylpenicillin
procaine benzyl penicillin
spectinomycin
sulfamethoxazole + trimethoprim

azithromycin*
cefixime*
cefotaxime*
ceftriaxone*
chloramphenicol
ciprofloxacin*
clarithromycin*
piperacillin + tazobactam*
meropenem*
vancomycin*

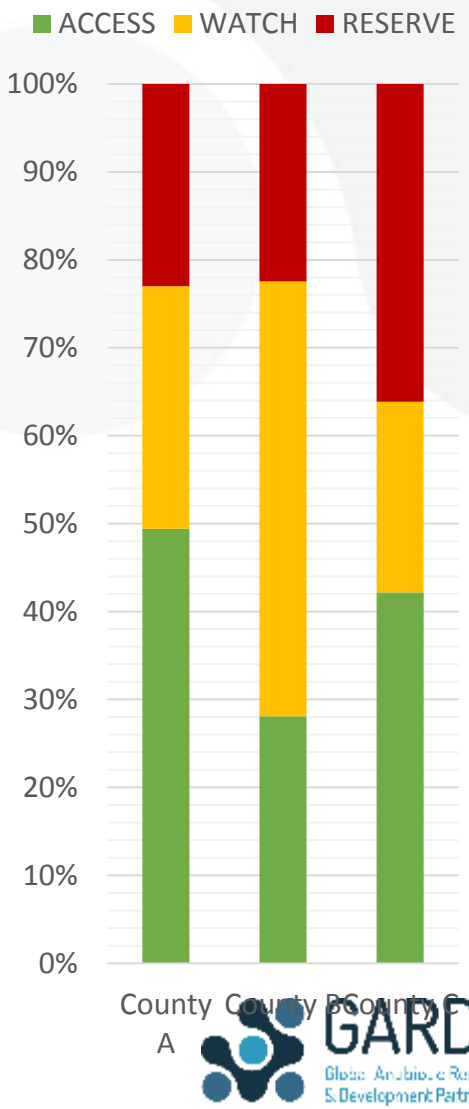
** denotes antibiotics which are also in the Watch group*

WATCH

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

RESERVE

Aztreonam
Cephalosporins, 4th Generation (e.g. cefepime)
Cephalosporins, 5th Generation (e.g. ceftaroline)
Daptomycin
Fosfomycin (IV)
Oxazolidinones (e.g. linezolid)
Polymyxins (e.g. polymyxin B, colistin)
Tigecycline



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Neonatal (Pediatric) sepsis – 2017 WHO

5. Management of neonatal sepsis

Prophylactic antibiotics for prevention of sepsis

- A neonate with risk factors for infection (i.e. membranes ruptured >18 hours before delivery, mother had fever >38 °C before delivery or during labour, or amniotic fluid was foul smelling or purulent) should be treated with the prophylactic antibiotics ampicillin (Intramuscular – IM – or intravenously, IV) and gentamicin for at least two days. After two days, the neonate should be reassessed and treatment continued only if there are signs of sepsis or a positive blood culture.

  (Weak recommendation, very low quality evidence) Source

Empirical antibiotics for suspected neonatal sepsis

- Neonates with signs of sepsis should be treated with ampicillin (or penicillin) and gentamicin as the first line antibiotic treatment for at least 10 days.

  (Strong recommendation, low quality evidence Source

- If a neonate with sepsis is at greater risk of staphylococcus infection (e.g. extensive skin pustules, abscess, or omphalitis in addition to signs of sepsis), they should be given cloxacillin and gentamicin instead of penicillin and gentamicin.

  (Strong recommendation, quality of evidence not graded) Source

- Where possible, blood cultures should be obtained before starting antibiotics. If an infant does not improve in two to three days, antibiotic treatment should be changed, or the infant should be referred for further management.

  (Strong recommendation, quality of evidence not graded) Source

NeoAMR Feasibility - Empiric Antibiotics used

Country	City/Town		Early Onset Sepsis			Late Onset Sepsis	
		Antibiotic 1	Antibiotic 2	Antibiotic 3	Antibiotic 1	Antibiotic 2	Antibiotic 3
Bangladesh	Dhaka	Ceftazidime	Amikacin		Ceftazidime	Amikacin	
Brazil	Rio De Janeiro	Ampicillin	Gentamicin		Oxacillin	Piperacillin + BLI	Amikacin
Brazil	São Paulo	Ampicillin	Gentamicin		Oxacillin	Amikacin	
Cambodia	Siem Reap	Ampicillin	Gentamicin		Ampicillin	Gentamicin	
China	Shenzhen	Ceftazidime	Ceftriaxone		Meropenem		
China	Beijing	Ceftazidime	Amoxicillin +BLI		Ceftazidime	Amoxicillin+BLI	
China	Tianjin	Benzylpenicillin	Ceftriaxone	Latamoxef	Benzylpenicillin	Ceftriaxone	Latamoxef
China	Shenzhen	Other	Ceftazidime		cefoperazone/sulbactam	Meropenem	Vancomycin
China	Beijing	Cefepime	Meropenem	Amoxicillin + BLI	Vancomycin	Meropenem	
China	Guangzhou	Benzylpenicillin	Ceftazidime		Benzylpenicillin	Ceftazidime	
Greece	Athens	Ampicillin	Gentamicin		Meropenem	Vancomycin	
Greece	Thessaloniki	Ampicillin	Gentamicin		Cefepime	Vancomycin	
India	Manipal/Udupi	Ampicillin	Amikacin		Amikacin	Cefotaxime	
India	Andhra Pradesh	Ampicillin	Amikacin		Ciprofloxacin	Amikacin	
India	Kochi	Ampicillin	Amikacin			Amikacin	Meropenem
India	New Delhi	Cloxacillin	Amikacin		Cloxacillin	Amikacin	
India	Jamnagar	Ampicillin	Amikacin		Cefotaxime	Vancomycin	Piptazo
South Africa	Cape Town	Benzylpenicillin	Gentamicin		Piperacillin + BLI	Amikacin	
South Africa	Johannesburg	Ampicillin	Gentamicin		Tazobactam	Amikacin	
South Africa	Johannesburg	Benzylpenicillin	Gentamicin		Meropenem	Vancomycin	
Thailand	Bangkok	Ampicillin	Gentamicin		Ampicillin	Cefotaxime	
Thailand	Chiang Rai	Ampicillin	Gentamicin	Cefotaxime	Ceftazidime	Amikacin	Meropenem
Thailand	Phayao	Ampicillin	Gentamicin		Ampicillin	Gentamicin	
Thailand	Khon Kaen	Ampicillin	Gentamicin		Cefotaxime	Amikacin	

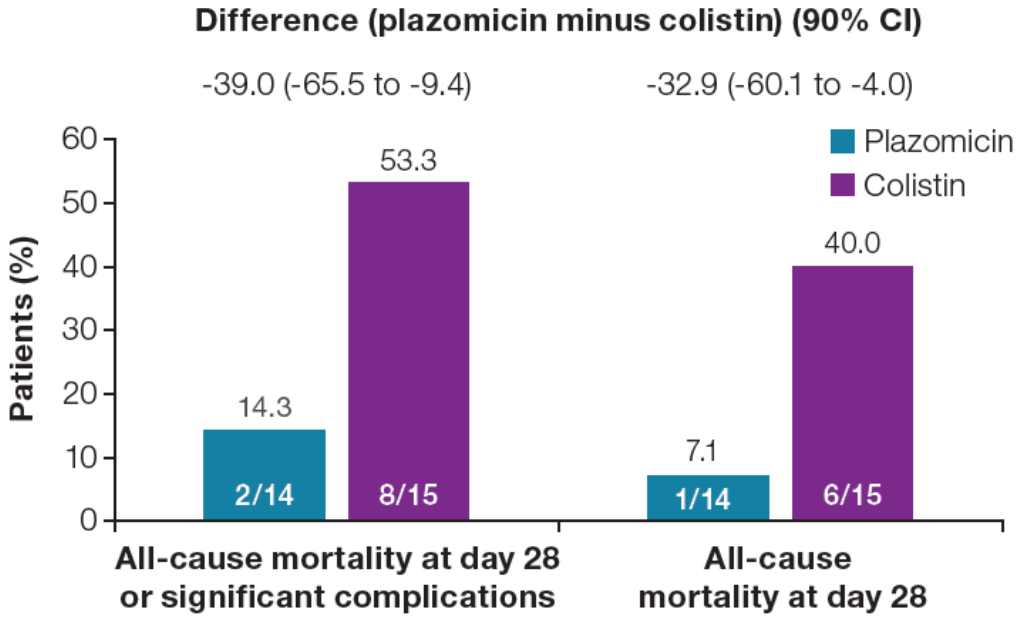
GARPEC PPS Paediatric sepsis

- 658 children with sepsis with 984 antibiotic prescriptions
- Median 1 prescription per child, range 1-6
- 165 different treatments regimens (1 or more antibiotic)
- Six children (0.9%) received WHO-recommended first-line treatment (ampicillin/gentamicin or penicillin/gentamicin)
- 85 (12.9%) received WHO-recommended second-line treatment (ceftriaxone):
  - 76/314 (24.2%) of those with CAI
  - 7/311 (2.3%) of those with HAI

NEW ANTIBIOTICS

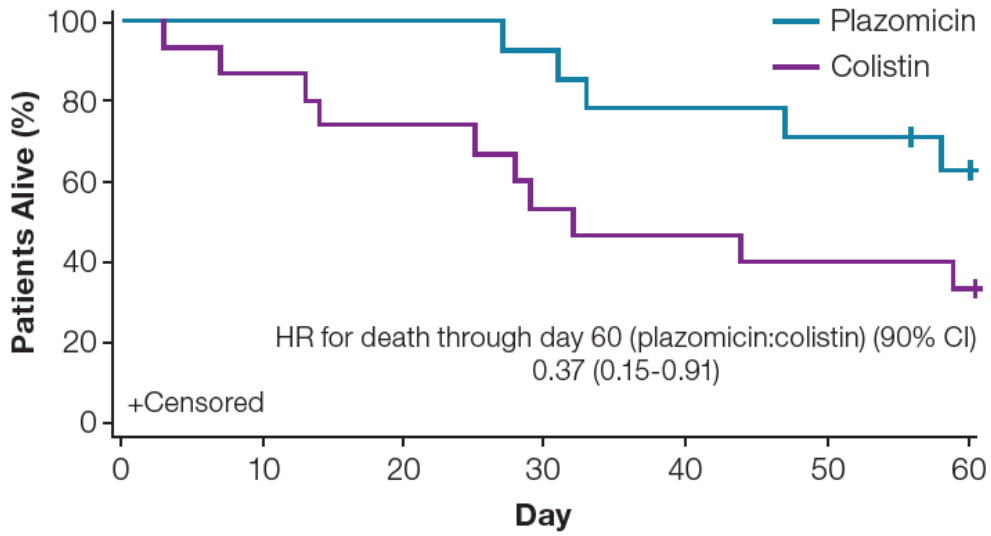
Improved Outcomes With Plazomicin Compared With Colistin in Patients With Bloodstream Infections Caused by Carbapenem-resistant Enterobacteriaceae (CRE) Results From the CARE Study

Figure 2. Mortality-Based Outcomes



Two-sided 90% CI calculated based on the unconditional exact method.

Figure 3. Survival Through Day 60



Time to death through day 60 was estimated with the Kaplan–Meier approach and the hazard ratio (HR) was calculated using a Cox proportional hazards regression model.

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NeoAMR prospective observational hospital based cohort study of empirical treatment and outcome

Primary Endpoint

The mortality at day 28 after start of empiric treatment of infants treated for clinical sepsis

Trial Design

Prospective, multinational, multicentre, observational cohort study of the inpatient management of neonatal sepsis in approximately 15-20 sites.

Sample size

Recruiting 200 infants per site provides >80% power to detect differences in mortality of 50% in 5% blood culture positives vs 10% in 95% blood culture negatives, as observed in DENIS study, assuming an inflation factor of 15% to allow for lost to follow-up (2 sided alpha =0.05).

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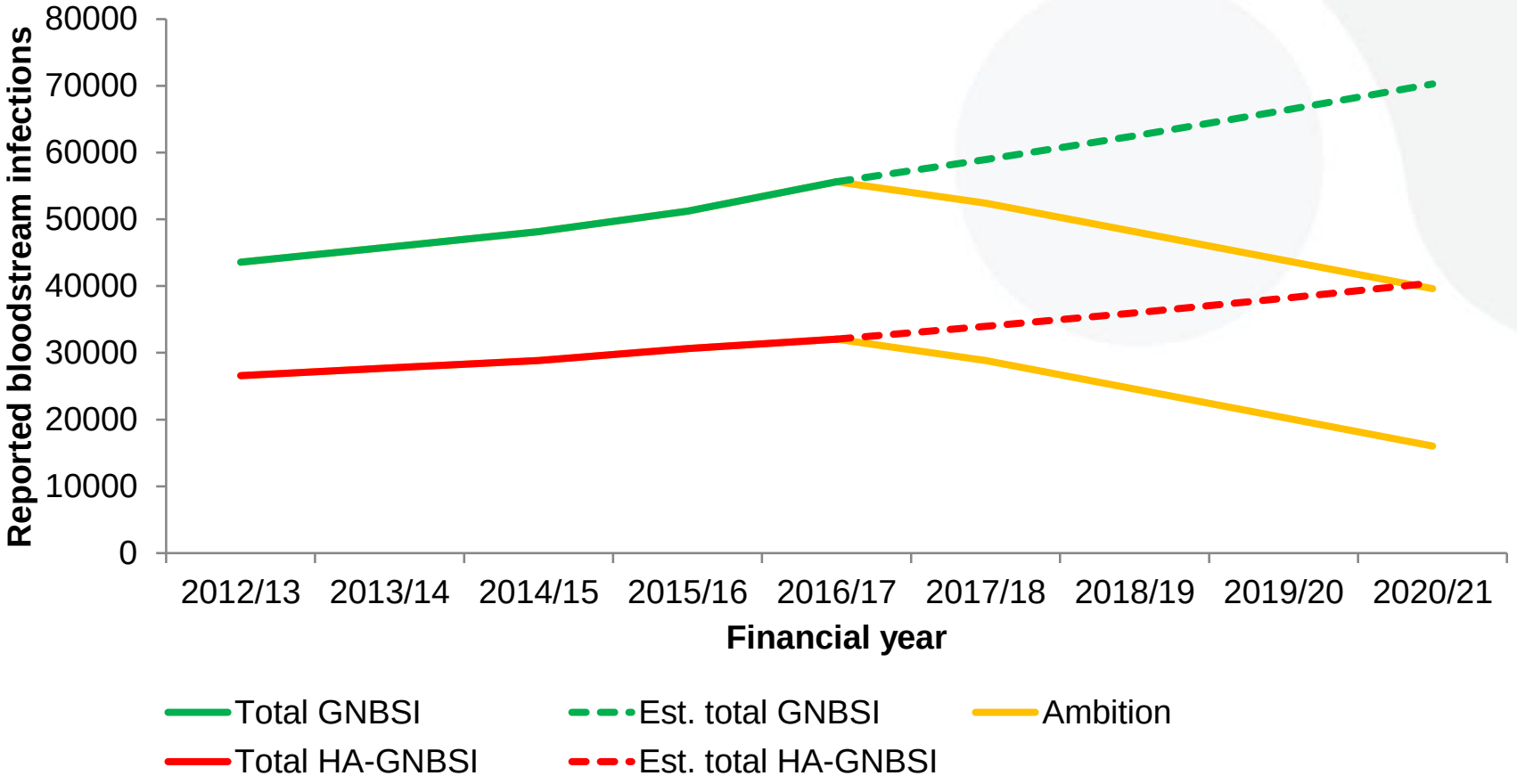
DH Ambition - Gram-negative bloodstream infections 50% reduction by end of FY 2020/21



Thank You

Acknowledgment and special thanks to:

All the SGUL team

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