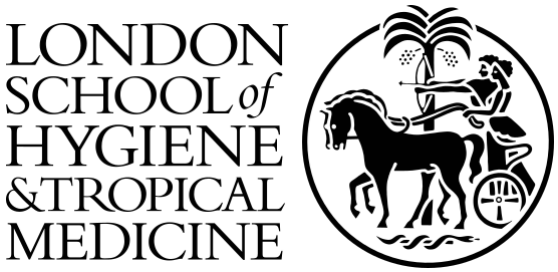

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Reviewing the WHO guidelines for antibiotic use for sepsis in neonates and children

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ABSTRACT

Background: Guidelines from 2005 for treating suspected sepsis in low- and middle-income countries (LMIC) recommended hospitalisation and prophylactic intramuscular (IM) or intravenous (IV) ampicillin and gentamicin. In 2015, recommendations when referral to hospital is not possible suggest the administration of IM gentamicin and oral amoxicillin. In an era of increasing antimicrobial resistance, an updated review of the appropriate empirical therapy for treating sepsis (taking into account susceptibility patterns, cost and risk of adverse events) in neonates and children is necessary.

Methods: Systematic literature review and international guidelines were used to identify published evidence regarding the treatment of (suspected) sepsis.

Results: Five adequately designed and powered studies comparing antibiotic treatments in a low-risk community in neonates and young infants in LMIC were identified. These addressed potential simplifications of the current WHO treatment of reference for infants for whom admission to inpatient care was not possible. Research is lacking regarding the treatment of suspected sepsis in neonates and children with hospital-acquired sepsis, despite rising antimicrobial resistance rates worldwide.

Conclusions: Current WHO guidelines supporting the use of gentamicin and penicillin for hospital-based patients or gentamicin (IM) and amoxicillin (oral) when referral to a hospital is not possible are in accordance with currently available evidence and other international guidelines, and there is no strong evidence to change this. The benefit of a cephalosporin alone or in combination as a second-line therapy in regions with known high rates of non-susceptibility is not well established. Further research into hospital-acquired sepsis in neonates and children is required.

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Introduction

Sepsis remains a leading cause of mortality and morbidity, especially during the first five days of life and in low- and middle-income countries (LMIC) [1]. In 2015, of the 5.9 million deaths of children under the age of 5 years, 45% were of neonates, and this figure exceeded 50% in several regions [2]. Neonatal sepsis is the third most common cause of death in this age group with an estimated 0.4 million deaths in 2015, the vast majority of which were in LMIC [3]. Beyond the neonatal period, the first year of life carries the highest risk of death from sepsis.

In high-income countries (HIC), early-onset neonatal sepsis (EONS) is defined by occurring in the first 72 h after birth, as opposed to late-onset neonatal sepsis (LONS, onset ≥ 72 h after birth). In LMIC, many neonates are born outside health care facilities, and might become infected with community-acquired pathogens even after 72 h of life. As a result, neonatal sepsis in LMIC is often classified as community- and hospital-acquired instead of early- and late-onset [4].

WHO provides guidelines for the management of common childhood illnesses, through the Pocket Book of Hospital Care for Children published for the first time in 2005 [5]. The second edition was published in 2013 [6]. It is one of a series of documents and tools supporting the Integrated Management of Childhood Illness (IMCI). These guidelines focus on management of the major causes of childhood mortality in countries with limited health care (and other) resources. Recommendations for preventing neonatal infection and for the management of possible serious bacterial infection remain the same in the second edition. It recommends providing prophylactic intramuscular (IM) or intravenous (IV) ampicillin and gentamicin in neonates with documented risk factors for infection for at

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least 2 days and then to reassess. Treatment should be continued only if there are signs of sepsis (or positive blood culture). It recommends hospitalisation and IM or IV antibiotic therapy with a combination of gentamicin and benzylpenicillin or ampicillin for at least 7–10 days in infants aged <2 months who fulfil the case definition of serious bacterial infection. If infants are deemed to be at risk of staphylococcal infection, IV cloxacillin and gentamicin are recommended.

In many LMIC, these parenteral treatments might only be available where inpatient neonatal and paediatric care can be provided, and access to these treatments is limited by transportation, financial and/or cultural factors. In previous studies, even when these constraints were addressed, a substantial proportion of families still refused referral to hospital for young infants with possible serious bacterial infection (PSBI). A body of research undertaken in the past decade led to the development and publication in 2015 of the first guideline for Managing Possible Serious Bacterial Infection in Young Infants When Referral is not Possible [7] in infants aged <59 days. The guideline recommends (Table 1):

> *Option 1*: IM gentamicin 5–7.5 mg/kg (for low-birthweight infants gentamicin 3–4 mg/kg) once daily for 7 days and twice daily oral amoxicillin, 50 mg/kg per dose for 7 days.
>
> *Option 2*: IM gentamicin 5–7.5 mg/kg (for low-birthweight infants gentamicin 3–4 mg/kg) once daily for 2 days and twice daily oral amoxicillin, 50 mg/kg per dose for 7 days.

Thus, penicillin/gentamicin is recommended for community neonatal sepsis, hospital neonatal sepsis and all sepsis in children. It is known, however, that in many countries, agents with a broader spectrum such as third-generation cephalosporins (e.g. ceftriaxone) are commonly used to treat neonatal and infant sepsis [8]. Against this background, concerns are increasing regarding bacterial pathogens with reduced susceptibility to empirical medication with variations both between and within LMIC [9].

The potential need to revise the existing WHO guidelines based on new antimicrobial resistance (AMR) data or evidence relating to drug safety in neonates and children must be evaluated. This review collates evidence to support current empirical antibiotic recommendations for suspected or confirmed sepsis in neonates and children according to the most recent (≥year 2012) relevant studies.

Methods

An iterative systematic literature search was undertaken to identify published clinical evidence relevant to the review question. Searches were conducted in MEDLINE and Embase. Databases were searched using relevant medical subject headings, free-text terms and study-type filters, where appropriate. Search terms included variations of 'anti-bacterial agents', 'antibiotic', 'sepsis' and 'bacteraemia'. Limits were set for the appropriate population, i.e. 'all child (0 to 18 years)'. Studies published in languages other than English were not reviewed. The search was undertaken for manuscripts published from 2012 to cover the most recent WHO guidelines (WHO Pocket Book of Hospital Care for Children, 2013).

Potentially relevant studies were identified from the search results by reviewing titles and abstracts. Full papers were then obtained and reviewed against pre-specified inclusion (antimicrobial choice, comparisons between different antibiotics and/or antibiotic classes and/or comparisons with placebo, drug therapeutic use, drug efficacy, drug safety and harm, drug resistance) and exclusion criteria (only bacterial sepsis was considered, case reports were not considered) to

Table 1. Current WHO recommendation for antibiotic therapy in infants aged 0–59 days with signs of possible serious bacterial infection or for prophylaxis.

Reference	Conditions	Antibiotics	Dosing regimen
Pocket Book of Hospital Care for Children, 2013	Prophylaxis in neonates with documented risk factors	IM or IV ampicillin and gentamicin for at least 2 days	*Gentamicin* (IM/IV): First week of life Low-birthweight infants: 3 mg/kg once a day; normal birthweight: 5 mg/kg per dose once a day Weeks 2–4 of life: 7.5 mg/kg once a day *Ampicillin* (IM/IV): First week of life: 50 mg/kg every 12 h Weeks 2–4 of life: 50 mg/kg every 8 h *Benzylpenicillin (penicillin G)* (IM): First week of life: 50,000 U/kg every 12 h; weeks 2–4 and older: 50,000 U/kg every 6 h *Procaine benzylpenicillin* (IM): 50,000 U/kg once a day *Cloxacillin* (IV): First week of life: 25–50 mg/kg every 12 h Weeks 2–4 of life: 25–50 mg/kg every 8 h
	Case definition PSBI	IM or IV gentamicin and benzylpenicillin or ampicillin for at least 7–10 days	
	Greater risk of staphylococcus infection	IV cloxacillin and gentamicin for at least 7–10 days	
Managing possible serious bacterial infection in young infants when referral is not possible, 2015	Referral to hospital for young infants with PSBI is not possible	Option 1: IM gentamicin once daily for 7 days and oral amoxicillin twice daily for 7 days Option 2: IM gentamicin once daily for 2 days and oral amoxicillin twice daily for 7 days	*Gentamicin*: IM 5–7.5 mg/kg (for low-birthweight infants gentamicin 3–4 mg/kg) once daily *Amoxicillin*: Oral 50 mg/kg twice daily

identify studies that addressed the review question. Fungal and viral sepsis were not taken into account in this review, although invasive candidiasis is an important emerging cause of LONS.

The Cochrane Database for Systematic Reviews was also searched using the terms 'sepsis' AND 'antibiotic'.

Five international guidelines were reviewed: the Surviving Sepsis Campaign endorsed by the Infectious Diseases Society of America (IDSA) [10], the National Institute for Health and Care Excellence (NICE) [11,12], the American Academy of Pediatrics (AAP) [13–15], the British Medical Journal (BMJ) Clinical Evidence [16] and the British National Formulary for Children (BNFc) [17].

Results

Evidence for current WHO recommendations: penicillin and gentamicin in community-based neonatal sepsis

A randomised controlled trial (RCT) undertaken in three low-income communities in Pakistan evaluated the failure rates of three clinic-based antibiotic regimens in young infants with clinical signs of PSBI (≤59 days old, *n* = 434) whose families refused hospital referral [18]. Infants were randomly allocated to receive: (i) procaine penicillin and gentamicin, reference arm, (ii) ceftriaxone or (iii) oral trimethoprim–sulfamethoxazole and gentamicin for 7 days. Results showed that the efficacy of a procaine benzylpenicillin–gentamicin combination was much higher than that of trimethoprim/sulfamethoxazole–gentamicin [treatment failure was significantly higher with trimethoprim/sulfamethoxazole–gentamicin compared with penicillin–gentamicin (relative risk 2.03, 95% confidence interval 1.09–3.79)]. Differences were not significant in the ceftriaxone versus penicillin–gentamicin comparison (relative risk 1.69, 95% CI 0.89 to 3.23).

The two SATTs (Simplified Antibiotic Therapy Trial) were large RCTs, one of which was conducted in five centres in Bangladesh (four urban hospitals and one urban field) [19] and the other in five centres in Pakistan [20]. It included young infants (≤59 days old, *n* = 2367 and ≤ 59 days old, *n* = 2251 per protocol, respectively) for whom referral to hospital was not possible. The trial compared the standard treatment of injectable procaine benzylpenicillin–gentamicin for 7 days (group A) with two alternative regimens: (i) injectable gentamicin and oral amoxicillin for 7 days (group B), and (ii) intramuscular procaine benzylpenicillin and gentamicin for 2 days, then oral amoxicillin for 5 days (group C). The results suggested that the two alternative regimens were as efficacious as the standard regimen when hospital admission was refused. In the SATT trial in Bangladesh, treatment failed in 78 (10%) infants in group A compared with 65 (8%) infants in group B and 64 (8%) in group C. The risk difference between groups B and A was −1.5% (95% CI −4.3 to 1.3) and between groups C and A was −1.7% (95% CI −4.5 to 1.1). Non-fatal severe adverse events were rare. Three infants in group A, two in group B and three in group C had severe diarrhoea [19]. In the SATT trial in Pakistan, treatment failed within 7 days of enrolment in 90 (12%) of infants in group A compared with 76 (10%) infants in group B and 99 (13%) in group C. The risk difference between groups B and A was −1.9% (95% CI −5.1 to 1.3) and between groups C and A was −1.7% (−2.3 to 4.5) [20].

One of two large RCTs from the AFRINEST (AFRIcan NEonatal Sepsis Trial) Group compared oral amoxicillin with injectable procaine benzylpenicillin plus gentamicin in five African centres in young infants (≤59 days old, *n* = 2333) with fast breathing as a single sign of PSBI illness when referral was not possible. In the procaine benzylpenicillin–gentamicin group, 234 infants (22%) failed treatment compared with 221 (19%) infants in the oral amoxicillin group (risk difference 2.6%, 95% CI −6.0 to 0.8). The results were taken to indicate that young infants with fast breathing alone can be effectively treated with oral amoxicillin as outpatients when referral to hospital is not possible [21].

The second large RCT from the AFRINEST Group, undertaken in the same countries, compared the current reference treatment for PSBI of injectable procaine benzylpenicillin–gentamicin for 7 days (group A) with a simplified regimen in young infants (≤59 days old, *n* = 3564) when referral was not possible. The following simplified regimens were investigated: (i) injectable gentamicin and oral amoxicillin for 7 days (group B), (ii) injectable procaine benzylpenicillin–gentamicin for 2 days, then oral amoxicillin for 5 days (group C), (iii) or injectable gentamicin for 2 days and oral amoxicillin for 7 days (group D) [22]. Treatment failed in 67 (8%) infants in group A compared with 51 (6%) in group B (risk difference −1.9%, 95% CI −4.4 to 0.1), 65 (8%) in group C (risk difference −0.6%, 95% CI −3.1 to 2.0) and 46 (5%) in group D (risk difference −2.7%, 95% CI −5.1 to 0.3). The results suggest that the three simplified regimens were as effective as injectable procaine benzylpenicillin–gentamicin for 7 days on an outpatient basis in young infants with clinical signs of severe infection, without signs of critical illness, and whose caregivers could not accept referral for hospital admission.

In these five aforementioned studies [18–22], the equivalence margin was predefined at 5%. Based on *in vitro* data from LMIC on a benzylpenicillin and gentamicin regimen (~4000 blood culture isolates) [23], a significant proportion of bacteraemia is not covered: 43% in neonates and 37% in infants of 1–12 months. However, this was not confirmed by the SATT trial in Pakistan which, of the five aforementioned studies, is the only one which obtained blood cultures in the majority of patients (84%) [20]. Thirty-two (86%) of 37 pathogens tested for antimicrobial susceptibility were sensitive to amoxicillin and gentamicin [20]. Interestingly, of the

2067 blood cultures obtained, only 81 (4%) were positive for a micro-organism. Overall, mortality was low in the SATT and AFRINEST studies: it was 2% in each group comparing the reference treatment of injectable procaine benzylpenicillin–gentamicin for 7 days with two alternative regimens [19], <1% in each group comparing amoxicillin with benzylpenicillin–gentamicin [20,21] and ≤2% in each group comparing the reference treatment of injectable procaine benzylpenicillin–gentamicin for 7 days with the three simplified dosing regimens [22].

Drug management in hospital-based neonatal sepsis

Two other studies in the Asian region were found. One, a retrospective study in hospitalised neonates and children (≤59 months of age, $n = 183$) in Bangladesh, investigated injected ampicillin and gentamicin as a first-line combination for the management of sepsis [24]. Another single-centre prospective study in India of hospitalised neonates (≤59 months old, $n = 90$) compared two empirical regimens: a cloxacillin and amikacin combination ($n = 40$) versus a cefotaxime and gentamicin combination ($n = 50$) for at least 10 days in cases of late-onset sepsis [25]. The study analyses of these reports are unclear and either they do not address the stated primary outcome (mortality between the two groups) or specify the statistical methods used for analyses, or do not provide numerical values for non-significant results [24,25].

All other studies retrieved since 2012 which compared the impact of different antibiotic regimens and/or routes of administration on outcome were undertaken in hospitalised patients in HIC, mainly in North America. Because of the considerable differences in pathogen spectrum, resistance patterns, but also levels and types of underlying diseases, it is unlikely that the results of these studies are directly generalisable to LMIC [26,27].

Third-generation cephalosporin monotherapy versus *in combination with another antibiotic*

Historically, combination therapy has been used to increase coverage and because of its potential additive clinical effect. While studies tend to show that there is no difference in clinical outcomes or mortality between mono- and combined therapy, increased toxicities with combination therapy has been documented [28,29].

Four studies since 2012 were found which compared β-lactam monotherapy with β-lactam combined with aminoglycoside in hospitalised paediatric patients in the USA [27,29–31].

In the retrospective studies by Berkowitz et al. [30] ($n = 203$) and Tama [29] ($n = 879$), there was no difference in 30-day mortality between the β-lactam monotherapy and the combination therapy of aminoglycoside and β-lactams for Gram-negative bacteria in children. Combination therapy consisting of a β-lactam agent and an aminoglycoside was not superior to monotherapy with a β-lactam agent alone for managing enterobacteriaceae bacteraemia in children. But patients receiving combination therapy had approximately twice the risk of nephrotoxicity compared with those receiving monotherapy (odds ratio 2.15, 95% CI 2.09 to 2.21) [29].

In a study of neonates and young infants (≤59 days old, $n = 265$), based on *in vitro* susceptibilities from isolates, third-generation cephalosporins combined with ampicillin would have been effective for 98.5% of infants but unnecessarily broad with a third-generation cephalosporin use for 83.8% of infants with suspected serious bacterial infection [27]. Because of the 20 *Enterococcus faecalis* isolates (7.5% of identified pathogens), intrinsically resistant to cephalosporins, third-generation cephalosporin monotherapy was less effective than either combination ($p < 0.001$).

In a retrospective study in which children receiving empirical combination therapy were matched 1:1 with children receiving empirical monotherapy [31], the 10-day mortality was similar in children (aged > 2 months to 14 years, $n = 452$) receiving empirical combination therapy versus empirical monotherapy (odds ratio 0.84, 95% CI 0.28 to 1.71). A survival benefit was observed when empirical combination therapy was prescribed for children growing multidrug-resistant Gram-negative organisms ($n = 46$) in the bloodstream (odds ratio 0.70, 95% CI 0.51 to 0.84).

A systematic review in 2013 assessed β-lactam monotherapy versus β-lactam-aminoglycoside combination therapy in patients with sepsis. It included 69 randomised and quasi-randomised trials but only four included children. In trials comparing the same β-lactam, there was no difference between study groups with regard to all-cause mortality (Relative Risk RR 0.97, 95% CI 0.73 to 1.30) and clinical failure ((RR) 1.11, 95% CI 0.95 to 1.29). In studies comparing different β-lactams, a trend for benefit with monotherapy for all-cause mortality (RR 0.85, 95% CI 0.71 to 1.01) and a significant advantage for clinical failure (RR 0.75, 95% CI 0.67 to 0.84) was observed, but the studies included were generally classified as being of low quality. No significant disparities emerged from analyses of participants with Gram-negative infection. Nephrotoxicity was significantly less frequent with monotherapy (RR 0.30, 95% CI 0.23 to 0.39) [28].

Evidence for alternative antibiotic treatment options

One RCT conducted in India compared amikacin monotherapy with piperacillin/tazobactam monotherapy as empirical treatment for suspected EONS ($n = 187$) [32]. In this neonatal unit, amikacin or piperacillin–tazobactam was the standard regimen since reported resistance rates previously ranged between 86% and 89% for ampicillin, gentamicin and cefotaxime. Treatment failure defined as a blood culture isolate resistant to the allocated

antibiotic or as a change of antibiotic was very low ($n = 3$ and $n = 2$, respectively, $p = 0.44$). No increased risk or significant difference between the two study groups in the incidence of secondary infection within 7 days of stopping the study antibiotic was observed, nor any difference in the incidence of fungal sepsis, nor a difference in all-cause mortality at days 7 and 28. However, only five blood cultures were positive.

A retrospective single-centre study in neonates (5–37 days old, $n = 10$) with persistent CoNS bacteraemia (LONS) investigated the addition of rifampicin to vancomycin for infection resolution [33]. Bacteraemia persisted for a median of 9 days (range 6–19) until the initiation of rifampicin. In all cases, the bacteraemia resolved with vancomycin–rifampicin without serious side effects and in all patients the blood cultures became negative on vancomycin–rifampicin taken 24–72 h after the initiation of rifampicin. No serious side effects were observed.

Synopsis of international guidelines

Table 2 summarises recommendations by international organisations. When selecting empirical treatment regimens, most guidelines suggest relying on data on antibiotic resistance patterns in locally prevalent pathogens at the institutional level but do not define how this should be done. They recommend individualising empirical antibiotic recommendations according to local antibiotic protocols and local pathogen susceptibility. There is little if any detail on how such data are to be used to select treatment regimens. For EONS, most guidelines are in line with WHO recommendations: NICE, AAP, BMJ and BNFc recommend the use of benzylpenicillin or ampicillin combined with gentamicin as empirical treatment and list third-generation cephalosporins as an alternative. Of note, guidelines often state that the aim is to target the most common pathogens in EONS, i.e. group B streptococcus (GBS) and *Escherichia coli* in HIC. More variability is seen in the suggested empirical treatment for LONS.

Dosing consideration

International guidelines differ on dosing regimens for gentamicin, from 4 to 5 mg/kg every 24–36 h. Current WHO guidelines recommend a once-daily dosing regimen, from 3 to 7.5 mg/kg/day according to age and birthweight.

Gentamicin has a narrow therapeutic index. Efficacy of aminoglycosides has been associated with high peak concentrations relative to minimum inhibitory concentration (MIC) of the infecting micro-organism with a ratio peak concentration/MIC of >8–10, whereas low trough concentrations appear to be associated with reduced risk of nephro- and ototoxicity (at least <2 mg/L, but <1 mg/L is also often advocated) [34,35].

Although the incidence of ototoxicity detected following aminoglycoside exposure remains low (1–3%) and less than that reported in adults, gentamicin appears to be the least cochleotoxic. The specific association between hearing loss and aminoglycoside exposure is complicated, mainly owing to the presence of many other confounding factors in this population, e.g. low gestational age and birthweight, intrauterine and postnatal infections, neonatal asphyxia, requirement for prolonged oxygen therapy and respiratory support, congenital malformations, family history of hearing impairment, genetic abnormalities [36]. An association with high peak concentration has been suggested in the past but recent studies are not so categorical [35,36].

A recent systematic review considered the risk of gentamicin toxicity in neonates treated for PBSI in LMIC with the WHO recommended first-line antibiotics (gentamicin with penicillin) [37]:

- Six trials reported formal assessments of ototoxicity outcomes in neonates treated with gentamicin, and the pooled estimate for hearing loss was 3% (95% CI 0 to 7%).
- Nephrotoxicity was assessed in 10 studies but could not be evaluated owing to variation in the case definitions used.
- Estimates of the number of neonates potentially affected by gentamicin toxicity were not undertaken owing to insufficient data.

The authors concluded that data were insufficient to assess the potential for harm in terms of toxicity associated with gentamicin treatment.

The volume of distribution of gentamicin is larger in preterm neonates as a consequence of a higher percentage of body water compared with term neonates. Kidney function is reduced in preterm neonates owing to incomplete nephrogenesis. As a consequence, recent trends are in favour of higher doses (>4 mg/kg up to 5 mg/kg) with extended dose intervals in preterm neonates (>24 h up to 48 h for the most preterm infants or more according to some authors) [38–42] to achieve higher peak concentrations for improved efficacy while maintaining low trough concentrations for safety. According to currently available knowledge, term infants should receive about 4.0–4.5 mg/kg every 24 h [43–45].

However, rates of multidrug-resistant Gram-negative (MRD GN) infections are increasing worldwide, particularly in LMIC. As a result, many enterobacteraciae gentamicin MIC are 4 or higher nowadays, compared with 0.5 or 1 in the past when dosing recommendations were developed, and so determining the appropriate dosing recommendations has become very challenging. It might be possible that even higher doses are required to reach effective exposure (10× MIC) with longer extended dosing interval periods (to prevent toxicity). Such questioning emphasises the urgent need for further prospective

Table 2. Current international guidelines for the empirical treatment of suspected sepsis or blood infection.

Guideline	Last update	Recommendations
Surviving Sepsis Campaign(endorsed by IDSA)	2012	• Administration of effective intravenous antimicrobials within the first hour of recognition of septic shock (grade 1B) and severe sepsis without septic shock (grade 1C) is the goal of therapy • *Initial empiric anti-infective therapy* of *one or more drugs* which have *activity against all likely pathogens* (bacterial and/or fungal or viral) and penetrate in adequate concentrations into tissues presumed to be the source of sepsis (grade 1B) • *Combination empirical therapy* for neutropenic patients with severe sepsis (grade 2B) and for patients with difficult-to-treat, multidrug-resistant bacterial pathogens such as acinetobacter and pseudomonas spp. (grade 2B). For patients with severe infections associated with respiratory failure and septic shock, combination therapy with an *extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone* is recommended for *P. aeruginosa* bacteremia (grade 2B). A combination of *beta-lactam and macrolide* for patients with septic shock from bacteraemic *Streptococcus pneumoniae* infections (grade 2B) is recommended • Empirical combination therapy should not be administered for more than 3–5 days (grade 2B) • Duration of therapy typically 7–10 days; longer courses may be appropriate in patients with a slow clinical response, undrainable foci of infection and bacteremia with *S. aureus*; also some fungal and viral infections or immunologic deficiencies, including neutropenia (grade 2C) • *Special pediatric consideration:* • The empiric drug choice should be changed as epidemic and endemic ecologies dictate (grade 1D) • *Clindamycin* and anti-toxin therapies for toxic shock syndromes with refractory hypotension (grade 2D) • *Clostridium difficile* colitis should be treated with enteral antibiotics if tolerated. *Oral vancomycin* is preferred for severe disease (grade 1A)
NICE	2016	• Neonates presenting in hospital with suspected sepsis in their first 72 h: IV *benzylpenicillin* 25 mg/kg twice daily (increase to 3 times daily if clinically concerned) and *gentamicin* (starting dose 5 mg/kg every 36 h). Minimum 7-day course of IV antibiotics for strong suspicion of sepsis or a positive blood culture • Neonates, community-acquired sepsis: • >40 weeks corrected gestational AGE: *ceftriaxone* 50 mg/kg once daily unless already receiving an intravenous calcium infusion at the time • ≤ 40 weeks corrected gestational age or receiving an intravenous calcium infusion: *cefotaxime* 50 mg/kg every 6–12 h, depending on the age of the neonate • Up to 17 years, community acquired sepsis: *ceftriaxone* 80 mg/kg once a day with a maximum dose of 4 g daily at any age • Up to 17 years, hospital acquired sepsis or patients who are known to have previously been infected with or colonised with ceftriaxone-resistant bacteria: *consult local guidelines* for choice of antibiotic • For children younger than 3 months, give an additional antibiotic active against listeria (for example, *ampicillin or amoxicillin*)
AAP	2012, 2015	• Early-onset sepsis: • Broadspectrum antimicrobial agents [*ampicillin* 150 mg/kg per dose intravenously (IV) every 12 h and an aminoglycoside (usually *gentamicin* 4 mg/kg per dose IV every 24 h)]. Once a pathogen is identified, antimicrobial therapy should be narrowed (unless synergism is needed) • Third-generation cephalosporins (e.g. cefotaxime) represent a reasonable alternative to an aminoglycoside. Bacteraemia without an identifiable focus of infection is generally treated for 10 days Notes: • Antimicrobial therapy should be discontinued at 48 h in clinical situations in which the probability of sepsis is low (controversial) • Risk of resistance to cefotaxime. Owing to excellent CSF penetration, suggest to restrict to infants with meningitis attributable to Gram-negative organisms • To cover group B streptococcus (GBS) and *Escherichia coli* • Late-onset sepsis admitted from the community: *ampicillin* 75 mg/kg per dose IV every 6 h and *gentamicin* 4 mg/kg per dose IV every 24 h • Late-onset sepsis, hospitalised since birth: *vancomycin*: 10 to 20 mg/kg every 12 to 48 h according serum creatinine level and *gentamicin* 4 mg/kg per dose IV every 24 h
BMJ Clinical Evidence	2016	Treatment should be initiated with broad-spectrum antibiotic cover appropriate for the prevalent organisms for each age group and geographical area. This should be changed to an appropriate narrow-spectrum antibiotic regimen once a causative pathogen is identified • Early-onset sepsis: *cited as example*: *benzylpenicillin* plus *gentamicin* (from NICE guidelines) OR *ampicillin* plus *gentamicin* or *cefotaxime* Note: To cover group GBS and Gram-negative bacilli Late-onset sepsis: (selective therapy for empirical antibiotics regimen): • *Cited as an example: ampicillin* plus *gentamicin* OR *cefotaxime*, OR *vancomycin* plus *gentamicin* OR *cefotaxime* • *Ceftazidime* or *piperacillin/tazobactam* may be added to the empirical regimen if Pseudomonas is suspected • *Metronidazole* or *clindamycin* may be added to the empirical regimen to cover for anaerobes/necrotising enterocolitis • Infants and young infants, community-acquired infection: • *Third-generation cephalosporin* (e.g. cefotaxime, ceftriaxone) • Infants and young infants, hospital-acquired infection: • *Extended-spectrum penicillin* (e.g. piperacillin/tazobactam) OR *carbapenem* (e.g. meropenem) • Additional broadening of this cover (e.g. with gentamicin, ciprofloxacin, or vancomycin) may be considered depending on case-specific factors. *Clindamycin* should be used for toxin-induced toxic shock syndromes with refractory hypotension

Table 2. (*Continued*).

Guideline	Last update	Recommendations
BNFc	2015/16	• Septicaemia in neonates ≤72 h old: • Benzylpenicillin sodium, 50 mg/kg in neonate under 7 days every 12 h, in neonate 7–28 days every 8 h • AND • *Gentamicin* 5 mg/kg in neonates up to 6 days every 36 h; in neonates 7–28 days: every 24 h • If Gram-negative septicaemia suspected: ADD *cefotaxime* IM or IV 25 mg/kg in neonates under 7 days every 12 h, in neonates 7–21 days every 8 h; neonates 21–28 days every 6–8 h; dose is doubled in severe infection and meningitis AND stop benzylpenicillin sodium if Gram-negative infection confirmed • Septicaemia in neonates >72 h old: • *Flucloxacillin*, oral 25 mg/kg in neonate under 6 days twice daily; neonates 7–20 days 3 times daily; neonates 21–28 days 4 times daily; IV 25 mg/kg in neonates under 6 days every 12 h; in neonates 7–20 days every 8 h; in neonates 21–28 days every 6 h; may be doubled in severe infection • AND • *Gentamicin* (see dose above) • OR *Amoxicillin* IV 50 mg/kg in neonates under 7 days every 12 h; in neonates 7–28 days every 8 h, • OR *Ampicillin* IV 50 mg/kg in neonates up to 6 days every 12 h; in neonates 7–20 days every 8 h; in neonates 21–28 days every 6 h • AND • *Cefotaxime* (see dose above) • For 7 days • Child 1 month – 18 years, community-acquired sepsis: • Aminoglycoside, e.g. *gentamicin* initially 7 mg/kg, then adjusted according to serum gentamicin concentration *or* multiple daily dose regimen with child aged 1 month–12 years: 2.5 mg/kg every 8 h; child 12–18 years 2 mg/kg every 8 h • AND • *Amoxicillin* 50 mg/kg every 4–6 h (max. 2 g every 4 h) • OR *Ampicillin* 50 mg/kg every 4–6 h (max. per dose 2 g every 4 h) • OR *Cefotaxime alone* 50 mg/kg every 8–12 h; increase to every 6 h in very severe infections and meningitis (max. 12 g daily) OR ceftriaxone alone IM or IV 1 g daily, increased to 2–4 g daily, increased dose to be used in severe infections • If pseudomonas or resistant micro-organism suspected: broad-spectrum anti-pseudomonal beta-lactam [*piperacillin–tazobactam:* 90 mg/kg (max. 4.5 g) every 6 h] • If anaerobic infection suspected, ADD *metronidazole*, oral in child 1–2 months 7.5 mg/kg every 12 h; in child 2 months–12 years 7.5 mg/kg (max. 400 mg) every 8 h; in child 12–18 years 400 mg every 8 h; rectal in child 1 month–1 year 125 mg 3 times daily for 3 days, then twice daily thereafter; in child 1–5 years 250 mg 3 times daily for 3 days, then twice daily thereafter; in child 5–10 years 500 mg 3 times daily for 3 days then twice daily thereafter; in child 10–18 years 1 g 3 times daily for 3 days then twice daily thereafter; IV in child 1–2 months 15 mg/kg as a single loading dose followed after 8 h by 7.5 mg/kg every 8 h; in child 2 months–18 years 7.5 mg/kg (max. 500 mg) every 8 h • If Gram-positive infection suspected, ADD *glucloxacillin* oral in child 1 month–1 year 62.5–125 mg 4 times daily; in child 2–9 years 125–250 mg 4 times daily; in child 10–17 years 250–500 mg 4 times daily; IM in child 1 month–18 years 12.5–25 mg/kg every 6 h (max. 500 mg every 6 h); IV in child 1 month–18 years 12.5–25 mg/kg every 6 h (max. 1 g every 6 h); may be doubled in severe infection • OR *Vancomycin* 15 mg every 8 h (max. 2 g per day) • OR *Teicoplanin* initially 10 mg/kg every 12 h (max. 400 mg per dose) for 3 doses, then (by IV infusion or IM injection) 6 mg/kg once daily (max. 400 mg per dose); (After initial 3 doses subsequent doses can be given by IM route, if necessary, although, IV is preferable). For severe infection: Initially 10 mg/kg every 12 h for 3 doses, 10 mg/kg once daily for 5 days • Child 1 month–18 years, hospital-acquired sepsis: • Broadspectrum anti-pseudomonal beta-lactam: *piperacillin-tazobactam* 90 mg/kg (max. 4.5 g) every 6 h OR *ticarcillin/clavulanic acid*, child under 40 kg: 80 mg/kg every 8 h (increased if necessary to 80 mg/kg every 6 h, increased frequency used for more severe infections); child ≥40 kg: 3.2 g every 6–8 h (increased if necessary to 3.2 g every 4 h, increased frequency for more severe infections) • OR *Imipenem/cilastatin*, in child 1–2 months IV 20 mg/kg every 6 h; in child 3 months–17 years IV 15 mg/kg every 6 h (max. 500 mg per dose) (life-threatening infection: 25 mg/kg every 6 h, max. 1 g per dose) • OR *meropenem*, in child 1 month–11 years (bodyweight ≥50 kg) 2 g every 8 h; in child 12–17 years 2 g every 8 h • If pseudomonas or resistant micro-organism suspected ADD *aminoglycoside* (see dose above) • If MRSA suspected ADD *vancomycin* OR *teicoplanin* (see dose above) • If anaerobic infection suspected ADD **metronidazole** (see dose above) to a broadspectrum **cephalosporin** (see dose above for cefotaxime and ceftriaxone) for 5 days

Note: IDSA – Infectious Diseases Society of America.

studies in populations with MRD GN specifically collecting PBSI isolates (there are few isolates to date) with MICs to gentamicin, actual dosing and peak concentration/trough estimation, and both clinical outcomes (infection resolution, toxicity).

Using the 24-h dosing interval for all neonates suggested by WHO may expose a large proportion of patients to the risk of toxicity, especially when treatment is prolonged (>48 h), because of the possibility of drug accumulation. However, providing various dosing intervals that stratify neonates may complicate feasibility and acceptability.

Pharmacokinetics data for neonates are scarce and so it is difficult to summarise current dosing regimens

Table 3. Safety data summary for empirical antibiotic treatment used in possible serious bacterial infection.

Antibiotic	Adverse events and contraindications	Relevant interactions
Natural penicillin: *Benzylpenicillin sodium* Aminopenicillin: *Ampicillin* *Amoxicillin* Antistaphylococcal penicillin: *Cloxacillin*	Serious toxicity is rare in association with penicillin therapy • Diarrhoea is the most common • Incidence is increased following use of amoxicillin/clavulanate (broad-spectrum therapy) compared with the use of amoxicillin • There is some evidence that different ratios of the amoxicillin to clavulanic acid components may affect the proportion of children who experience diarrhoea • The incidence of diarrhoea following amoxicillin use was significantly lower for b.i.d. than with t.i.d. regimen (6.7–9.6 vs. 10.3–26.7%, respectively) in one study • Drug-induced rash, hypersensitivity, anaphylaxis • Penicillin allergy has been estimated to affect 1–10% of people given penicillins. True incidence of penicillin allergy in patients who report that they are allergic is actually <10% • Very rarely, seizures • Important consideration if higher than usual doses or dose frequencies, or following rapid administration of high intravenous doses (therefore should be infused over at least 30 min) • Electrolyte imbalances (e.g. sodium salts) • Hepatotoxicity, mild/moderate gastro-intestinal effects	Concomitant use of bacteriostatic antibacterial agents (i.e. tetracyclines, sulfonamides, erythromycins, chloramphenicol) should be avoided Caution should also be exerted with the use of certain other β-lactam antibiotics, namely cephalosporins (especially 1st- and 2nd-generation, e.g. cefalexin, cefaclor) and carbapenems (e.g. meropenem) as cross-reactivity in the allergies between these classes can occur (but its importance has frequently been overstated)
3rd-generation cephalosporin: *Cefotaxime*	• Mainly hypersensitivity and gastro-intestinal effects (mostly diarrhoea) • •Rarely causes nephrotoxicity or seizures in neonates	Concurrent use of cephalosporin with: • Nephrotoxic drugs (aminoglycosides) increased risk of nephrotoxicity • Warfarin may result in an increased risk of bleeding
3rd-generation cephalosporin: *Ceftriaxone*	• Mainly hypersensitivity and gastro-intestinal effects (mostly diarrhoea) • Hyperbilirubinemia (ability of ceftriaxone to displace bilirubin from serum albumin binding sites) • Cholestasis and pseudolithiasis owing to biliary sludging (with high concentration of ceftriaxone in the system) • Concomitant administration of intravenous ceftriaxone and calcium-containing solutions is not recommended since concurrent administration with calcium-containing solutions may produce insoluble precipitates (ceftriaxone-calcium salts) leading to cardiorespiratory complications	Concurrent use of cephalosporin with: • Nephrotoxic drugs (aminoglycosides) increased risk of nephrotoxicity • Warfarin may result in an increased risk of bleeding
Broadspectrum antibiotics and prolonged duration of antibiotic therapy	• Increased risk of invasive candidiasis and death • Increased risks of necrotising enterocolitis (NEC), death and late-onset sepsis	

of β-lactams in this review. Antibacterial activity of β-lactams is best characterised by time-dependent killing. The pharmacokinetic-pharmacodynamic parameter that correlates with the clinical and bacteriological efficacy of β-lactam antibiotics is the percentage of time that the serum free drug concentration exceeds the MIC for the pathogen (time above the MIC). Overall, β-lactams present a favourable safety profile and most dosing recommendation suggested by WHO are in line with current knowledge [45].

Review of harm and toxicity – safety

Safety and harm toxicity data for empirical antibiotic treatment used in PSBI are summarised in Table 3 [37,46–55].

Pathogen distribution and antimicrobial resistance patterns

Pathogen distribution. In HIC, the most common causes of EONS are GBS and *E. coli*. The remaining cases of EONS are caused by *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), *Listeria monocytogenes* and other Gram-negative bacteria [4]. In LONS (mainly in very low-birthweight infants), the main pathogens are CoNS, responsible for half of the episodes. Other important aetiological agents are *E. coli*, klebsiella spp. and candida spp. Less common causes of LONS include *S. aureus*, enterococcus spp. and *Pseudomonas aeruginosa* [4,56].

Aetiological data from LMIC, particularly from rural, community-based studies, are very limited. In systematic reviews on this topic, the commonest causes of neonatal bacteraemia in LMIC are *S. aureus*, *E. coli* and klebsiella spp. and, in older infants, *S. aureus*, *Streptococcus pneumoniae*, klebsiella spp. and *E. coli*, and non-typhoidal salmonella [23,57]. Although there are some similarities between community- and hospital-acquired sepsis, available data are of insufficient quality to justify firm conclusions [4]. Acinetobacter spp., for example, appear to be predominant in some regions [58,59], while the incidence is very low in other regions. GBS is responsible for only 2–8% of cases in LMIC. It is possible that infants with GBS infection are underreported, since this pathogen usually presents very early in life and infected newborns might die or be adequately treated before blood cultures or other relevant microbiological samples are obtained. CoNS is responsible for a lower proportion of hospital-acquired infections than in HIC [4], and this may be related to the use of invasive medical devices, e.g. central venous catheters. Interestingly, in the SATT

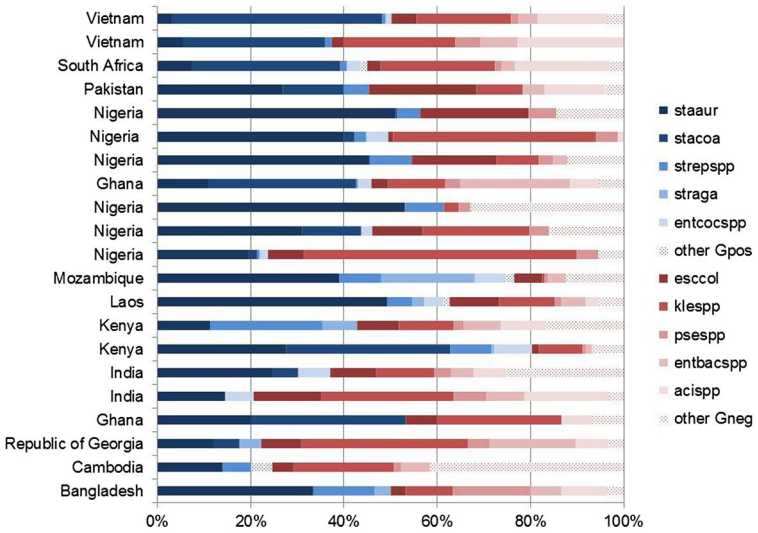

Figure 1. Pathogen distribution for studies conducted in a specific setting and reported after 2005 in neonates.
Notes: Staaur, *S. aureus*; stacoa, coagulase-negative staphylococci; strepspp, streptococci; straga, *S. agalactiae*; entcocspp, enterococci; other Gpos, other Gram-positive pathogens; esccol, *E. coli*; klespp, klebsiella spp; psespp, pseudomonas spp; entbacspp, enterobacter spp; acispp, acinetobacter spp., other Gneg: other Gram-negative pathogens.

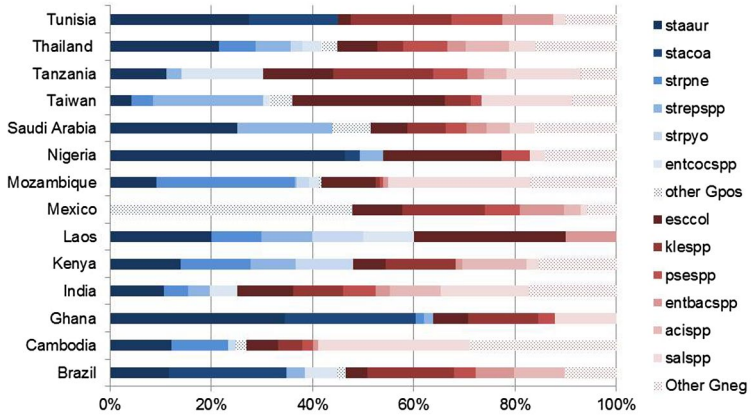

Figure 2. Pathogen distribution for studies conducted in a specific setting and reported after 2005 in children.
Notes: Staaur, *S. aureus*; stacoa, coagulase-negative staphylococci; strpne, *S. pneumonia*; strepspp, streptococci; strpyo, *S. pyogenes*; entcocspp, enterococci; other Gpos, other Gram-positive pathogens; esccol, *E. coli*; klespp, klebsiella spp; psespp, pseudomonas spp; entbacspp, enterobacter spp; acispp, acinetobacter spp; salspp, salmonella spp; other Gneg, other Gram-negative pathogens.

in Pakistan which obtained blood cultures from 2067 (84%) infants, a high frequency of campylobacter was found in the absence of diarrhoea (22% of the positive blood cultures) [20].

Regarding local variations, Figures 1 (neonates) and 2 (children) show the pathogen distribution for studies conducted in specific LMIC reported after 2005. These data demonstrate the heterogeneity likely to be encountered in settings for which the WHO essential medicines list is relevant. In particular, it is not presently possible to definitively delineate the specific role played by bacteria which are difficult to treat, e.g. *Klebsiella* spp. and *Acinetobacter* spp. The relative incidence of these pathogens may have a considerable impact on the probable cover by different empirical regimens as certain bacteria are intrinsically resistant or display high levels of acquired resistance to commonly used antibiotics, which lowers their coverage.

Antimicrobial resistance patterns

Only very limited reliable data on antimicrobial susceptibility are available from Asia, Latin America and Africa. It is evident from existing summaries of the data that there is considerable antibiotic resistance to many commonly used antibiotics with variations both between and within regions in LMIC [57,60].

According to a systematic review and meta-analysis by Downie et al. [23], more than 40% of cases of community-acquired neonatal bacteraemia in LMIC are resistant or have reduced susceptibility to a combination of penicillin and gentamicin and to third-generation cephalosporins, thus suggesting that third-generation cephalosporins are no more effective in treating sepsis than the currently recommended antibiotics, benzylpenicillin and gentamicin. More than 35% of cases of community-acquired bacteraemia in infants aged

1–12 months are resistant or have reduced susceptibility to the combination of penicillin and gentamicin and to third-generation cephalosporins. In neonates, the gaps in antibiotic coverage with either benzylpenicillin/ampicillin and gentamicin or third-generation cephalosporins regimens were mostly in infections owing to enteric Gram-negative bacilli, particularly klebsiella spp. [23]. However, in the Pakistan SATT trial, it was reassuring that the majority of micro-organisms tested (32/37) were susceptible to gentamicin and amoxicillin [20].

Similar findings were reported in a 2015 systematic review of studies which estimated AMR rates in Gram-negative bloodstream infections in children in LMIC [58]. Gram-negative bacteria accounted for 67% of all episodes. The predominance of klebsiella spp. with a high prevalence of resistance to gentamicin in Asia (69%, Interquartile Range (IQR) 19–95%) and Africa (54%, IQR 0–68%) and the overall level of resistance of Gram-negative bacteria to third-generation cephalosporins (Asia 84%, IQR 45–95%; Africa 50%, IQR 0–87%) were very concerning.

All reviews published to date note the very low number of studies with adequate data. In particular, many of the studies reviewed had a high risk of bias with substantial uncertainty about how representative the data are for each setting. There are concerns that the data published are mainly from larger tertiary neonatal units, many of which might have higher rates of resistance owing to a nosocomial outbreak. In addition, virtually no clinical outcome data are reported (a finding confirmed by this review), particularly relating to the underlying disease, pathogen phenotype, empirical antibiotic treatment and clinical outcome. This imposes major limitations to selecting empirical regimens on the basis of their clinical impact.

Discussion

Since 2012, only suspected community neonatal sepsis has been addressed and there have been no adequate studies in other settings. Five adequately designed and powered studies which compared antibiotic treatments in a low-risk community setting in neonates and young infants (0–59 days) in LMICs were found [18–22]. They addressed potential simplifications of the current WHO treatment of reference, particularly for infants for whom admission to inpatient care was not acceptable or possible. In this group of infants, evidence suggests that treatment regimens could potentially be simplified, for example, by using injectable gentamicin for 2 days and oral amoxicillin for 7 days for young infants [22]. We hypothesise that the regimen of injectable gentamicin for 2 days and oral amoxicillin for 7 days would offer advantages over others investigated by requiring fewer invasive procedures with only two injections, promoting treatment adherence, and by allowing administration of high doses of aminoglycoside to target high MIC, while preventing drug accumulation over days and thus potential toxicity (mostly nephrotoxicity) based on a once-daily dosing regimen. However, these studies did not evaluate regimens and/or agents outside of those currently on the essential medicines list. Also, they were limited to a specific subpopulation of infants and children (≤59 days old, weight ≥ 1500 g) with suspected sepsis. Enrolment according to the diagnosis of PSBI was based on the presence of any sign of clinical severe infection except signs of critical illness (unconsciousness and convulsions) [19–22]. As it was a community-based, low-risk study, a considerable proportion of treated infants might not have had a bacterial infection. Indeed, in the single trial that performed blood cultures (Pakistan SATT trial), only 4% were positive for a pathogen [20]. It is also unclear what the rates of antimicrobial resistance were in these settings, but sensitivities to the aminoglycoside-based regimens are likely to be higher than in facility-based settings, and the results of susceptibility testing in the Pakistan SATT trial tend to confirm this, although the number of samples tested (37) was very low. In the Pakistan SATT, the presence of bacteraemia did not predict treatment failure in per-protocol infants [10 (13%) of 75 children with bacteraemia and 227 (12%) of 1618 without bacteraemia had treatment failure (risk difference 1.03, 95% CI −6.8 to 8.9)]. Overall, studies assessing the efficacy of specific antibiotic regimens in infants and children with blood culture-proven sepsis and/or the effectiveness of different regimens in infants and children with nosocomial sepsis are virtually lacking. Given the challenges of increasing levels of antibiotic resistance in LMIC (based on evaluation of blood cultures usually collected from inpatients or at least on presentation at hospital) and the considerable variation in the patterns of bacteria causing bacteraemia, for example, with the predominance of klebsiella spp. and acinetobacter spp., it might be expected that additional antibiotic options will be required. Closing the existing gaps in evidence must be made a priority so that any additions/changes to the recommended regimens are based on robust data. All the other trials addressing antibiotic regimens in neonatal and paediatric sepsis that were identified were disappointing in terms of design (often retrospective), power (low sample size) and outcomes (not performed in LMIC, method not always well-reported, drug dose often not reported). In addition, it is essential to have more data on causative pathogens and their susceptibilities in order to understand which treatment regimens could be effective and should be prioritised for further investigation. There are virtually no relevant studies with rigorous methods to direct therapeutic options in children. Fundamental concepts of effective antimicrobial therapy in critically ill children (proper culture techniques, timely initiation of therapy, selection of agents with a high likelihood of susceptibility and sufficient penetration

to the site of infection, adequate doses and intervals to enhance bactericidal activity) are often impractical in LMIC owing to limited resources and infrastructure. Overall, a recommendation to amend the current WHO antibiotic regimens for PSBI cannot be made.

The utility of third-generation cephalosporins as second-line treatment is under debate based on the sparse microbiological surveillance data available. Additionally, there is major concern about the widespread use of third-generation cephalosporins and selection for multidrug Gram-negative infections in neonatal units. Further efforts are urgently needed to investigate alternative older off-patent therapeutic antimicrobials such as colistin, polymixin B or fosfomycin, to delineate their efficacy and safety in the paediatric population and to determine their potential contribution to antimicrobial regimens in LMIC settings.

In conclusion, current WHO guidelines which support the use of gentamicin and penicillin for inpatients or gentamicin (IM) and amoxicillin (IM, *per os*) when admission is not possible accord with currently available evidence and other international guidelines, and there is no strong evidence to change this guidance. The absence of almost any adequate evidence to suggest revision of the guidance for sepsis in hospital setting for neonates or any setting for children is a major concern.

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