THE LANCET Infectious Diseases

Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

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Appendix 1: Characteristics of Included Studies

	Author	Year Published; Years Data Collected	Study Design	Title	Setting (primary / secondary / tertiary); Community v's Hospital Acquired Infections	Location	Age Range (Neonate / Paediatric)	Microbiology Techniques / Quality	Findings	GRADE Level of Evidence (Comments)
1	Blomberg et al.[1]	2007; patients presenting 2001-2002.	Cohort	**Antimicrobial resistance predicts death in Tanzanian children with bloodstream infections: A prospective cohort study**	Urban tertiary setting; Both community- and hospital-acquired infections	Tanzania	0-7 years (average age 8.5 months); n=1,787 of n=1,828 admissions presenting with signs of sepsis were included in the study to have blood cultures collected	1-5ml of Blood inoculated in BACTEC blood-culturing vials were incubated for 6 weeks, then subcultured in agar and isolates identified by AEI20E/API20NE/API20AUX systems (aerobic cultures only). Susceptibilities against antimicrobial agents were tested by disk diffusion methods according to the CLSI guidelines. Gram-negative bacteria were investigated for extended-spectrum beta-lactamases with E-test, PCR and DNA sequencing. *Enterococcal* isolates were investigated by PCR to affirm identity and vancomycin resistance.	• At least 2/3 of the included patients had received antimicrobial therapy prior to blood cultures being collected • The incidence of laboratory-confirmed bloodstream infection was 13.9% (255 of 1,828 admissions) • A single pathogen was identified in 224 children (12.3%); 31 children (1.7%) had polymicrobial infection with 2-4 isolates identified • Half of all laboratory-confirmed bloodstream infections were identified as potentially hospital-acquired • *Salmonella* and *E Coli* were the most common isolates in **community-acquired** infections; and *Klebsiella* and *Staphylococcus Aureus* were the most common **hospital-acquired** infections • *Klebsiella* was the most common cause of neonatal bloodstream infection (54%) • In children >1 month *Salmonella* spp. were the most frequently isolated pathogen • Children with laboratory-confirmed bloodstream infection had a 3-fold increased risk of mortality; with Gram-negative blood stream infection being twice as fatal as malaria (45.6% vs 20.2%) and Gram-positive sepsis being the least common cause of mortality (16.7%)	B (Large sample size; prospective design; identification of prior treatment with antibiotics)

									• *Enterobacteriaceae* displayed high frequency of resistance to commonly-used antimicrobials:
									  ○ 80% resistance to Ampicillin
									  ○ 33% resistance to gentamicin
									  ○ However, there was almost universal sensitivity to Ciprofloxacin
									• *Salmonella* spp. Non-suscpetibility:
									  ○ 33% to Chloramphenicol
									  ○ 50% to ampicillin and co-trimoxazole
									• ESBL was found in 18% of *Enterobacteriacaeae* phenotypes; and these isolates were resistant to almost all tested antimicrobials aside from Ciprofloxacin and Meropenem
									• The majority of *Staphylococcus aureus* isolates were sensitive to commonly used anti-staphylococcal agents (including cloxacillin and gentamicin)
									• Antimicrobial treatment prior to blood culture collection was significantly associated with resistance to co-trimoxazole and chloramphenicol in Gram-negative isolates; with resistance to erythromycin (36% vs 0%) and chloramphenicol (46% vs 0%) identified in *Staphylococcus aureus* isolates
									• Hospital-acquired infections were significantly associated with resistance to amoxicillin-clavulanate and Cephalosporins in *E Coli* infection; and with co-trimoxazole resistance in *Klebsiella* infection
									• 53% of all *Klebsiella* isolates were resistant to gentamicin (as well as inherent resistance to ampicillin), rendering empiric therapy of limited utility;	

									subsequently there was a high incidence of case-fatality of *Klebsiella* bloodstream infections • Malnutrition: 1/6 (243/1,603) of the patients were malnourished, and this was a risk factor for death; while in those who survived, it was associated with a prolonged hospital stay • *E. Faecium* and *E.Faecalis* isolates commonly displayed high-level gentamicin resistance (overall 44%) and ampicillin resistance (overall 47%)	
2	Enwere et al.[2]	2006; Recruited 2000-2003	Cohort	**Epidemiologic and Clinical Characteristics of Community-Acquired Invasive Bacterial Infections in children 2-29 months in The Gambia**	Urban secondary and tertiary Settings; Community-acquired infections	The Gambia	2-29 months (7,369 specimens were cultured); infants presenting to a government vaccination post with signs of an acute lower respiratory tract infection who were investigated for invasive bacterial infection.	Bacteria were isolated from blood using automated blood-culture system (Bactec 9050) and inoculated under aerobic and 5% CO2 conditions for 18-24 hours. Identification of *S. Pneumoniae* and *Salmonella* species was by cultural morphology, & susceptibility to analytical profile indices. Resistance to antimicrobials was assessed by disk diffusion for all bacteria and was investigated further by measuring MICs for *Pnuemococci* and *n*on-typhoidal *Salmonella*, but not for other bacteria.	• The most **community-acquired** common organism isolated was *Streptococcus Pneumonia* (35% of episodes) • Non-Typhoidal *Salmonella* was cultured in 28% of isolates • In order of decreasing frequency, the most common other organisms (frequency not specified) were: *-E Coli* *-S. Aureus* *-Meningococcus* *-Streptococcus spp.* *-Shigella spp.* *-Pseudomonas spp.* *-Klebsiella spp.* • Among isolates of non-typhoidal *Salmonella*, resistance was high to ampicillin (65%), co-trimoxazole (60%) and chloramphenicol (24%); yet all isolates were susceptible to cefotaxime • Among *Pneumococcal* isolates, resistance was found to chloramphenicol (9.6%), co-trimoxazole (16.5%) and tetracycline (44.3%) but no isolates were resistant to penicillin, ampicillin or cefotaxime	B (Data collected as part of a randomised, double-blinded, placebo-controlled trial; prospective design; systematic patient recruitment; external quality assurance)

3	Sigauque et al.[3]	2009; patients presenting 2001-2006.	Cohort	**Community-acquired bacteraemia among children admitted to a rural hospital in Mozambique**	Rural tertiary setting; Community-acquired infections	Mozambique	0-15yrs n=19,896 admitted children underwent blood culture investigation of which n=1,592 were bacteraemic	Blood cultures were collected for children with axillary temperatures >39 on admission, inoculated into paediatric culture bottles and incubated in an automated BACTEC 9050 system for 4 days. Positive cultures were examined by Gram stain and subcultured on agar plates then identified according to standard microbiologic procedures. Antibiotic susceptibility was determined by disk diffusion according to CLSI guidelines; and MICs were estimated for *Pneumococcus* using E-strips.	• Bloodstream infections were identified in 8% of paediatric hospital admissions. Non-typhoidal *Salmonella* (26%) and *Pseudomonas* (25%) were the most prevalent pathogens isolated overall • In neonates, *Staphylococcus aureus* (39%) and *Group B Streptococcus* (20%) predominated • Community-acquired bacteraemia associated mortality accounted for 21% of all hospital deaths • Resistance to antibiotics commonly used in Mozambique was high: Pneumococcal isolates were predominantly susceptible to penicillin (89%) and chloramphenicol (93%) but resistant to trimethoprim-sulfamethoxazole • Among non-typhoidal *Salmonella* isolates, 74% were resistant to ampicillin, 66% to trimethoprim-sulfamethoxazole and 54% to chloramphenicol; while 38% were resistant to amoxicillin-clavulanic acid • *Staphylococcus aureus* isolates were 90% resistant to ampicillin and 9% resistant to Oxacillin • *Haemophilus Influenzae* exhibited high resistance to chloramphenicol (50%), penicillin/ampicillin (54%) and co-trimoxazole (23%) • *Group B Streptococcus* isolates exhibited 100% susceptibility to penicillin/ampicillin; 71% susceptibility to chloramphenicol, and 85% susceptibility to co-trimoxazole.	B (Large patient cohort, systematic patient recruitment, prospective study design)

4	Falade et al[4]	2009; patients presenting 2005-2006	Cohort	**Invasive Pneumococcal disease in Children aged <5 years admitted to 3 Urban hospitals in Ibadan, Nigeria.**	Tertiary Urban; Community-acquired infections	Nigeria	Age 2-59 months; n=1,210 cases of suspected community-acquired pneumococcal disease investigated with blood and/or CSF cultures	Inoculated blood culture bottles were incubated in the laboratory for 24-48 hours and then until day 7 if there was no initial growth. Subcultures were performed twice (on days 2 and 3). Further identification of bacterial cultures was conducted by morphological and biochemical methods. Serotyping of Pneumococcal isolates was performed with capsular and factor-typing sera. MIC susceptibility testing was performed using E-strips	• 1,210 children with suspected bacterial disease were investigated over a 24-month period. There were 481 cases of meningitis clinical syndrome, 299 cases of pneumonia and 200 cases of septicaemia; 21 children had invasive *pneumococcal* disease. • 11 *S. pneumoniae* serotype isolates from CSF and blood specimens were susceptible to penicillin, chloramphenicol, cefotaxime, erythromycin and ciprofloxacin; they all showed intermediate resistance to tetracycline and were fully resistant to trimethoprim-sulfamethoxazole	B (Prospective multi-centre study; systematic patient recruitment; external quality control of laboratory procedures)

5	Schwarz et al[5]	2010; patients presenting 2007-2009	Prospective cohort	**Systemic bacteraemia in children presenting with clinical pneumonia and the impact of non-typhoid salmonella (NTS)**	Rural Tertiary; Community-acquired infections	Ghana	n=1,032 blood cultures were collected between children 2 months – 5 years of age presenting with clinical pneumonia; of which n=90 (9%) were positive with presumed contaminants and n=209 (20%) were positive with presumed pathogenic bacteria.	BC incubated in a BACTEC automated BC system for 5/7 or until positive. Broth from positive bottles was directly examined by Gram stain and 20 µl were cultured further on agar Identification of *S. pneumoniae* was based on morphology of colonies and the optochin test. Oxacillin discs were used to determine sensitivity to penicillin. Antibiotic susceptibility testing was performed using the disc diffusion method with the susceptibility breakpoints suggested by CLSI. Lab undertakes external quality assurance programme.	○ The most common isolates were non-typhoidal *Salmonella* (n=16, 9.3%); *S.pneumoniae* (n=8, 4.6%); *S.aureus* (n=5, 2.9%); *S. Typhi* (n=4, 2.3%); *Klebsiella* spp. (n=2, 1.2%) **Non-typhoidal *Salmonella* Susceptibility:** • Amoxicillin/Ampicillin 15.5%; • Co-amoxiclav 25.7%; • Cefuroxime 46.5%; • Ceftriaxone 100%; • Co-trimoxazole 23.5%; • Ciprofloxacin 100%; • Gentamicin 70.9%; • Tetracycline 89%; • Chloramphenicol 18% • **Multi-drug resistance** against the three standard drugs amoxicillin, chloramphenicol and co-trimoxazole was 75.5% ***Streptococcal pneumoniae* Susceptibility:** • Amoxicillin/Ampicillin: 80% • Augmentin 88.9%; • Cefuroxime 100%; • Ceftriaxone 100%; • Co-trimoxazole 0%; • Ciprofloxacin 52.6^; • Gentamicin 22.2%; • Tetracycline 25%; • Chloramphenicol 88.9%	B (Prospective study design; systematic patient recruitment; external quality control of laboratory procedures)
6	Nielsen et al.[6]	2012 patients presenting 2007-2009	Prospective Cohort	**Incidence and Characteristics of Bacteremia among Children in Rural Ghana**	Rural Tertiary; Community-acquired infections	Ghana	n=1,196 children aged 0-5 years admitted to a rural hospital in Ghana had blood cultures collected; of which n=238 (20%) were culture positive	Blood cultures were incubated using automated BACTEC for 5/7 or until positive; then examined directly by Gram stain microscopy and sub-cultured on standard media plates. Identification of the organisms was obtained by biochemical and serological tests. Isolates of non-pathogenic microorganisms or skin flora were considered to be contaminants. Susceptibility to penicillin, amoxicillin/ampicillin, amoxicillin & clavulanic acid, flucloxacillin, cefuroxime, ceftriaxone,	The most frequently (**community-acquired)** isolated pathogens were: • Non-typhoidal Salmonella (n=129; 53.3%) • *S. aureus* (n=32; 13.2%) • *S. pneumoniae* (n=22; 9.1%) • *S. Typhi* (n=17; 7%) • Yearly cumulative incidences per 1,000 was 46.6 cases per 1,000 (CI 40.9-52.2) • Wasting was positively associated with bacteraemia and systemic non-typhoidal Salmonellae infection **NON-SUSCEPTIBILTY:** • ***Salmonella Typhi:*** 65% multidrug resistant; yet	B (Systematic patient recruitment although ~10% had missing data and were excluded. Relatively large sample size; prospective study design).

								erythromycin/azithromycin, co-trimoxazole, ciprofloxacin, gentamicin, tetracycline and chloramphenicol was tested using the Kirby-Bauer disc diffusion method. Multi-drug resistance of Salmonella enterica was defined as simultaneous resistance to amoxicillin, co-trimoxazole and chloramphenicol. S. enterica were screened for resistance to fluoroquinolones (FQ) by nalidixic acid disc diffusion following the CLSI guidelines. Nalidixic acid resistant strains were further tested by ciprofloxacin E test.	sensitive to Ciprofloxacin and Ceftriaxone (100% sensitivity) • **NTS**: 98% susceptible to Ciprofloxacin, 100% sensitive to Ceftriaxone; yet 77% of isolates were multi-drug resistant • ***Staphylococcus aureus***: 48% susceptible to penicillin; 83% to flucloxacillin; 54% to co-trimoxazole; 68% to ciprofloxacin; 71% to gentamicin; 35% to tetracycline; 6% to chloramphenicol • ***Strep pneumoniae***: 76% susceptible to penicillin; 77% to amoxicillin/ampicillin; 100% to cefuroxime, ceftriaxone and 5% to co-trimoxazole (Multi-drug resistance of *Salmonella enterica* was defined as simultaneous resistance to amoxicillin, co-trimoxazole and chloramphenicol)	
7	Mando-mando et al.[7]	2009; patients presenting 2001-2003.	Cohort	**Antimicrobial Susceptibility and Mechanisms of resistance to *Shigella* and *Salmonella* isolates from children under five years of age with diarrhea in rural Mozambique**	Tertiary; Community-acquired	Rural Mozambique	n=109 *Shigella* spp. isolates and n=49 *Salmonella spp*. isolates children <5 years who presented to the outpatient department with diarrhea. Number who attended (denominator) and number with bloody diarrhea not given;	PCR detection of genes encoding beta-lactamases associated in *Shigella* and *Salmonella* isolates presenting with full resistance.	• Very high levels of resistance in *Shigella* isolates to trimethoprim-sulfamethoxazole (84%), tetracycline (66%), ampicillin (56%) and chloramphenicol (52%) • *Salmonella* exhibited resistance to ampicillin (25%) and trimethoprim-sulfamethoxazole (18%), tetracycline (15%), and chloramphenicol (15%) Multi-drug resistance was detected within 65% of *Shigella* isolates and 23% of *Salmonella* isolates	C (Limitations in study design; no denominator identifying number of patients sampled or proportion presenting with bloody diarrhoea)
8	Phoba et al[8]	2014 patients presenting 2008-2012	Retro-spective cohort study	**Epidemic increase in Salmonella bloodstream infection in children, Bwamanda, the Democratic Republic of Congo**	Rural Tertiary; Community-acquired infections	Democratic Republic of Congo	Between 2008-2012; 3,311 children <5 years old were admitted, n=626 blood cultures were collected of which n=168 were positive	Children >28/7 with axillary temperature ≥ 38 °C or ≤ 35.5 °C, with suspected septic shock, or signs of invasive bacterial infection. BC samples were cultured via BacT and shipped to Kinshassa INRB, where they were incubated at 35 °C and checked daily for growth by visual inspection of the	The most common causes of **community-acquired** bacteraemia were (in order of frequency): -NTS -*Salmonella Typhi* -*Klebsiella* spp. -*Staphylococcus Aureus* -*Escherichia Coli* -Enterobacter **NON-SUSCEPTIBILTY:**	C (Retrospective study design; evidence of prior antibiotic use which biases towards non-susceptibility; infections not

							More than three-quarters (169 out of 216, 78.2 %) were on antibiotics ≤ 48 h prior to sampling (mostly ampicillin, chloramphenicol or TMP-SMX), but yield of CSO in this group did not significantly differ from those who were not on antibiotics (70 out of 169 [41.4 %] versus 18/47 [38.3 %] respectively	chromogenic growth indicator at the bottom of the vials. Skin or environmental bacteria were categorised as contaminants; the other bacteria were considered as clinically significant organisms (CSO). Isolates were further identified to the species level using standard biochemical methods.	• 72.2% of *Salmonella typhi* were co-resistant to ampicililn and co-trimoxazole; with 33% of these showing additional resistance to chloramphenicol (Classified as MDR) • NTS: 95% MDR (resistant to ampicillin, chloramphenicol and co-trimoxazole) • 96.7% of NTS isolates were MDR	delineated as CA vs HA; referral pathways unclear)
9	Ndir et al.[9]	2016; patients admitted 2012-2013	Case Control	**Epidemiology and Burden of Bloodstream Infections caused by Extended-Spectrum Beta-Lactamase Producing *Enterobacteriaceae* in a Paediatric Hospital in Senegal**	Urban tertiary setting; Both community- and hospital-acquired infections	Senegal	Ages 0-16yrs; n=1,800 suspected patients with bloodstream infections yielded n=84 cases of patients with ESBL-E positive infections and n=26 ESBL negative *Enterobacteriaceae* infections	Blood samples were drawn from all inpatients with suspected bloodstream infections (n=1,800) and considered hospital acquired if this occurred 48h after admission (72h for neonates). The BSI were defined as ESBL-positive when the blood sample yielded ESBL-producing *Enterobacteriaceae* and ESBL-negative when the strain was *Enterobacteriaceae* susceptible to beta-lactams; identified with API 20E strips and double disc diffusion method using antibiotic discs of cefepime, cefotaxime and ceftazidime	• The overall incidence rate of **hospital-acquired**-BSI caused by ESBL-E strains was 1.52 cases/1,000 patient-days (95% CI 1.2-5.6) • ESBLs were produced by 88% of *Enterobacteriaceae*. isolates, 82% of *Klebsiella* spp. isolates and 58.3% of *E Coli* isolates • Patients with ESBL-positive BSI were significantly younger than patients with ESBL-negative BSI (2.5 yrs vs 4.4 yrs, p=0.021) and were more likely to suffer from sickle cell disease (33.3% vs 11.5%, p=0.044) and be malnourished (38.1% vs 15.4%, p=0.034) • Initial antibiotic therapy (with a third generation cephalosporin in 90% of cases) was inadequate to treat 79.1% of BSI infections (n=87) • 50 patients with a BSI caused by *Enterobacteriaceae* died during the study period (45.5%). The case fatality rate was significantly higher in ESBL-positive patients (54.8%) than in ESBL-negative patients (15.4%, p<0.001). • Rates of ESBL (at 1.52 cases/1,000 patient days) were much higher than recently documented in developed	C (Retrospective study design – case-case-control nested in a cohort; however systematic patient recruitment; prior antibiotic use evident which biases towards increased non-susceptibility)

									world settings, such as France (0.054/1,000 patient days in 2012) • This raises the question as to the choice of third generation cephalosporins as systemic empirical treatment, which is inadequate to treat ESBL-positive BSIs	
10	Gray et al.[10]	2007; patients presenting 2004-2005.	Case Series	**Invasive *Group B Streptococcal* Infection in Infants, Malawi**	Urban tertiary centre; Hospital- v's community-acquired not clearly specified	Blantyre District, Malawi	0-90 days; n=57 neonates with blood and CSF cultures isolating *Group B Streptococcus*	Disc diffusion antimicrobial susceptibility testing performed in accordance with the British Society for Antimicrobial Chemotherapy Guidelines on *Isosensitest* agar; in a laboratory enrolled in the UK National External Quality Assessment Service for Microbiology	Of neonates presenting with invasive group B *Streptococcus* infection, cultures exhibited: • 100% sensitivity to penicillin • 100% sensitivitity to ceftriaxone • 81% sensitivity to chloramphenicol • 79% sensitivity to erythromycin • 4% sensitivity to tetracycline	C (Prospective case series yet external quality control of laboratory; noted issues in clarifying numerator and denominator)

11	Talbert et al.[11]	2010; patients admitted 2001-2009	Case Series	**Invasive bacterial infections in neonates and young infants born outside hospital admitted to a rural hospital in Kenya.**	Rural tertiary centre; Both community- and hospital-acquired (neonates born in hospital and at home)	Kilifi District, Kenya	0-60 days; n=4,849 blood cultures (systematic, all outborn admissions) and 2,140 CSF cultures	Antibiotic sensitivity was assessed using British Society for Antimicrobial Chemotherapy methods; with external quality monitoring via the UK National External Quality Assessment Service.	Non-susceptibility of *Acinetobacter* spp. (with 95% CI) were: • Penicillin/Ampicillin: 56% (42-70) • Gentamicin 27% (14-39) • Ceftriaxone 35% (22-48) Non-susceptibility of *Klebsiella Pneumoniae* were: • Penicillin/Ampicillin: 96% (91-100) • Gentamicin 49% (35-63) • Ceftriaxone 43% (29-57) Non-susceptibility of *E. Coli* were: • Penicillin/Ampicillin: 78 %(65-91) • Gentamicin 10% (1-19) • Ceftriaxone 17% (5-29) There was a reduction in the sensitivity of isolates to ampicillin/gentamicin (WHO Guidelines) over the study period from 88% susceptibility in 2001 to 66% susceptibility in 2009 ($p<0.001$)	C (Case series of prospectively collected data on a large number of systematically collected participants over prolonged study period; internal and external quality control of laboratory procedures)

12	Nantanda et al.[12]	2008 Patients presenting 2005-2006	Cohort;	**Bacterial aetiology and outcome in children with severe pneumonia in Uganda.**	Urban Tertiary; Community-acquired infections only	Uganda	n=157 children 2-59 months with clinically severe pneumonia; of which n=25 (15.9%) had positive blood cultures and n=79 had positive sputum cultures	157 children aged 2-59 months with symptoms of severe pneumonia (according to WHO guidelines) were recruited over a 4-month period in 2005-2006. Blood and induced sputum were obtained for culture after premedication with Salbutamol and hypertonic saline. Culture and sensitivity for blood and sputum was via manual disk diffusion methods after inoculation on agar plates and incubation for >24/24.	• The mortality rate was 15.3% (n=24) • The most common organisms causing clinically severe pneumonia were: *Strep Pneumoniae* (46%), *Staphylococcus Aureus* (36%), *Haemophilus Influenzae* (24%) and *Klebsiella* species (22%). • ***Staphylococcus Aureus*** was positive on 36% of blood cultures and was positively associated with severe malnutrition. SENSITIVITY PATTERNS: o Erythromycin: 77% o Chloramphenicol (1st line therapy in the unit): 33% o Gentamicin: 66% • ***Streptococcal Pneumoniae*** SENSITIVITY PATTERNS: o Chloramphenicol: 87% o Erythromycin: fully sensitive o Ampicillin: 94% • ***Haemophilus Influenzae*** isolates were completely resistant to Ampicillin and Chloramphenicol • ***Klebsiella*** spp. SENSITIVITY PATTERNS: o Ampicillin: 0% o Chloramphenicol: 40% o Ceftriaxone: 100% o Gentamicin: 50% • ***Escherichia Coli*** **SENSITIVITY PATTERNS** o Chloramphenicol: 10% o Erythromycin: 75% o Ceftriaxone: 100%	C (Prospective study design, patients systematically recruited yet small sample size, analysed CA infections)
13	Dramowski et al.[13]	2015; patients presenting 2008-2013	Case Series	Trends in Paediatric Bloodstream Infections at a South African referral hospital	Urban tertiary; Both hospital (defined as >72 hours) - and community-	Cape Town, South Africa	0-14 years; n=17,001 cultures of which n=935 were positive and n=864 corresponded with n=864 episodes of bacteraemia. Blood cultures were	Bactec / BacT/Alert system utilized to analyse paediatric blood culture bottles; with susceptibility testing performed with the automated Vitek II system using CLSI breakpoints. (935 culture-positive specimens yielded 979 pathogens)	• 94.7% of blood stream infections were monomicrobial and 5% were polymicrobial (2-3 pathogens) • The median age of affected patients was 7.5 months • Blood culture contamination rates were high (6.6%), most	C (Retrospective review of patients presenting over extended [5 year] period; yet

					acquired infections (analysed separately)		obtained from all children with suspected sepsis or severe infection with a focal site.		commonly with *coagulase negative staphylococci* • Nearly half of all infectious were hospital-acquired (46.8%; classified as positive >72 hours post hospitalization) • Gram-negative organisms predominated (60%) followed by Gram-positives (32.4%) and fungi (7.4%) • The most common organisms were *Klebsiella* (17%), *Staphylococcus Aureus (14%)* and *Escherichia coli (11%)* • Overall mortality for blood stream infections was 20.4% (176/864); patients with HA BSI experienced **higher mortality than CA BSI** (25% [101/404] vs 16.3% [75/460]; p=0.002) • *Acinetobacter* spp. were associated with the highest BSI mortality • No carbapenem resistant *Enterobacteriaceae* (CRE) or Vancomycin-resistant *Enterococci* (VRE) were isolated • Overall, the prevalence of antimicrobial resistance was much higher in hospital-acquired infections (65.8%) than community acquired isolates (25%) p<0.0001. This was an overall figure based on a subset of four pathogens: **MRSA, multi-drug resistant *Acinetobacter baumannii* and ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae*.** • There was not a significant increase in antimicrobial resistance between 2008 and 2013 • <u>ESBL Resistance Rates:</u> -*Klebsiella*: CA: 75.7%; HA 78.3% (p=0.82) -*Escherichia coli*: CA:11.7%; HA 21.7% (p=0.3) • 78% of *Acinetobacter Baumannii* samples were multi-drug resistant	large sample size; CA vs HA clearly delineated; ICU vs ward-based patient population analysed)

									• 44% of *Staphylococcus Aureus* samples were methicillin resistant	
14	Mhada et al.[14]	2012; patients admitted between 2009-2010	Case Series	**Neonatal sepsis at Muhimbili National Hospital, Dar es Salaam, Tanzania: Aetiology, Antimicrobial sensitivity pattern and clinical outcome**	Urban tertiary centre; Did not clearly specify hospital- v's community-acquired patient population (or location of neonatal birth)	Dar es Salaam, Tanzania	0-30 days; n=330 neonates admitted with a clinical diagnosis of sepsis; of which 302 had a culture proven bacterial infection (228 isolates from swabs, 5 isolates from blood, and 69 isolates positive from both swabs and blood; resulting in a total positive blood culture proportion of n=74). Swabs included those taken from cord stump (66.6%) and skin pustules (33.3%).	Culture positive infection of which 69% were bacteria isolated from swabs (umbilical cord stump and skin pustules), 1.5% from blood and 20.9% from both swabs and blood. Details as to antimicrobial susceptibility testing was not provided.	Resistance patterns of *Klebsiella* spp. (based on blood culture isolates): • Penicillin/Ampicillin 100% • Gentamicin 77% (57-90) • Ceftriaxone 18% (7-39) Resistance patterns for *Escherichia Coli* (based on blood culture isolates): • Penicillin/ampicillin 93% (69-99) • Gentamicin: 43% (1-19) • Ceftriaxone 14% (4-40) Resistance patterns for *Staphylococcus Aureus*: • Cloxacillin 81.5% (blood culture); 80.3% (skin swab) • Ampicillin 85% (blood); 88% (swab) Only single cases of *Group B Streptococcus* and *Pseudomonas* infections were found; these data were not included due to sample size	D (Case series which did not delineate HA vs CA infections in data analysis; location of birth unknown; details as to antimicrobial susceptibility testing not provided)

15	Marais et al.[15]	2009; samples collected 2005-2006	Case series	**Antimicrobial susceptibility of methicillin-resistant *Staphylococcus Aureus* isolates from South Africa**	Laboratory-based study (did not present clinical cases)	South Africa	<18yrs; n=248 samples of laboratory-confirmed *mec*A-positive MRSA isolates (142 from NHLS laboratories, 106 from private laboratories; 236 samples had complete data available for specimen source).	23 National Health Laboratory Services and Private Diagnostic Laboratories from 9 provinces in South Africa collected consecutive MRSA isolates, identified by genomic DNA for PCR using the 'rapid lysis' procedure to identify the *mecA* gene. Antibiotic susceptibility was performed using the Kirby-Bauer disc diffusion method according to CLSI guidelines.	Non-susceptibility for *Staphylococcus aureus* to: • Nitrofurantoin (38%) • Gentamicin (85%) • Clindamycin (21%) • Erythromycin (58%) were found. • Non-susceptibility was higher in NHLS laboratories than private laboratories	D (Laboratory-based study which did not correlate with clinical outcomes; multitude of clinical settings investigated relationship between private vs public systems yet CA vs HA and rural vs urban settings not identified)
16	Kayange et al.[16]	2010; Neonates admitted in 2009	Cross-Sectional	**Predictors of positive blood culture and deaths among neonates with suspected neonatal sepsis in a tertiary hospital, Mwanza- Tanzania**	Urban Tertiary; Did not specify community-v's hospital-acquired infections	Tanzania	n=300 neonates admitted with clinical sepsis; of which n=57 and n=92 had positive blood cultures due to early and late onset sepsis (respectively).	Blood cultures were inoculated agar and incubated for 7 days or until positive. Antimicrobial susceptibility of isolates was determined by disk diffusion methods according to the CLSI. Isolates were screened for ESBL production using MacConkey agar with 30ug/ml Cefotaxime and confirmed using disc approximation methods.	• Gram-negative bacteria were more frequently isolated than gram positive bacteria (n=91; 61.1%) • Gram-negative sepsis had higher mortality than gram positive sepsis (36.3% case fatality vs 19% case fatality ; p<0.0001), with increased mortality seen in ESBL (52% case fatality vs 25% case fatality , p=0.008) and MRSA isolates (55% vs 21% case fatality , p=0.008) • The most common isolates were *Klebsiella pneumoniae*, *Staphylococcus aureus* and Escherichia coli. • Most *Klebsiella pneumoniae* and *Escherichia coli* were resistant to ampicillin and gentamicin: • ***Klebsiella***: Ampicillin resistance 100%; Gentamicin resistance 67%; Ceftriaxone resistance 50%; Cefotaxime 49%; Ceftazidime 49%; Ciprofloxacin 8% • ***Escherichia Coli*****:** Ampicillin resistance 100%; gentamicin	D (Prospective cross-sectional study; systematic patient recruitment yet small sample size; EOS vs LOS and location of delivery taken into account in analysis yet CA vs HA infections not specified)

									resistance 68%; Ceftriaxone resistance 50%; Cefotaxime 50%; Ceftazidime 50%; Ciprofloxacin 4.5% • The majority of *Klebsiella* spp. and *Escherichia coli* species were ESBL producers (49% and 50% respectively) • The majority of Gram-negative isolates were sensitive to ciprofloxacin and meropenem • Among 32 ***Staphylococcus aureus*** isolates, 9 (28%) were found to be **Methicillin Resistant Staphylococcus aureus (MRSA**) (i.e resistant to oxacillin and cefoxitin) Penicillin resistance 90%; Erythromycin resistance 66%; Clindamycin resistance 44%; Cloxacillin resistance 28%; Bactrim resistance: 60%; Ciprofloxacin resistance 14%	

17	Roca et al.[17]	2009; patients presenting 2006-2007	Cohort	**Surveillance of Acute Bacterial Meningitis among Children Admitted to a District Hospital in Rural Mozambique**	Rural Tertiary; Community-acquired infections only	Maputo, Mozam-bique	n=642 children aged 0-15 years with suspected meningitis, of whom n=43 (7%) had positive CSF cultures.	CSF analysis using two sterile tubes to assess CSF glucose, Gram staining, bacterial culture, cell count, protein measurement and latex agglutination for detection of pneumococcus; Hib; meningococcus A, B, C, and W135; and streptococcus B antigens. Blood samples were cultured using an automated blood culture system (Bactec 9050; Becton Dickinson) while the CSF samples were cultured using manual (conventional) methods) and bacterial isolates were identified by colony morphologic analysis and growth requirements. Antibiotic susceptibility testing was performed by disk diffusion or E test	• The most common causes of bacterial meningitis were *Haemophilus Influenzae* Type B (n=14); *Pneumococcus* (n=9); *Meningococcus* (n=7) • All 9 pneumococci isolates were susceptible to chloramphenicol, and 8 were susceptible to penicillin (1 had intermediate resistance) • Of the 10 HiB isolates tested, only 1 was susceptible to chloramphenicol (90% resistance); and 5 were susceptible to ampicillin (50% resistance) • *Neisseria meningitidis* exhibited 50% resistance to Ampicillin and 90% resistance to Chloramphenicol	D (Systematic collection of LPs on all children presenting with defined symptoms of meningitis; yet large proportion had concurrent malaria parasitaemia; HIV status of children unclear; data collated over a short period which may affect variations of disease occurrence for specific pathogens)

18	Nwadioha et al.[18]	2011; patients presenting 2006-2008	Retrospective blood culture analysis (laboratory-based)	**Bacterial isolates in blood cultures of children with suspected septicaemia in urban Kano: a two-year study.**	Tertiary; Did not specify community- vs hospital acquired infections	Nigeria	n=3840 blood cultures were collected in children presenting with clinical signs of sepsis, of which n=700 were positive	Blood culture samples were incubated for 7 days on MacConkey, blood and chocolate agar media. Organisms were isolated by conventional methods. Antibiotic susceptibility tests were done against locally available antibiotics by using disk diffusion method in accordance with the NCCLS / CLSI criteria.	• Out of a total of 3840 blood culture samples, only 18.2% (n=700) were culture positive. • Gram-negative and Gram-positive bacteria constituted 69.3% (n=2661) and 30.7% (n=1179) respectively. • The most prevalent bacterial isolates were ***Escherichia coli*** with 44.3% (n=310/700) and ***Staphylococcus aureus*** 30.7% (n=215/700). • *Escherichia coli* were sensitive to ceftriaxone ***Escherichia coli* SENSITIVITY:** o Ampicillin 50%, o Gentamicin 80%, o Ceftriaxone 90% ***Klebsiella* spp. NON-SUSCEPTIBILITY:** • Ampicillin 45% • Gentamicin 49%	D (Retrospective design; CA vs HA not delineated; laboratory based data not lined to clinical outcome)

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