Pathogens Associated With Sepsis in Newborns and Young Infants in Developing Countries

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Introduction: Knowledge of pathogens causing infections in young infants (up to 90 days of life) is essential for devising community-based management strategies. Most etiological data from developing countries are hospital-based and may have little relevance to communities in which most babies are born at home.

Methods: We searched the literature for studies from developing countries reporting etiology of community-acquired infections (sepsis, pneumonia, meningitis) published since 1980. Hospital-based studies reporting early onset sepsis, sepsis among babies admitted from, or born at home were included.

Results: Of 63 studies, 13 focused on community-acquired infections, but limited data were available from home-born neonates. In the first week of life (3209 isolates), *Klebsiella* species (25%), *Escherichia coli* (15%), and *Staphylococcus aureus* (18%) were major pathogens. Group B streptococci (GBS) were relatively uncommon (7%), although regional differences existed. After the first week of life (835 isolates), *S. aureus* (14%), GBS (12%), *Streptococcus pneumoniae* (12%), and nontyphoidal *Salmonella* species (13%) were most frequent. *S. pneumoniae* (27%) was most common in the postneonatal period (among 141 isolates). Gram-negatives predominated (77%) among home-delivered babies (among 170 isolates).

Conclusions: Limited information is available on etiology of serious bacterial infections in community settings. Hospital-based studies suggest that most infections in the first week of life are due to Gram-negative pathogens, and many may be environmentally rather than maternally-acquired, owing to unhygienic delivery practices. Such practices may also explain the predominance of Gram-negative infections among home-born infants, although data from home settings are limited. These findings have implications for developing prevention and management strategies in communities and hospitals.

Key Words: neonatal infections, etiology, pathogens, community, developing country

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Neonatal sepsis is classified as "early onset" if it occurs within the first week of life and as "late onset" if occurring after the first week until the end of the neonatal period.[1] Early onset sepsis is conventionally regarded as maternally-acquired, with causative organisms, such as *Escherichia coli* and Group B *Streptococcus* (GBS) usually found in the maternal genital tract, whereas late onset sepsis is considered environmental in origin–either hospital or community acquired. Commonly implicated organisms in hospital acquired infections are coagulase-negative staphylococci, *Staphylococcus aureus*, and Gram-negative organisms such as *Klebsiella* and *Pseudomonas* species.[1,2]

In developing countries, the majority of babies are born at home, and hospital-based etiological data, which are the predominant source of information from these regions,[3] have little relevance to community settings, particularly for late onset sepsis. The reasons behind lack of etiological data from community settings are numerous and include the lack of laboratory and culture facilities in most primary and secondary health facilities and rural areas, as well as delays in, and reluctance of families to seek care—resulting in most babies succumbing to serious infections within their homes without coming to medical attention.[4]

Knowledge of the common etiological agents causing neonatal sepsis in these communities is critical to devising community-based strategies for managing serious infections. A brief review[5] of etiology of sepsis in young infants (with combined data for babies up to 90 days of life) draws attention to the limited data for community-acquired infections from middle and low income countries, presenting only 2 such reports.[6,7] In this more expansive review, we aim to synthesize data from published as well as selected unpublished studies from developing countries, to update what is known regarding the etiology of community-acquired late onset infections as well as maternally-acquired early onset infections in young infants, with a specific focus on the neonatal period.

METHODOLOGY

Searches of PubMed were conducted to identify studies published between 1980 and 2007 (date of last search May 7, 2007) using combinations of MeSH (Medical Subject Heading) and text words, including infant*, newborn*, neonat* and gram, spectrum, organisms, etiology, pathogens, infection*, bacter*, sepsis, septic*, meningitis, pneumonia, as well as communit*, home, hospital, unit, center. References were screened based on title, abstracts, and full-texts as required. All low- and middle-income countries as defined by the World Bank[8] were included. Abstracts of non-English language studies were included if sufficient information was available in English. The searches were supplemented by screening the author's collection, reference list of an earlier hospital-based review for early onset etiology,[3] as well as screening-related links of relevant articles.[9,10] Studies reporting viral, only nosocomial infections, or other infections such as tuberculosis, or congenital syphilis were excluded. Studies with erroneous or otherwise internally inconsistent data were also excluded.

Definitions Used and Methodological Considerations

We included studies of infants (0–90 days) with sepsis, meningitis, and pneumonia. Data for pathogens isolated from any sterile body site were included. The term neonatal sepsis includes all serious infections (bacteremia, pneumonia, meningitis) in the newborn. Very early onset sepsis was defined as sepsis occurring within the first 3 days of life, early onset sepsis as occurring within the first week, and late onset sepsis as that occurring after the first week of life until the end of the neonatal period (28 days of life). The 29- to

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90-day category refers to the postneonatal period. The 7- to 59-day period was included to correspond to the age categorization used by WHO in Integrated Management of Childhood Illness (IMCI) guidelines.[11] Hospital-based studies reporting etiology of early onset neonatal sepsis were included in this review, as these infections are usually considered maternally acquired due to exposure to genital flora.[1]

Coagulase negative *Staphylococcus* (CoNS) noted to be important in hospital-acquired infections were, for the purpose of this review on maternally-acquired and community-acquired infections, considered contaminants and excluded from all reports.

RESULTS

In all, 63 studies, including 1 unpublished community-based report (Zaidi AKM, 2007; unpublished data) were eligible for inclusion. Twenty-four studies were from South Asia, 22 from Africa, 7 from Middle East and Central Asia, 6 from East Asia and Pacific (including China), and 4 from Latin America and Caribbean. After excluding CoNS and other contaminants, the culture positivity rate, among 35 studies where this information was available, ranged from below 15%[7,9,10,12–14] to as high as 62%,[15] suggesting considerable variations in quality of data, inclusion criteria, microbiological capability, or some combination of the above. Some disparities in definitions used particularly for early onset sepsis were also noted among included studies (eg, studies defined the very early period as either within the first 2, or within the first 3 days of life, and early onset sepsis as occurring within day 0–6 or 0–7 days of life).

Twenty-eight studies[9,10,12,13,15–37] (Zaidi AKM, 2007; unpublished data) provided some information on community-acquired infections in young infants. Apart from 1 unpublished community-based report (Zaidi AKM, 2007; unpublished data), only 12 published studies attempted to focus on community-acquired infections: 2 from the same rural first level referral hospital in Kenya,[9,12] 1 from a rural referral hospital in Philippines,[10] 4 reports[24–27] of the multicenter Young Infant Study conducted in the 1990s (YIS),[7] and 5 facility-based studies from India, Pakistan, Nigeria, and Malawi.[22,28,32,33,36] Four additional facility-based reports provided disaggregated data for non-nosocomial infections.[21,31,34,35] The remaining facility-based reports included data from rural areas or had out-born or out-patient data. Table 1 provides details of the 28 studies, and specifies whether nosocomial infections were excluded, community-acquired criteria defined, and the rationale for inclusion in the community-acquired category if these definitions were not available. Because of the paucity of community-based data as well as inadequate reporting of methodological details, assumptions of community-acquired infections were made, if this was implied by the setting described. Thus, for a certain proportion of infections in this category, the possibility of inclusion of some nosocomial infections cannot be clearly ruled out.

Information on pathogens in specific age groups and in different settings is presented below.

Community-Acquired Infections in the Neonatal Period (0–28 Days)

Nineteen studies reported data for the entire neonatal period (Zaidi AKM, 2007; unpublished data) (Table 2).[10,12,15,17,19,21–28,31,34–37] A total of 2594 isolates were community-acquired or adjudged predominantly community-acquired (see Table 1 for rationale for studies adjudged to be community-acquired). Gram-negatives predominated in aggregated data (Gram-negative to Gram-positive ratio 1.6:1) and 3 organisms *S. aureus*, *E. coli*, and *Klebsiella* species caused nearly half (44%) of all infections. This pattern was repeated across East Asia and Pacific,[10,24,25,31] Middle East and Central Asia,[21,34,35] and South Asian regions[15,17,22,28] (Zaidi AKM, 2007; unpublished data), although certain differences were noted: *Pseudomonas* species were less frequent in the Middle Eastern and Central Asian region, and in South Asia fewer *S. aureus* and *E. coli*, and comparatively more *Klebsiella* species were isolated. GBS was infrequent in East Asia and Pacific regions. In the African region,[12,19,23,26,27,36,37] however, GBS, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*, in addition to *S. aureus* were most frequent, with an overall Gram-positive predominance. Also in contrast to other regions, the most frequent Gram-negative isolates in the African region were nontyphoidal *Salmonella* species.

Very Early Onset Sepsis

All 20 published studies[15,19,21,38–54] reporting 834 pathogens causing sepsis in the first 3 days of life were based in hospital settings (Table 3). *Klebsiella* species predominated, causing 26% of all infections. *S. aureus*, GBS, and *E. coli* were next most frequently isolated pathogens, causing 13% to 17% of infections. The ratio of Gram-negatives to Gram-positives was 1.4:1.

Early Onset Sepsis

Of 44 published facility-based studies[7,9,10,14,15,18,19,21,35–70] reporting etiology of sepsis in the first week of life (including studies reporting very early onset sepsis), only 4 attempted to focus on community-acquired infections (Table 3).[7,9,10,36] In addition, 1 unpublished report provided community-based data with a predominance of home-born babies (Zaidi AKM, 2007; unpublished data). A single pathogen, *Klebsiella*, accounted for 25% of all 3209 isolates. *S. aureus* and *E. coli* caused 15–18% of infections; 7% were caused by GBS, only half as common in this compared with the very early period. *Acinetobacter* and *Pseudomonas* (total 11.8%) increased slightly compared with the very early period. The overall Gram-negative to Gram-positive ratio was 2:1. In the regional disaggregation[9,10,14,15,18,19,21,24,35–70] (Zaidi AKM, 2007; unpublished data) (Fig. 1) of these data, however, certain differences are unmasked: Gram-positive organisms seems to be almost as frequent as Gram-negatives in African countries, and GBS seems to be very uncommon in the South Asian region. *Pseudomonas* and A*cinetobacter* are particularly common in East Asia and Pacific and South Asian regions and *S. aureus* appears less common in East Asia and Latin America compared with the other regions.

Community-Acquired Infections in the 7- to 59-Day Period

In the 7- to 59-day group, 11 studies[7,9,10,13,21,30,32,33,35,36] (Zaidi AKM, 2007; unpublished data) contributed 835 isolates (Table 3). Of these, 8 published studies[7,9,10,21,32,33,35,36] either used some criteria for excluding nosocomial infections or focused on community-acquired infections (Table 1). Nearly half of the isolates (48%) were contributed from a facility-based Malawian study[36] where most babies were admitted from home, and half of remaining isolates were from the YIS studies and a rural referral Kenyan facility.[7,9] Frequent isolates included *S. aureus*, *S. pneumoniae*, GBS, *S. pyogenes* (10%-14% each), nontyphoidal *Salmonella* species (13%), and *E. coli* (9%). Compared with the first week of life, the proportion of *Salmonella*, *Haemophilus influenzae*, *S. pneumoniae*, and *S. pyogenes* was higher, and *Klebsiella* species was much lower. The Gram-negative to Gram-positive ratio was 0.8:1.

Community-Acquired Infections in the 29- to 90-Day Period

In this group, 6 studies[7,10,12,29,32] (Zaidi AKM, 2007; unpublished data) contributed 141 isolates (Table 3). *S. pneumoniae* (27%), *S. pyogenes*, and *S. aureus* (11%-13% each) were most frequent, and *E. coli*, Haemophilus, and *Salmonella species* were reported in 8% to 9% of cases. Gram-negative to Gram-positive ratio was 0.8:1.

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TABLE 1. Table of Studies With Community-Acquired, Home Delivered or Rural Referral Hospital-Based Data

Author	Location	Hospital Type	Year of Study	Culture/Sub-Category	Early Onset Sepsis
Africa					
Adhikari et al[19]	Durban, South Africa	Neonatal unit and general pediatric wards	1988–1991	CSF	≤3 and ≤7 (n = 24)
Ghiorghis[20]	Addis Ababa, Ethiopia	Neonatal unit	1992–1993	Blood	
Campagne et al[23]	Niamey, Niger	Central laboratory registers	1981–1996	CSF	
Muhe et al[26]	Addis Ababa, Ethiopia	Primary and tertiary level	1991–1993	Blood†	
Mullholand et al[27]	The Gambia	Primary and referral	1990–1992	Blood/CSF	
Ayoola et al[32]	Ibadan, Nigeria	Emergency ward, referral	1998	Blood	
English et al[12]	Kilifi District, Kenya	Rural 1st referral level	1999–2001	Blood/CSF	Used Berkley et al
Adejuyigbe et al[33]	Ile-Ife, Nigeria	Outpatient center	2001	Blood	
Berkley et al[9]	Kilifi District, Kenya	Rural 1st referral level	1998–2002	Blood	<7 (n = 129)
Milledge et al[36]	Blantyre, Malawi	District referral	1996–2001	Blood/CSF	0–7 (n = 380)
Herbert et al[13]	Kilifi District, Kenya	Rural 1st referral level	2004–2005	CSF	
Ojukwu et al[37]	Abakaliki, Nigeria	SCBU, tertiary	2002–2003	Blood	0–6 (n = 20)
Middle East and Central Asia					
Greenberg et al[21]	Israel‡	Primary and tertiary	1986–1994	Blood/CSF	<24 h and 2–7 (n = 119)
Biyikli et al[34]	Istanbul, Turkey	University hospital	1999–2002	Urine	
Taskin et al[35]	Turkey	NICU		Blood†	"Early onset" (n = 22)
South Asia					
Chaturvedi et al[16]	Sevagram, India	NICU, Rural	1983–1987	Blood	
Mondal et al[17]	Pondicherry, India	Referral	1988–1989	Blood	
Rao et al[18]	Karnataka, India	NICU, Rural referral	1988–1991	Blood/CSF	≤7 (n = 99)
Das et al[22]	Pondicherry, India	Referral	1994–1995	Blood†	
Tallur et al[15]	Karnataka, India	NICU, Rural	1996–1997	Blood	<24 h and 2–7 (n = 127)
Fikree et al[28]	Karachi, Pakistan	Tertiary	1987–1998	Blood	
Sahai et al[29]	Pondicherry, India	Tertiary urban	1994–1996	CSF	
Zaidi AKM, 2007, unpublished data	Karachi, Pakistan	Community surveillance	2003–2007	Blood	0–6 (n = 25)
Latin America and Caribbean					
Weiss et al[30]	Campinas, Brazil	Health department surveillance for meningitis	1997–1998	CSF, blood, etc.	
East Asia and Pacific					
Gatachalian et al[24]	Manila, Philippines	Govt. community and referral	1991–1993	Blood/CSF	0–7 (in regional break-up) (n = 9)
Lehmann et al[25]	Papua New Guinea	Outpatient department	1991–1993	Blood	
Yu 2001 et al[31]	China	Neonatal ward	1987–1998	Blood, other§	
Quiambao et al[10]	Bohol, Philippines	Rural 1st referral level	1994–2000	Blood/CSF	0–6 (n = 12)
YIS combined data[7]	Multi-center, studies mentioned above	Presentation to facilities above	1991–1993	Blood/CSF	0–7 (n = 27)

(*Continued*)

*Some studies reporting etiology in under 2 month are included in this category.
†Only this specimen culture data used to avoid overlap.
‡Included low income population.
§Also includes local infections.
¶Explicit criteria were used to screen community-acquired infections.
n indicates sample size, excluding coagulase negative *Staphylococcus aureus*.

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TABLE 1. (*Continued*)

7–59 Days*	0–28 Days	Postneonatal	Nosocomial Infections Excluded?	If Not, Rationale for Inclusion	Other Data Available (0–28 days)
	Neonates in general pediatric wards (n = 37)		No	Setting suggests community-acquired	
					Clinic born (n = 7); home-born (n = 11)
	<1 mo (n = 101)		No	Type of infection suggests community-acquired	
	0–30 (n = 28)		Yes¶		
	0–30 (n = 29)		Yes¶		
1–2 mo (n = 5)		1–2 mo (n = 5)	Yes	Excluded all infants with prior (1 wk) antimicrobial therapy	
Used Berkley et al	0–30 (n = 65)	31–90 (n = 21)	Yes	Most (95%) from home	Rural referral (n = 65)
7–55 (n = 37)			Yes	Excluded all infants with prior antimicrobial therapy	
7–59 (n = 112)			Yes		
8–30 (n = 404)	0–30 (n = 784)		Yes	Most (>95%) from home (author provided information)	
<2 mo (n = 6)			No	Setting suggests community-acquired	
	0–28 (n = 14)		No	Out-born (8 of 14 were home or traditional birth attendant assisted deliveries)	
8–28 (n = 30)	0–28 (n = 149)		Yes (for 8 to 28 only)		
	0–30 (n = 45)		Yes		
"Late onset" (n = 40)	Neonates (n = 62)		Yes	Separated from nosocomial infections (definition not reported)	
					Rural referral (n = 798)
	Neonates (n = 13)		No	Out-born data used (was compared with in-born data)	
					Rural referral (n = 207)
	Neonates (n = 27)		Yes	Home-born data	Home-born (n = 27)
	0–28 (n = 55)		No	Out-born data. Setting suggests community-acquired	Rural referral (n = 148); home-born (out-born data used) (n = 55)
	Neonates (n = 223)		Yes		Home-born (n = 17)
		1–3 mo (n = 5)	No	Type of infection suggests community-acquired	
7–59 (n = 32)	0–28 (n = 47)	29–59 (n = 10)	Yes¶		Home-born (n = 34)
≤2 mo (n = 33)			No	Type of infection suggests community-acquired	
YIS combined data used	0–30 (n = 16)	YIS combined data used	Yes¶		
	0–30 (n = 19)		Yes¶		
	Neonates (n = 858)		Yes		
7–59 (n = 22)	0–29 (n = 22)	30–59 (n = 12)	Yes¶		Rural referral (n = 22), home-born (n = 26) (author provided additional data)
8–59 (n = 114)	Regional break-up used	30–90 (n = 88)	Yes¶		

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TABLE 2. Etiology of Community-Acquired Neonatal Sepsis (0–28 Day) in Developing Countries by Region

Organism Isolated	Africa		East Asia and Pacific		Middle East and Central Asia		South Asia		All Regions	
	N	%	N	%	N	%	N	%	N	%
Total	1058	100	915	100	256	100	365	100	2594	100
Staphylococcus aureus	112	10.59	146	15.96	51	19.92	36	9.86	345	13.30
Streptococcus pyogenes	71	6.71	8	0.87	2	0.78	3	0.82	84	3.24
Group B streptococci	161	15.22	2	0.22	20	7.81	26	7.12	209	8.06
Group D streptococci/*Enterococcus*	4	0.38			13	5.08	22	6.03	39	1.50
Group G streptococci	1	0.09	1	0.11					2	0.08
Streptococcus pneumoniae	129	12.19	4	0.44	7	2.73	7	1.92	147	5.67
Other *Streptococcus* species/unspecified	3	0.28	40	4.37	1	0.39	43	11.78	87	3.35
Other gram positives	72	6.81					2	0.55	74	2.85
All gram positives	553	52.27	201	21.97	94	36.72	139	38.08	987	38.05
Klebsiella species	82	7.75	134	14.64	49	19.14	85	23.29	350	13.49
Escherichia coli	94	8.88	237	25.9	68	26.56	44	12.05	443	17.08
Pseudomonas species	7	0.66	134	14.64	8	3.13	37	10.14	186	7.17
Enterobacter species	3	0.28	52	5.68	8	3.13	15	4.11	78	3.01
Serratia species			39	4.26	2	0.78			41	1.58
Proteus species	5	0.47			7	2.73	1	0.27	13	0.50
Salmonella species	118	11.15	4	0.44			2	0.55	124	4.78
Citrobacter species							4	1.10	4	0.15
Haemophilus influenzae	12	1.13	1	0.11	2	0.78	1	0.27	16	0.62
Nisseria meningitidis	11	1.04			3	1.17			14	0.54
Acinetobacter species			94	10.27	2	0.78	13	3.56	109	4.20
Other gram negatives	132	12.48	19	2.08	1	0.39	20	5.48	172	6.63
All gram negatives	464	43.86	714	78.03	150	58.59	222	60.82	1550	59.75
Other	41	3.88			12	4.69	4	1.10	57	2.20

TABLE 3. Etiology of Sepsis in Young Infants up to 90 Days of Age in Developing Countries by Age of Onset

Organism Isolated	≤3 Days of Life		≤7 Days of Life		7-59 Days of Life*		29-90 Days of Life†	
	N	%	N	%	N	%	N	%
Total	834	100	3209	100	835	100	141	100
Staphylococcus aureus	144	17.3	560	17.5	114	13.7	18	12.8
Streptococcus pyogenes	3	0.4	33	1	81	9.7	16	11.3
Group B streptococci	109	13.1	207	6.5	96	11.5		
Group D streptococci/*Enterococcus*	44	5.3	80	2.5	7	0.8	1	0.7
Group G streptococci			1	0.03	1	0.1		
Viridans streptococci	3	0.4	5	0.2	1	0.1	1	0.7
Streptococcus pneumoniae	9	1.1	49	1.5	103	12.3	38	27
Other *Streptococcus* species/unspecified	19	2.3	32	1.0	3	0.4	2	1.4
Listeria monocytogenes	4	0.5	5	0.2				
Other gram positives			69	2.2	27	3.2		
All gram positives	335	40.2	1041	32.4	433	51.8	76	53.9
Klebsiella species	220	26.4	813	25.3	47	5.6	6	4.3
Escherichia coli	105	12.6	490	15.3	78	9.3	13	9.2
Pseudomonas species	49	5.9	224	7.0	15	1.8	4	2.8
Enterobacter species	30	3.6	141	4.4	10	1.2	5	3.5
Serratia species	4	0.5	10	0.3	1	0.1	1	0.7
Proteus species	5	0.6	27	0.8	4	0.5	1	0.7
Salmonella species	6	0.7	37	1.2	111	13.3	11	7.8
Citrobacter species	3	0.4	43	1.3				
Moraxella species					2	0.2	2	1.4
Haemophilus influenzae	1	0.1	5	0.2	17	2.0	11	7.8
Nisseria meningitidis			1	0.03	5	0.6		
Acinetobacter species	18	2.2	153	4.8	15	1.8	4	2.8
Other gram negatives	37	4.4	167	5.2	63	7.5	3	2.1
All gram negatives	478	57.4	2111	65.8	368	43.9	61	43.1
Other	21	2.5	57	1.8	34	4.1	4	2.8

*Includes some data for infants under 2 months of age. Also includes studies reporting 8 to 28 and 29 to 59 days etiology.
†Includes infants 29 to 60 days of age.

Home Born, Rural Referral, and Maternity Hospital and Clinics

Six studies provided data or disaggregated data on request for home-born babies[10,15,20,22,28] (Zaidi AKM, 2007; unpublished data) (Table 4). Five studies were based in rural referral facilities[10,12,15,16,18] and 6 provided maternity hospital[41,42,49,50,71] and clinic-born data.[20] Gram-negative organisms were over 3 times as common as Gram-positives (3.3:1 among home births, 3.5:1 among

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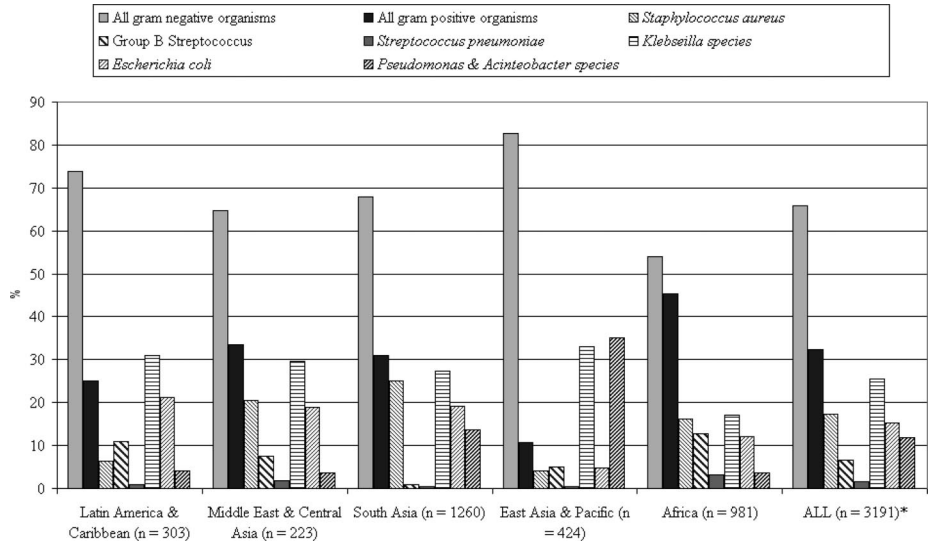


FIGURE 1. Regional variations in etiology of early onset sepsis (≤7 days) in developing countries.
*Sample size smaller than that in Table 3, as Young Infant Study's regional break-up was only available for 1 study from the East Asia and Pacific region.[24]

TABLE 4. Etiology of Neonatal Sepsis in Home Born, Maternity Hospitals, and Rural Referral Hospitals

	Home Delivered*		Maternity Hospital		Rural Referral	
	N	%	N	%	N	%
Total	170	100	1095	100	1240	100
Staphylococcus aureus	14	8.2	230	21	204	16.5
Streptococcus pyogenes	4	2.4	4	0.4	7	0.6
Group B streptococci	5	2.9	72	6.6	13	1
Group D streptococci/*Enterococcus*	6	3.5	13	1.2	6	0.5
Streptococcus pneumoniae	6	3.5	6	0.5	10	0.8
Other *Streptococcus* species/unspecified	3	1.8	3	0.3	35	2.8
Other gram positives	2	1.2	2	0.2		
Total gram positives	40	23.5	330	30.1	275	22.2
Klebsiella species	48	28.2	327	29.9	379	30.6
Escherichia coli	21	12.4	87	7.9	210	16.9
Pseudomonas species	20	11.8	54	4.9	207	16.7
Enterobacter species	11	6.5	82	7.5	8	0.6
Acinetobacter species	8	4.7	140	12.8	46	3.7
Serratia species			4	0.4		
Proteus species	2	1.2	8	0.7	14	1.1
Salmonella species	5	2.9	9	0.8	36	2.9
Citrobacter species	1	0.6			27	2.2
Moraxella species					2	0.2
Haemophilus influenzae	2	1.2	1	0.1	2	0.2
Nisseria meningitidis			1	0.1		
Other gram negatives	12	7.1	20	1.8	30	2.4
Total gram Negatives	130	76.5	733	66.9	961	77.5
Other			32	2.9	4	0.3

*Includes few babies 30 to 60 days of age, from Quiambao et al.[10]

rural referral hospitals) and twice as common among babies at maternity hospitals (2.2:1). Four organisms *E. coli*, *Klebsiella*, *Pseudomonas* species, and *S. aureus* accounted for as many as 61% to 81% of all infections in home-born babies, in maternity hospitals, and in rural referral hospitals.

CONCLUSIONS

The findings of this review suggest that *Klebsiella* species, *E. coli*, and *S. aureus* are major causes of infections the first week of life. However, data for the first week of life from community settings are particularly scarce, and the contribution of environmental factors in the causation of infection among hospital born babies cannot be excluded. Beyond the first week of life—although based on relatively few reports of community-acquired infections—*E. coli*, GBS, and *S. aureus*, as well as *S. pneumoniae*, *S. pyogenes*, and *Salmonella* species are commonly isolated.

As underscored in a recent review of hospital-associated infections in newborns,[3] although early onset sepsis is commonly considered maternally-acquired, the overwhelming majority of Gram-negative organisms, such as *Klebsiella*, *Pseudomonas*, and

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Acinetobacter and the frequency of *S. aureus* isolated in the first week of life among the studies reviewed, suggests that these infections may in fact be acquired from the hospital or community environment due to poor hygienic practices during delivery and postnatal care, rather than reflecting vertical transmission to the infant from exposure to vaginal tract flora. This has important implications for treatment and prevention of early onset neonatal infections. Lack of hygiene during and after delivery, poor cord care, and unhygienic newborn care practices in hospitals are major factors in acquisition of these infections in both hospital and community settings.[3,72–75]

A similar preponderance of Gram-negative organisms and *S. aureus* is also noted in home-delivered babies, although data again were extremely limited. From the WHO-sponsored YIS study from Philippines, the authors[24] also note a predominance of Gram-negatives among home-delivered babies (76% of 21 babies), although the etiological break up was not presented.

Although GBS–relative to other organisms and relative to data from industrialized countries[2,4]–were not as frequently reported, particularly in the first week of life, they appear common in African countries and very uncommon in the South Asian region. However, intercountry variations are also apparent, with some South Asian reports suggesting higher prevalence of GBS[28,45,76] and some African reports the converse, or even no GBS isolates.[14,20,26,38,51,52,59,77] The reasons for such inter-regional variations are not clearly understood, and variations in risk factors such as vaginal colonization, strain virulence, antibody levels, or cultural practices are thought to contribute.[4]

Among pathogens in the 7- to 59-day period, only a limited number of facility-based studies clearly attempted to exclude hospital-acquired infections. These data were dominated by a single Malawian study,[36] and more than half of remaining data were from multicenter Young Infant Studies (YIS) and rural Kenya.[7,9] Data from YIS indicated that *S. pneumoniae*, *S. aureus*, *E. coli*, *S. pyogenes*, and nontyphoidal *Salmonella* species were important pathogens beyond the first week of life, whereas in Kenya and Malawi, in addition to above pathogens, GBS were also common. The spectrum in the late onset age group can, in general, be considered a transitional phase between neonatal and postneonatal periods–where organisms associated with neonatal sepsis (*S. aureus*, *E. coli*, GBS), as well as those associated with postneonatal sepsis (*S. pyogenes*, *S. pneumoniae*), are equally important. It is worth noting that published information on community-acquired sepsis in the late neonatal and postneonatal period from South Asia is strikingly absent, although this region contributes very heavily to the global burden of neonatal and child mortality.

Gram-positive pathogens played a major role in etiology of sepsis in the postneonatal and early infant period, and *S. pneumoniae* emerged as the single most important pathogen in this age group. Other important pathogens in this group included *Salmonella* species and *Haemophilus influenzae*. *H. influenzae* are almost certainly under-estimated, especially in South Asia because of inadequate bacteriological laboratory resources to isolate this fastidious pathogen, and frequent use of antibiotics by children before submitting specimens for culture. Indeed, *S. pneumoniae*, *H. Influenzae*, and *Salmonella* are frequently reported in etiology of pneumonia, meningitis, and septicemia in children under 5 years of age from African and South Asian countries, and from other regions, especially when nonculture methods such as antigen detection are used.[29,78–86] However, the postneonatal and early infant groups are often excluded or not disaggregated from infant age groups. All of these factors contribute to the paucity of data available in this age group category.

In conclusion, there is very limited information regarding etiology of community-acquired young infant sepsis from developing countries. Data from community-based studies were extremely limited. Because the bulk of available data are from home-born babies who are brought to first-level facilities, or outpatient or emergency departments of referral hospitals, the etiological spectra could possibly differ from babies who succumb to infection within their homes and never reach medical facilities. However, given the challenges and cost considerations of conducting etiological studies in community settings that can provide better evidence in the near term,[84,87,88] these data do provide valuable insights that should be helpful in devising antibiotic regimens for use in evaluating case management strategies for serious infection in young infants in out-patient or home settings in developing countries.

Future research should focus on defining etiology of serious infections and sepsis-like illnesses in young infants in areas of high neonatal mortality using explicitly defined criteria for community-acquired infections and state-of-the-art microbiologic diagnostic methods.

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