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Review

Incidence and aetiology of bacterial meningitis among children aged 1–59 months in South Asia: systematic review and meta-analysis

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ABSTRACT

Background: Bacterial meningitis is a significant cause of morbidity and mortality worldwide among children aged 1–59 months. We aimed to describe its burden in South Asia, focusing on vaccine-preventable aetiologies.

Methods: We searched five databases for studies published from January 1, 1990, to April 25, 2017. We estimated incidence and aetiology-specific proportions using random-effects meta-analysis. In secondary analyses, we described vaccine impact and pneumococcal meningitis serotypes.

Results: We included 48 articles cumulatively reporting 20,707 cases from 1987 to 2013. Mean annual incidence was 105 (95% confidence interval [CI], 53–173) cases per 100,000 children. On average, *Haemophilus influenzae* type b (Hib) accounted for 13% (95% CI, 8–19%) of cases, pneumococcus for 10% (95% CI, 6–15%), and meningococcus for 1% (95% CI, 0–2%). These meta-analyses had substantial between-study heterogeneity ($I^2 > 78\%$, $P < 0.0001$). Among studies reporting only confirmed cases, these three bacteria caused a median of 78% cases (IQR, 50–87%). Hib meningitis incidence declined by 72–83% at sentinel hospitals in Pakistan and Bangladesh, respectively, within two years of implementing nationwide vaccination. On average, PCV10 covered 49% (95% CI, 39–58%), PCV13 covered 51% (95% CI, 40–61%), and PPSV23 covered 74% (95% CI, 67–80%) of pneumococcal meningitis serotypes. Lower PCV10 and PCV13 serotype coverage in Bangladesh was associated with higher prevalence of serotype 2, compared to India and Pakistan.

Conclusions: South Asia has relatively high incidence of bacterial meningitis among children aged 1–59 months, with vaccine-preventable bacteria causing a substantial proportion. These estimates are likely underestimates due to multiple epidemiological and microbiological factors. Further research on vaccine impact and distribution of pneumococcal serotypes will inform vaccine policymaking and implementation.

Contents

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1. Introduction

Bacterial meningitis a significant cause of death among children aged 1–59 months, with an estimated 115,000 deaths worldwide in 2015 [1]. Disease burden is high in South Asia, with over 21,000 deaths in 2015 in India alone [1]. Among survivors, up to half have permanent neuropsychological sequelae such as hearing loss or developmental delay [2].

Three bacteria account for most cases in infants and young children: *Haemophilus influenzae* type b (Hib), *Streptococcus pneumoniae* (pneumococcus), and *Neisseria meningitidis* (meningococcus) [3,4]. Although safe and effective vaccines have existed for years [5], vaccination rates remain suboptimal in South Asia [6–10]. Yet the impact of vaccine implementation has been substantial among low- and middle-income countries (LMICs) that have achieved high levels of coverage [11–15].

South Asian countries have only recently incorporated conjugate Hib and pneumococcal vaccines into their immunisation programs. All countries have introduced the pentavalent conjugate Hib vaccine, with routine nationwide vaccination first implemented by Sri Lanka in 2008 [16], and most recently by India (which completed its phased introduction in September 2016); Bangladesh, Bhutan, Nepal and Pakistan implemented the pentavalent vaccine in the interim [17]. For pneumococcus, only three countries in the region have implemented a protein-conjugate vaccine (PCV10)—Pakistan (2012), Nepal (2015), and Bangladesh (2015) [17]; India began rolling out PCV13 in May 2017 [18]. No country in the region has incorporated any meningococcal vaccine into their routine immunisation programs [17,19].

Since robust nation- or region-wide routine surveillance systems for bacterial meningitis do not exist in South Asia, we aimed to synthesise evidence within the published literature on the incidence and aetiology of bacterial meningitis among children aged 1–59 months in the region. Synthesising data on disease burden and vaccine impact may identify areas for future research and guide vaccine policymaking and implementation in South Asia.

2. Methods

2.1. Search strategy and study selection

We searched five databases (Embase®, Global Health®, Medline®, Scopus®, and Web of Science®) without language restrictions for studies published between January 1, 1990, and April 25, 2017, that described the incidence or aetiology of bacterial meningitis among children aged 1–59 months in South Asia, defined as Bangladesh, Bhutan, India, Nepal, Pakistan, and Sri Lanka (see supplementary appendix for search strategy). Two authors (MA and BC) independently screened titles, abstracts, and full-text articles, excluding duplicates and studies that did not report original data, did not pertain to bacterial meningitis, did not include children aged 1–59 months (or a subset of this age range), only included neonates (<1 month), did not include cases diagnosed in South Asia, or did not report data necessary to calculate incidence or aetiology-specific proportions. Discrepancies were resolved by consensus with the senior author (SKM). We identified additional papers by reviewing bibliographies of included articles and corresponding with study investigators, as per Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The study was pre-registered on PROSPERO international register of systematic reviews (CRD42016029278).

2.2. Data extraction and study quality

Two authors (MA and BC) independently abstracted data regarding study design, demographics, case definition, diagnostic methods, and pertinent vaccine use. Data on total number of cases per case definition, by aetiology, and incidence data were also abstracted. If incidence was not reported, we abstracted data on catchment population size as defined by the study. We contacted study authors to request any supplemental data not reported in the published papers.

Without standardised scales to evaluate quality of surveillance studies, we appraised studies on three criteria—(1) prospective design, (2) use of a pre-specified case definition, and (3) involved community-based case ascertainment (versus exclusively hospital-based).

2.3. Case definitions

We used the WHO case definitions for surveillance of bacterial meningitis, which specifies three types of cases: suspected, probable, and confirmed (Box 1). Suspected cases are diagnosed using clinical signs and symptoms. Probable cases are usually suspected

Suspected	Acute fever (>38.0 °C axillary or >38.5 °C rectal) and at least one of: • Neck stiffness • Altered consciousness • Other meningeal sign
Probable	A suspected case with CSF exam showing at least one of: • Turbid ("cloudy") appearance • Leukocytosis (WBC count >100/mm^3) • Leukocytosis (WBC count ≥10/mm^3) with either elevated protein (>100 mg/dl) or decreased glucose (<40 mg/dl)
Confirmed	Identification of pathogenic bacteria in CSF or blood by culture, Gram staining, or antigen detection, in child with clinical syndrome consistent with bacterial meningitis

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cases with biochemical evidence of bacterial meningitis, such as cerebrospinal fluid (CSF) examination. Confirmed cases are those in which pathogenic bacteria are detected [20].

For studies reporting multiple case definitions, we used the probable case definition for estimation of incidence or aetiology-specific proportions. The suspected case definition does not reliably delineate bacterial meningitis from viral, mycobacterial, fungal, and non-infectious causes of central nervous system inflammation [20,21]. Conversely, the confirmed case definition depends on the proportion of suspected cases with CSF samples tested and the number of testing modalities with which bacteria are detected (e.g., Grain stain/culture, antigen-based testing, molecular methods). Thus, we argue that the probable case definition most closely approximates the true number of bacterial meningitis cases because it combines the higher sensitivity of the suspected case definition with reasonable specificity by incorporating laboratory evidence of bacterial infection.

However, we also included studies that did not report probable cases and reported only suspected and/or confirmed cases. For studies reporting both suspected and confirmed cases, we used the case definition that provided the more conservative estimate—confirmed cases to achieve a smaller numerator of cases (i.e., when estimating incidence) and suspected cases to achieve a larger denominator of cases (i.e., when estimating aetiology-specific proportions).

2.4. Data analysis

Incidence and aetiology-specific proportions were calculated by pooling study-specific estimates in random-effects meta-analyses. We calculated exact 95% confidence intervals (CI) based on the Poisson distribution for estimating incidence and binomial 95% CI using the Clopper–Pearson method for estimating aetiology-specific proportions [22]. For studies that included incidence and/or aetiology-specific proportions before and after vaccine implementation, we analysed only pre-vaccine data; we analysed post-vaccine data in a secondary analysis of vaccine impact (described below).

If meta-analyses included studies where both study setting and study period overlapped, we used the following approach to avoid potential double-counting of cases. First, for every combination of articles with potential for double-counting (based on study setting and study period), we contacted the relevant articles' corresponding authors to clarify whether double-counting was possible. If no study author responded within one month after two follow-up emails, we used the following criteria to select studies for the main analysis and ensure there were no overlapping study settings and study periods remaining. In order of decreasing importance, the criteria were: study included full age range (1–59 months); more recent end of study period; study with multiple sites (preferably urban and rural); probable case definition used; and used multiple fluid samples and/or diagnostic testing modalities. The studies excluded from the main meta-analysis due to potential double-counting were incorporated in a sensitivity analysis (described below).

Between-study heterogeneity was measured by χ^2 tests and the I^2 statistic. In meta-analyses with substantial between-study heterogeneity ($I^2 \geq 75\%$), we investigated potential explanatory variables using stratified meta-analyses, comparing estimates between studies according to pre-specified study-level characteristics (i.e., country, case definition, age range of patients, study period, antibiotic use prior to lumbar puncture [LP], study quality).

We conducted two sensitivity analyses per meta-analysis, as applicable. The first excluded studies reporting a case definition that could overestimate incidence (suspected cases) and aetiology-specific proportions (confirmed cases). In the second sensitivity analysis, we included all studies to determine whether removing studies with potential double-counting substantially affected estimates.

We performed two secondary analyses. The first was restricted to studies assessing vaccine impact, for which we summarised data as reported by each study. The second analysis was restricted to studies serotyping cases of pneumococcal meningitis, for which we performed random-effects meta-analyses to describe the proportion of pneumococcal meningitis cases with serotypes covered by PCV10, PCV13, and the 23-valent pneumococcal polysaccharide vaccine (PPSV23).

Analyses were performed using Stata MP version 14.1 (StataCorp) and R version 3.4.0 (R Foundation for Statistical Computing). All statistical tests were two-sided and $P < 0.05$ was considered statistically significant.

3. Results

3.1. Study characteristics

Among 2569 records identified, 47 articles met eligibility criteria (Fig. 1). After reviewing bibliographies of included articles, we identified one additional study, totalling 48 articles cumulatively reporting 20,707 meningitis cases.

There were 26 sentinel surveillance studies, 19 case series, four population-based surveillance studies, and one randomised controlled trial (Table 1) [23–70]. Thirteen studies took place in Bangladesh, nineteen in India, seven in Nepal, seven in Pakistan, and three in Sri Lanka; there were no studies from Bhutan. Study period ranged from 1987 to 2013. Thirty-nine studies included all children within the age range of interest (1–59 months), whereas nine studies included only children from a subset of this age range (e.g., 3–23 months).

Thirty studies reported the preferred probable case definition. The sensitivities of studies' case definitions varied considerably relative to WHO case definitions. Only 11 studies' case definitions were identical or similar to the corresponding WHO definition [20]. Of the remaining studies, 14 had a definition with lower sensitivity, five studies had a definition with higher sensitivity, and 17 studies had a definition of indeterminate sensitivity, compared to the corresponding WHO definition.

Twenty-six of 40 studies reported CSF testing rates, which ranged from 3 to 100% (median, 98%). In seven studies, less than 80% of enrolled cases underwent CSF testing. Twenty-one studies reported antibiotic use among cases prior to lumbar puncture (LP), which ranged from 0 to 93% (median, 39%) one to three days prior to presentation to the healthcare provider. In 11 studies more than half of cases reported antibiotic use prior to LP.

In total, 40 studies tested for Hib, 47 tested for pneumococcus, and 35 tested for meningococcus. For all three aetiologies, the median number of types of samples tested was one (CSF) and the median number of diagnostic testing modalities used was two (almost always Gram stain/culture and antigen-based testing).

Four studies investigated the impact of the Hib conjugate vaccine [24,35,53,65]. Only one study, in Nepal, was conducted after implementation of Hib conjugate vaccine. For pneumococcal vaccination, all studies were done prior to national implementation of PCV10 in Bangladesh, Nepal, or Pakistan.

In terms of study quality, only three studies met criteria of (1) prospective, (2) use of a pre-specified case definition, and (3) included community-based case ascertainment (versus exclusively hospital-based) (Table S1). Thirty-two studies met two criteria (usually, prospective study with standard case definition) and 11 studies met only one criterion. Three studies met none of the criteria.

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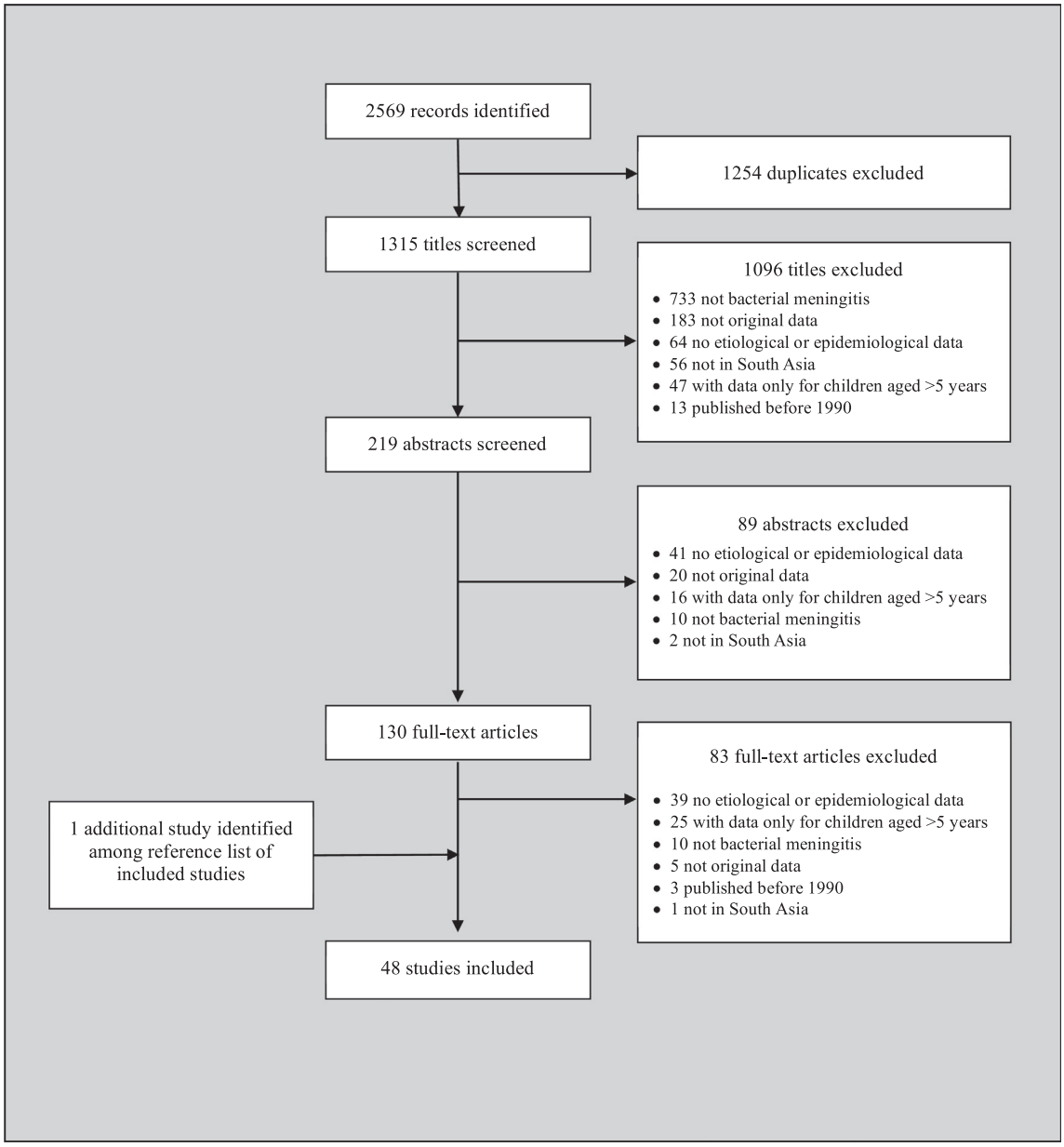

Fig. 1. Flow diagram for study selection process.

3.2. Annual incidence

Among 14 studies cumulatively reporting 1720 cases, pooled annual incidence across South Asia was 105 (95% CI, 53–173) cases per 100,000 children, with high between-study heterogeneity (I^2 = 99%, P < 0.0001) (Fig. 2). In a sensitivity analysis excluding three studies reporting only suspected cases, pooled annual incidence was 77 (95% CI, 37–130) cases per 100,000 children, with high between-study heterogeneity (I^2 = 99%, P < 0.0001) (Figure S1).

Stratified meta-analyses to investigate between-study heterogeneity revealed multiple potential explanatory variables (Fig. 3). Annual incidence per 100,000 children varied by country (P = 0.009), ranging from 24 (95% CI, 2–72) cases in Pakistan to 245 (95% CI, 0–855) cases in Sri Lanka. Annual incidence was also higher in studies with less specific case definitions (P_{trend} = 0.021), studies conducted more recently (P = 0.014), studies not reporting proportion of cases receiving antibiotics prior to LP (P = 0.004), and studies meeting fewer quality criteria (P_{trend} = 0.034). There were no associations by age (P = 0.82) or by extent of reported antibiotic use prior to LP (P = 0.31).

3.3. Proportion of cases due to three vaccine-preventable bacteria

In random-effects meta-analyses, Hib accounted for 13% (95% CI, 8–19%) of cases, pneumococcus for 10% (95% CI, 6–15%), and meningococcus for 1% (95% CI, 0–2%) (Fig. 4), with high between-study heterogeneity (all I^2 > 84% and P < 0.0001). These proportions were similar in both sensitivity analyses, which either excluded studies reporting only confirmed cases (Figure S2) or included all studies irrespective of potential double-counting (Figure S3). Restricting to 22 studies reporting only confirmed cases, a median of 78% cases (IQR, 50–87%) were attributed to either Hib, pneumococcus, or meningococcus, as compared to other bacteria.

Estimates of aetiology-specific proportions varied by country (Figure S4). The proportion of cases due to Hib ranged from 10%

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Table 1
Characteristics of included studies, by country.

	Study[a]	Surveillance or study design	Setting (study period)	Ages (mo)	No. cases	Case definition(s) analysed	Sensitivity of definition(s) relative to WHO[b]	% cases with CSF tested[c]	No. samples types tested (no. test modalities)[d]			% cases with abx prior to LP	Implementation of Hib vaccine[e]		Ref
									Sp	Hib	Nm		Study focus	In country program	
Bangladesh	Arifeen (2009)	Population-based	Mirzapur (2004–07)	1–59	175	Suspected/ confirmed	Similar/lower	22	2 (1)	0 (0)	0 (0)	NR	No	After study	22
	Baqui (2007)	Sentinel	Dhaka (2000–03)	3–23	41	Probable	Lower	92	0 (0)	1 (2)	0 (0)	45	Yes	After study	23
	Brooks (2007)	Population-based	Dhaka (2004–06)	0–59	18	Suspected/ confirmed	Similar/lower	44	1 (1)	0 (0)	0 (0)	100	No	After study	24
	Gurley (2009)	Sentinel	Dhaka, Mymensingh, Sylhet (2003–05)	0–59	536	Suspected	Higher	37	1 (3)	1 (3)	1 (3)	NR	No	After study	25
	Luby (2010)	Sentinel	Dhaka (2006–07)	0–59	161	Suspected	Lower	86	2 (1)	2 (1)	2 (1)	NR	No	After study	26
	Moisi (2009)	Sentinel	Dhaka (2006–07)	1–59	358	Probable	Higher	100	1 (2)	1 (2)	1 (2)	53	No	After study	27
	Rahman (2008)	Sentinel	Dhaka (1999–2003)	0–59	122	Probable	Indeterminate	100	1 (2)	1 (3)	1 (2)	65	No	After study	28
	Saha (2006)	Case series	Dhaka (NR)	2–59	127	Confirmed	Higher	NA	2 (2)	3 (2)	2 (2)	NR	No	After study	29
	Saha (1997)	Case series	Dhaka (1987–94)	1–59	521	Confirmed	Lower	100	1 (2)	1 (2)	1 (2)	NR	No	After study	30
	Saha (2009)	Sentinel	Dhaka, Chittagong, Mirzapur (2004–07)	0–59	842	Probable	Indeterminate	NR	2 (1)	0 (0)	0 (0)	NR	No	After study	31
	Saha (2012)	Sentinel	Dhaka (2001–09)	0–59	2490	Probable	Indeterminate	NR	2 (3)	1 (2)	1 (2)	54	No	After study	32
	Saha (2016)	Sentinel	Dhaka, Chittagong, Mirzapur (2007–13)	0–59	2000	Probable	Lower	13	2 (3)	2 (1)	2 (1)	NR	No	After study	33
	Sultana (2013)	Sentinel	Dhaka (2008–11)	0–12	344	Probable	Lower	NR	2 (1)	3 (3)	0 (0)	NR	Yes	During study	34
India	Chauhan (2015)	Sentinel	Shimla (2012–13)	1–59	250	Suspected	Higher	100	2 (3)	2 (3)	2 (3)	93	No	After study	35
	Chinchankar (2002)	Case series	Pune (1997–99)	1–59	54	Probable	Indeterminate	NR	1 (2)	1 (2)	1 (2)	39	No	After study	36
	Fitzwater (2013)	Sentinel	Chennai (2008–11)	1–23	127	Probable	Identical	78	1 (3)	1 (3)	1 (3)	78	No	After study	37
	Gitali (2014)	Case series	Assam (2009–10)	0–59	113	Suspected	Similar	NA	1 (1)	1 (1)	1 (1)	0	No	After study	38
	Gupta (2010)	Sentinel	Yamuna Nagar, Vellore, Kolkata (2005–07)	1–23	74	Probable	Lower	NR	1 (2)	1 (3)	0 (0)	NR	No	After study	39
		Population-based	Chandigarh (2005–07)	1–23	164	Suspected	Similar	9	0 (0)	0 (0)	0 (0)	36	No	After study	
		Population-based	Kolkata (2005–07)	1–23	72	Suspected	Similar	3	0 (0)	0 (0)	0 (0)	6	No	After study	
		Population-based	Vellore (2005–07)	1–23	89	Suspected	Similar	34	0 (0)	0 (0)	0 (0)	8	No	After study	
	Jagadevi (2015)	Case series	Bangalore (2012–13)	0–60	16	Confirmed	Lower	100	1 (2)	1 (2)	1 (2)	67	No	After study	40
	Kabra (1991)	Case series	Jaipur, Jodhpur, Kolkata, Delhi (1989–89)	0–59	643	Probable	Indeterminate	NR	1 (1)	1 (1)	1 (1)	NR	No	After study	41
	Khan (2011)	Case series	Aligarh (2001–09)	1–59	217	Confirmed	Lower	100	1 (1)	1 (1)	1 (1)	NR	No	After study	42
	Mani (2007)	Case series	Bangalore (1996–2005)	0–59	34	Probable	Lower	100	1 (2)	1 (2)	1 (2)	NR	No	After study	43
	Manoharan (2017)	Sentinel	Vellore (2011–15)	0–60	960	Suspected	Similar	NR	2 (1)	0 (0)	0 (0)	NR	No	After study	44
	Minz (2008)	Sentinel	Vellore (1997–99)	0–59	42	Probable	Indeterminate	100	1 (2)	1 (3)	1 (1)	28	No	After study	45
	Ramachandran (2013)	Sentinel	Chennai, Lucknow, New Delhi, Vellore (2008–10)	1–23	441	Probable	Identical	89	1 (3)	1 (3)	1 (3)	65	No	After study	46
Nepal	Sahai (2001)	Case series	Pondicherry (1994–96)	1–60	80	Probable	Indeterminate	NA	2 (1)	2 (1)	2 (1)	42	No	After study	47
	Seetha (1999)	Case series	Manipal (1996–1998)	1–11	359	Suspected	Indeterminate	NR	1 (2)	1 (2)	1 (2)	NR	No	After study	48
	Shah (2009)	Case series	Bangalore (2006)	1–60	484	Suspected	Indeterminate	NR	1 (1)	0 (0)	0 (0)	NR	No	After study	49
	Singhi (2002)	Case series	Chandigarh (NR)	1–12	60	Probable	Indeterminate	100	1 (3)	1 (3)	1 (3)	79	No	After study	50
	Vashishtha (2011)	Case series	Bijnor (2009–10)	1–59	50	Probable	Indeterminate	NA	1 (3)	1 (3)	1 (3)	36	No	After study	51
	Verghese (2009)	Sentinel	Vellore (1994–2005)	1–60	130	Confirmed	Lower	NA	1 (1)	1 (1)	0 (0)	NR	Yes	After study	52
	Viswanath (2007)	Case series	Davangere (2000–01)	0–12	150	Suspected	Indeterminate	100	1 (2)	1 (2)	1 (2)	NR	No	After study	53
	Ansari (2011)	Case series	Patan (2005–09)	0–60	9	Confirmed	Lower	NR	2 (1)	2 (1)	2 (1)	NR	No	After study	54
	Kelly (2011)	Case series	Kathmandu(2005–06)	2–60	73	Probable	Indeterminate	NR	1 (3)	1 (2)	1 (2)	NR	No	After study	55
	Rijal (2010)	Sentinel	Kathmandu (2004–08)	2–60	408	Suspected	Indeterminate	NR	1 (1)	0 (0)	0 (0)	NR	No	After study	56
	Shah (2009)	Sentinel	Kathmandu (2004–07)	2–59	182	Probable	Identical	100	2 (3)	2 (2)	2 (2)	27	No	After study	57
	Sharma (1996)	RCT	Kathmandu (1993–94)	5–60	23	Probable	Lower	NA	1 (1)	1 (1)	1 (1)	0	No	After study	58
	Shrestha (2015)	Case series	Kathmandu (2012–13)	1–60	90	Suspected	Indeterminate	NA	1 (3)	1 (3)	1 (3)	NR	No	Before study	59
	Williams (2009)	Sentinel	Kathmandu (2005–06)	2–59	47	Probable	Identical	NR	2 (3)	0 (0)	0 (0)	39	No	After study	60
Pakistan	Alam (2011)	Case series	Karachi (2005–06)	0–36	58	Probable	Indeterminate	100	2 (1)	2 (1)	2 (1)	NR	No	After study	61
	Attia (2016)	Case series	Lahore (2012)	1–60	199	Probable	Higher	100	2 (1)	2 (1)	0 (0)	NR	No	Before study	62
	Khowaja (2013)	Sentinel	Karachi, Hyderabad (2008–11)	0–59	188	Probable	Lower	NR	1 (2)	1 (2)	1 (2)	NR	No	During study	63
	Moisi (2009)	Sentinel	Karachi (2006–07)	1–59	275	Probable	Higher	100	1 (2)	1 (2)	1 (2)	12	No	After study	27
	Teleb (2013)	Sentinel	Lahore, Karachi (2005–10)	1–60	5300	Probable	Higher	NR	1 (1)	1 (1)	1 (1)	NR	Yes	During study	64
	Zaidi (2010)	Sentinel	Karachi, Hyderabad (2004–05)	0–59	237	Probable	Lower	NA	1 (2)	1 (2)	1 (2)	54	No	After study	65
	Zaidi (2009)	Sentinel	Karachi, Hyderabad (2005–06)	0–59	412	Probable	Identical	98	1 (2)	1 (2)	1 (2)	53	No	After study	66
Sri Lanka	Batuwanthudawe (2010)	Sentinel	Colombo (2004)	0–59	333	Probable	Indeterminate	100	1 (2)	1 (2)	1 (2)	15	No	After study	67
	Batuwanthudawe (2009)	Sentinel	Colombo (2005–07)	2–59	235	Probable	Lower	100	2 (2)	2 (2)	2 (2)	22	No	After study	68
	Kularatna (2015)	Population-based	Colombo (2008)	0–59	12	Suspected	Similar	NR	0 (0)	0 (0)	0 (0)	NR	No	After study	69
		Sentinel	Colombo (2005–09)	0–59	282	Suspected	Similar	79	1 (2)	0 (0)	0 (0)	NR	No	During study	

Abbreviations: abx, antibiotics; CSF, cerebrospinal fluid; Hib, *Haemophilus influenzae* type b; LP, lumbar puncture; NA, not applicable; Nm, *Neisseria meningitidis*; NR, not reported; RCT, randomized controlled trial; Sp, *Streptococcus pneumoniae*; WHO, World Health Organization.

[a] Three articles are described in multiple rows because they report population-based and sentinel surveillance data and/or data from different geographical sites separately.

[b] Since WHO's suspected case definition does not elaborate criterion of "other meningeal sign", we designated some studies' suspected case definition as "similar" (versus "identical").

[c] NA (not applicable) indicates that collection of a CSF sample was an inclusion criterion of the study.

[d] "Samples types tested" refer to the types of body fluids analyzed, namely CSF, blood, or urine. If a study collected only one type of fluid, that fluid was always CSF. "Test modalities" refer to the number of independent methods used to detect a particular bacterium, which could one or more tests of several modalities: Gram stain & culture, latex agglutination, or molecular testing.

[e] With regard to vaccines for *S. pneumoniae* and *N. meningitidis*, none were administered by any study, and all studies were completed before any implementation of these vaccines in national immunization programs in South Asia.

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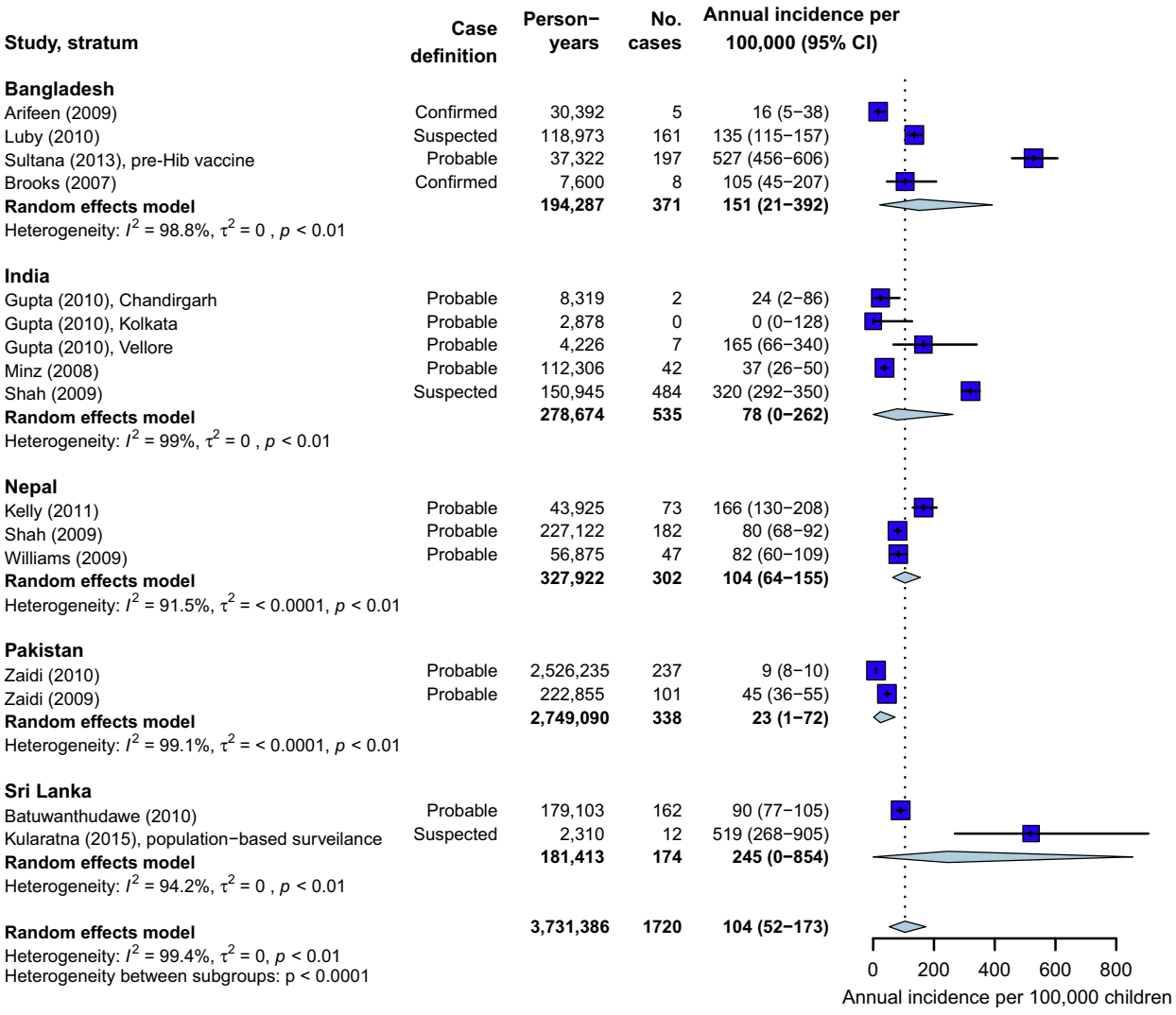

Fig. 2. Meta-analysis of annual incidence, by country.

(95% CI, 4–18%) in India to 22% (95% CI, 19–26%) in Sri Lanka (between-country heterogeneity, $P = 0.009$). The proportion of cases due to pneumococcus ranged from 7% (95% CI, 2–13%) in Sri Lanka to 25% (95% CI, 12–42%) in Bangladesh (between-country heterogeneity, $P = 0.039$). The proportion of cases due to meningococcus ranged from 0% (95% CI, 0–1%) in India to 4% (95% CI, 1–8%) in Bangladesh, though there was weaker evidence of between-country heterogeneity ($P = 0.058$).

In stratified meta-analyses to investigate between-study heterogeneity, aetiology-specific proportions were higher in studies that used a more specific case definition in the denominator to calculate proportions (all $P_{trend} < 0.002$; Figure S4. Age range of patients studied and reported antibiotic use prior to LP were also statistically significant for one or two, but not all three, aetiologies.

3.4. Impact of vaccination

Two studies described Hib conjugate vaccination effectiveness prior to implementation in South Asia. In Dhaka, an incident case–control study of a birth cohort of ~68,000 infants systematically replaced the diphtheria–pertussis–tetanus (DPT) vaccine with a combined DPT–HepB–Hib vaccine in selected study areas. Among under-2 children who received at least two doses of the Hib vaccine, vaccine effectiveness was 89% (95% CI, 28–100%) and 93% (95% CI, 53–100%) when compared to community and hospital controls, respectively [24]. The second study, in Vellore, India, investigated the association between Hib conjugate vaccine distribution in the private sector on Hib meningitis admissions among under-5 children at a referral hospital. In the pre-vaccine period, mean number of Hib meningitis cases was 10.7 annually, declining to 3.8 cases in the post-transition period (rate ratio, 0.35; 95% CI, 0.3–0.5; $P < 0.0001$) [53].

Two additional studies compared incidence and/or aetiology-specific proportions before and after national implementation of the Hib conjugate vaccine [35,65]. In Bangladesh, at two sentinel surveillance hospitals in Dhaka, annual incidence of Hib meningitis per 100,000 children aged <1 year declined by 83% between the pre-vaccine period (May 2008–April 2009) to the post-vaccine period (April 2009–May 2011). The proportion of cases attributable to Hib also declined, from 6% (95% CI, 3–10%) to 1% (95% CI, 0–5%). Notably, there was also a 30% decline in the annual incidence of probable bacterial meningitis per 100,000 children [35]. Second, in Pakistan, at two sentinel hospitals in Lahore and Karachi, the proportion of cases due to Hib among confirmed meningitis cases declined by 72% from the pre-vaccine period (14.2% in 2005–07) to the post-vaccine period (4.0% in 2010) [65].

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Study-level characteristic	No. studies	Person-years	No. cases	Annual incidence per 100,000 (95% CI)	P (P_{trend})
Country					
Bangladesh	4	194,287	371	151 (22–392)	
India	5	278,674	535	79 (0–262)	
Nepal	3	327,922	302	105 (64–156)	<0.0001
Pakistan	2	2,749,090	338	24 (2–73)	
Sri Lanka	2	181,413	174	245 (0–855)	
Case definition					
Suspected	3	272,228	657	277 (125–488)	
Probable	11	3,421,166	1050	83 (38–144)	(0.021)
Confirmed	2	37,992	13	48 (0–175)	
Age range					
All 5 years	12	3,678,641	1514	98 (46–168)	0.82
Under-2 only	4	52,745	206	119 (0–483)	
Study mid-year					
≤2005	9	3,406,413	857	61 (28–105)	0.014
>2005	7	324,973	863	189 (88–326)	
Antibiotics prior to LP					
Not reported	6	383,867	932	226 (107–388)	0.004
Reported	10	3,347,519	788	53 (23–93)	
<50% cases	7	590,829	442	62 (41–87)	0.31
≥50% cases	3	2,756,690	346	38 (8–90)	
Study quality criteria					
0 met	1	150,945	484	321 (293–350)	
1 met	1	118,973	161	135 (115–157)	(0.034)
2 met	9	3,408,053	1053	117 (58–196)	
3 met	5	53,415	22	44 (6–107)	

Abbreviations: LP, lumbar puncture.

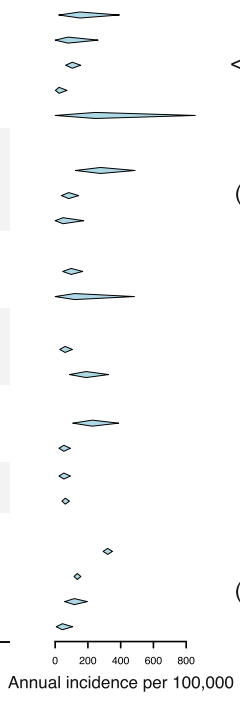
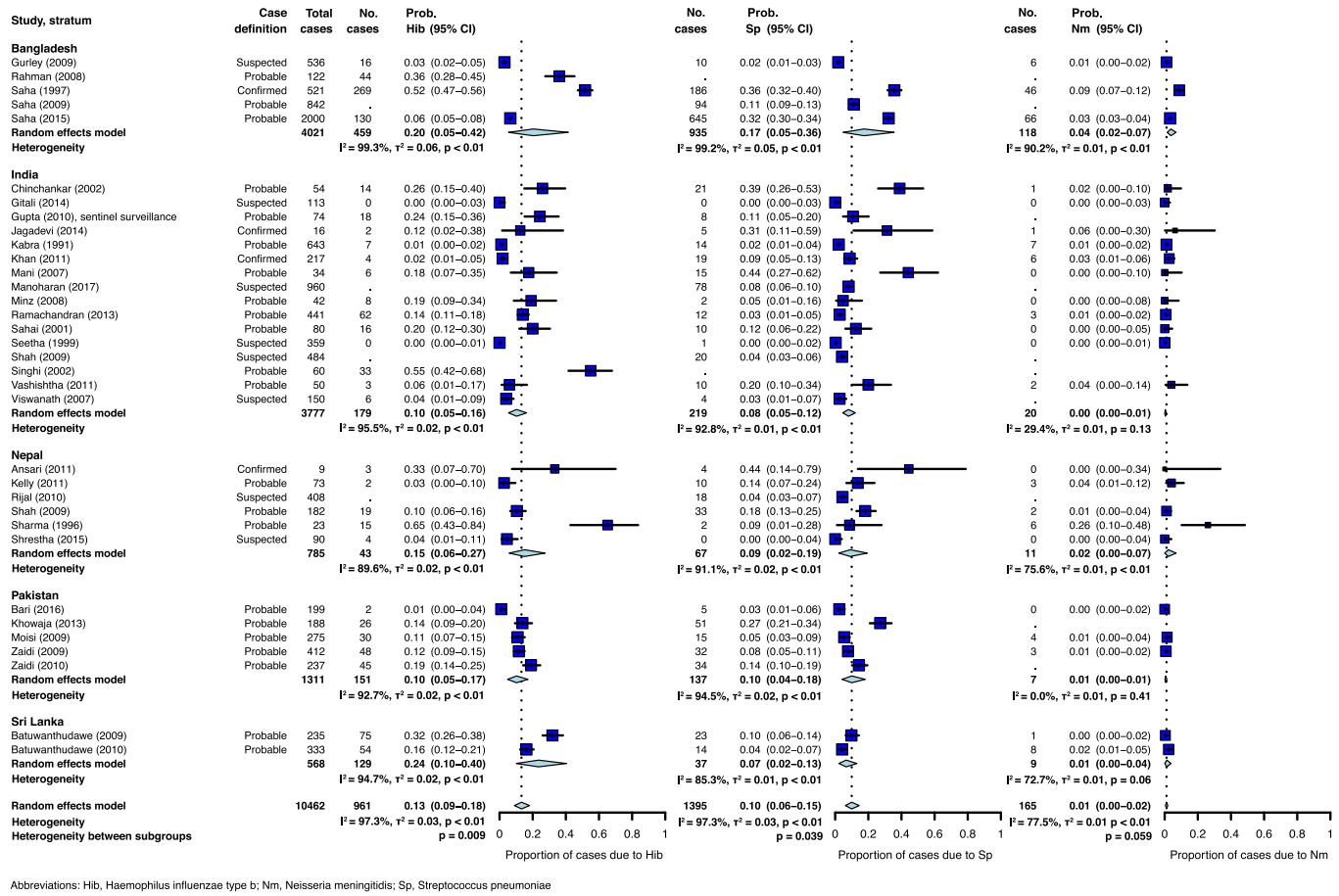


Fig. 3. Meta-analyses of annual incidence stratified by study-level characteristics.



Abbreviations: Hib, Haemophilus influenzae type b; Nm, Neisseria meningitidis; Sp, Streptococcus pneumoniae

Fig. 4. Meta analysis of proportion of cases by aetiology, by country.

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No studies have yet reported the impact of nationwide implementation of pneumococcal vaccination in Bangladesh, Nepal, or Pakistan.

3.5. Pneumococcal serotype distribution and coverage

Nine studies cumulatively reported 1048 cases of pneumococcal meningitis [31–34,45,56,67,71,72], including two studies excluded from our main analyses because they reported neither incidence nor aetiology-specific proportions [71,72]. A total of 882 (84%) cases were from Bangladesh; India (78; 8%), Pakistan (75; 7%), and Nepal (13; 1%) comprised the remainder.

One Pakistani study only determined the serogroup (e.g., 6A/B/C), not serotype (e.g., 6A), for some serotypes [72]. As per that study's methods, cases whose serogroup contained a serotype covered by a vaccine were included in the numerator to estimate pneumococcal serotype coverage and called "vaccine-related serotypes". We included this study in our analyses since excluding it did not substantially change the overall estimates presented below, except that mean pneumococcal serotype coverage in Pakistan was incalculable (data not shown).

In random-effects meta-analyses excluding two studies due to potential double-counting of cases, PCV10 covered 49% (95% CI, 39–58%) of reported serotypes on average, PCV13 covered 51% (95% CI, 40–61%), and PPSV23 covered 74% (95% CI, 67–80%) (Fig. 5); there was moderate to high between-study heterogeneity (all $I^2 > 57\%$ and $P \leq 0.029$). These proportions were similar in sensitivity analyses including all studies irrespective of potential double-counting (Figure S5).

Mean pneumococcal serotype coverage varied by country ($P < 0.0001$). There was lower serotype coverage for PCV10 and PCV13 in Bangladesh compared to India and Pakistan. For PCV10, serotype coverage in Bangladesh was 44% (95% CI, 40–49%), compared to 63% (95% CI, 51–74%) in India ($P = 0.003$) and 62% (95% CI, 49–74%) in Pakistan ($P = 0.009$). For PCV13, serotype coverage in Bangladesh was 46% (95% CI, 42–50%), compared to 63% (95% CI, 68–78%) in India ($P = 0.0002$) and 63% (95% CI, 50–76%) in Pakistan ($P = 0.011$). Lower PCV10 and PCV13 serotype coverage in Bangladesh was associated with higher reported prevalence of serotype 2 (165/882; 19% cases), compared to both India (4/78; 5%; $P = 0.002$) and Pakistan (0/75; 0%; $P < 0.0001$). Serotype coverage for PPSV23 was not statistically significantly different in Bangladesh when compared to India ($P = 0.68$) or Pakistan ($P = 0.08$).

4. Discussion

We synthesised data from 48 studies cumulatively reporting 20,707 cases of bacterial meningitis to describe its incidence and aetiology among children aged 1–59 months in South Asia. These cases occurred over a 27-year period (1987–2013) and were reported in articles published from January 1, 1990, through April 25, 2017. To our knowledge, ours is the first systematic review and meta-analysis of this topic. In random-effects meta-analysis, mean annual incidence was 105 (95% CI, 53–173) cases per 100,000 children. Three vaccine-preventable aetiologies—Hib, pneumococcus, and meningococcus—cumulatively caused 24% of cases, on average; however, this is likely a substantial underestimate since these three aetiologies accounted for a median 78% of cases among studies reporting only confirmed cases.

Our estimate of mean annual incidence is comparable to the Global Burden of Disease (GBD) study's median estimate of 104 cases per 100,000 children aged 1–59 months from 1990 to 2013 in South Asia, extracted using their online GBD Results Tool. This estimate is derived from a systems modelling approach that uses meta-regression to synthesize data from a systematic review of literature as well as surveillance notification data, stratifying estimates by age, sex, country, and year [73]. While our sensitivity analysis excluding studies that reported only suspected meningitis cases revealed a lower point estimate (77 cases per 100,000 children), there was large uncertainty around this number (95% CI, 37–130).

Our estimates of incidence and aetiology-specific proportions are likely to be underestimates for several reasons. First, a substantial proportion of cases received antibiotics prior to LP, with more than half reporting antibiotic use 1–3 days prior to presentation in 11 studies. Over-the-counter access to antibiotics and concomitant indiscriminate use in South Asia is well documented, with estimates ranging from 9 to 86% in the general population in a systematic review [74]. Even small doses of oral antibiotics inhibits bacterial growth, decreasing the yield of diagnostic tests, particularly Gram stain and culture, for bacterial meningitis [75].

Second, many studies were of suboptimal quality. Quality was considered ideal if the study was (1) prospective, (2) had a prespecified case definition, and (3) included community-based case ascertainment (versus exclusively hospital-based). Only three studies met all criteria. Studies that were retrospective, had exclusively hospital-based case ascertainment, or did not use a

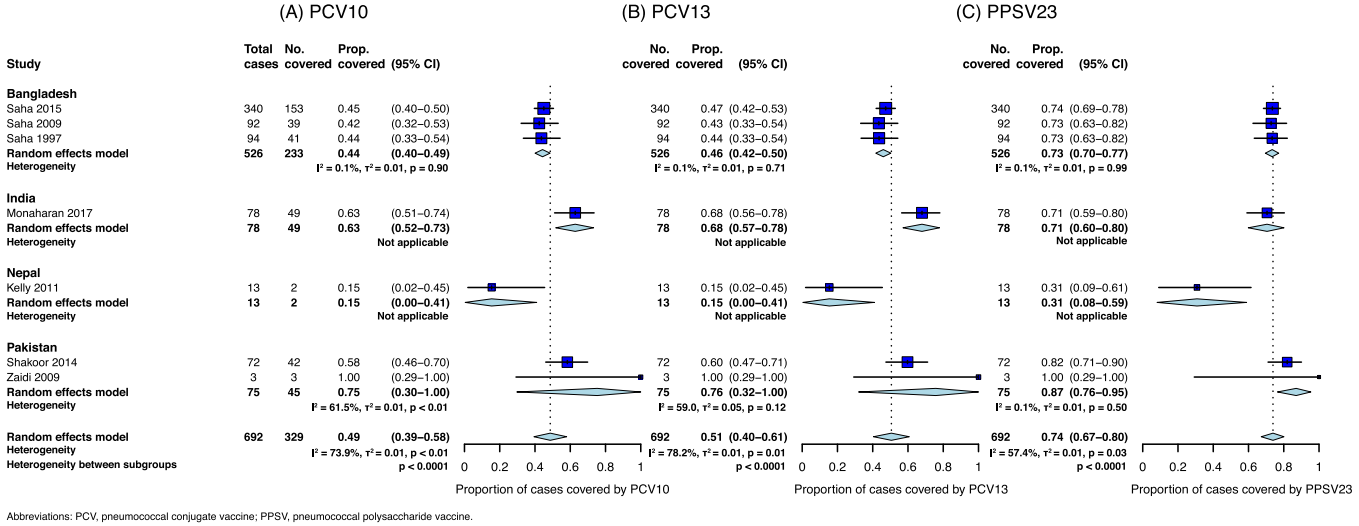

Fig. 5. Meta-analyses of proportion of pneumococcal meningitis cases covered by three available vaccines, by country.

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pre-specified case definition may have missed cases. Furthermore, studies with exclusively hospital-based case ascertainment may be prone to case ascertainment bias if patients who present to the hospital are systematically different in terms of morbidity or aetiology compared to those who remain in the community. In stratified meta-analyses, we found inconsistent associations with higher study quality—a positive association with proportion of cases due to Hib, non-significant associations with proportions of cases due to pneumococcus or meningococcus, and an inverse association with incidence. This latter finding may be confounded by other study-level characteristics associated with higher incidence (e.g., less specific case definition).

Third, case ascertainment is likely suboptimal regardless of study setting. Included hospital-based studies probably underestimated incidence because they tended to use local census data to estimate the population of under-5 children at risk, some of which may never present to hospitals. In one study of infant mortality in urban slums in Delhi, only 41% of infants with a severe disease, including meningitis, were *referred* to a hospital, among which only about half were *taken* to the hospital [76]. While some studies attempted to mathematically adjust for factors that affect case ascertainment (e.g., suboptimal hospital utilisation rates), it is difficult to account for all factors [35,50,53]. Even community-based studies may miss cases since they tend to identify cases early in the course of their illness. For bacterial meningitis, early detection and treatment could underestimate complications (morbidity), secondary transmission (incidence), and mortality.

Fourth, even among cases who presented to a hospital, detection was suboptimal. Ideally, almost every case would have CSF tested using multiple modalities [28]. In seven studies less than 80% of enrolled cases underwent CSF testing; among cases whose CSF was tested, the median number of testing modalities was two (usually Gram stain/culture and antigen-based testing). While these modalities usually have greater than 90% sensitivity for these bacteria, it is markedly lower among patients pre-treated with antibiotics, not uncommon in South Asia [74]. While molecular testing may have identified some false-negative cases [77], even studies using all aforementioned testing modalities can miss cases. One included study comparing incidence estimates pre- and post-Hib vaccine implementation in Dhaka found that Hib meningitis declined by 76 cases per 100,000 child-years, probable meningitis declined by 501 cases per 100,000 child-years, and pneumococcal meningitis increased by 14 cases per 100,000 child-years. The larger decline among probable meningitis cases may reflect that some Hib meningitis cases were undetected due to inadequate sensitivity of diagnostic testing [35].

Finally, we erred on the side of conservative estimates. Among studies reporting only suspected and confirmed cases, we used the case definition that provided the more conservative estimate—confirmed cases to achieve a smaller numerator (e.g., for incidence) and suspected cases to achieve a larger denominator (e.g., for aetiology-specific proportions).

Two studies—in Bangladesh [35] and Pakistan [65]—observed a 72–83% decline in incidence of Hib meningitis at sentinel surveillance hospitals within two years of national implementation of the Hib conjugate vaccine. These findings are consistent with recent research in other LMICs [11,12,78]. While these initial studies show promising impact, further research to demonstrate Hib vaccine impact throughout South Asia is needed. Furthermore, no studies have reported the impact of recent implementation of PCV10 in Bangladesh, Nepal, or Pakistan, which would also inform current and future vaccination efforts.

Impact of pneumococcal vaccination depends on multiple factors including uptake, type of vaccine used, and prevalent pneumococcal serotypes. In terms of serotypes, we found similar point estimates (~50%) for mean pneumococcal serotype coverage between PCV10 and PCV13. On average, serotype coverage was higher in India and Pakistan (about three of five cases) compared to Bangladesh (about two of five cases). The estimate from Pakistan may be an overestimate since it largely derives from one study that could only determine serogroups (e.g., 6A/B/C) and calculated serotype coverage using cases where the serogroup contained a vaccine serotype [72]. However, PPSV23 serotype coverage was not significantly different between these countries. These discordant results may be related to higher prevalence of serotype 2 in Bangladesh, which is only covered by PPSV23. About 20% of serotyped cases were due to serotype 2 in Bangladesh, compared to <5% in India and Pakistan. This serotype has high virulence, with 30-fold greater odds of meningitis in one analysis, and was the leading serotype-specific cause of meningitis in Bangladesh from 2001 to 2009 [33]. There is little published data on the serotype distribution among pneumococcal meningitis cases in Bhutan, Nepal, or Sri Lanka, which remains another area of research needed to inform vaccine policymaking and implementation.

In terms of meningococcal meningitis, our finding of relatively fewer cases among under-5 children does not preclude the importance of nationwide immunisation programs since its incidence follows a bimodal distribution, peaking in infancy as well as adolescence and young adulthood [79]. Future studies should describe the burden of meningococcal meningitis among older age groups in this region [80].

Our review has several limitations. Our estimates of uncertainty around incidence are likely to be overly precise. Most studies reporting incidence estimates were hospital-based, which inferred the population denominator of under-5 children at risk from local census data. However, because it is unlikely that *every* under-5 child with meningitis presented to the sentinel hospital, these population denominators are likely overestimates. While this causes our incidence estimates to be underestimates, we prioritised including all available data and providing a conservative estimate, rather than excluding this literature.

Our review primarily includes urban-based studies. Only two studies were done in a rural setting where epidemiology may differ, and without robust surveillance systems, it would be difficult to account for such cases. Specifically, in the analyses of aetiology-specific proportions, the majority were hospital-based case series that primarily relied on convenience sampling, limiting their generalisability.

Although our estimates of incidence and aetiology-specific proportions consistently varied by country and case definition used, a substantial amount of between-study heterogeneity remained unexplained. There was also wide variability in the representation of countries in this review. None of the 48 included studies reported data from Bhutan, whereas 19 studies reported data from India. The age range of patients included in the studies also varied; while most studies included all children within the age range of interest (1–59 months), nine studies included only children from a subset of this age range (e.g., 3–23 months). Another source of between-study heterogeneity is the large range of years covered in this review (1987–2013). Most studies reported cases prior to introduction of the Hib vaccine in this region and hence the overall and aetiology-specific epidemiology of meningitis among under-5 children in this region continues to change, requiring further surveillance and research. These sources of high between-study heterogeneity preclude more precise estimates of incidence and aetiology-specific proportions in this review.

Finally, as with any review, there may be reporting bias. However, we believe its probability is low since we queried five major international research databases without language restrictions, with both indexed and key-word terms to maximise search sensitivity.

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5. Conclusions

In summary, we synthesised data from 48 studies cumulatively reporting 20,707 cases of bacterial meningitis over a 27-year period (1987–2013) among children aged 1–59 months in South Asia. Mean annual incidence was 105 (95% CI, 53–173) cases per 100,000 children, the second-highest regional incidence in the world during this time period [73]. On average, almost one-quarter of cases were caused by two vaccine-preventable bacteria, Hib and pneumococcus, though, among studies reporting only confirmed cases, these aetiologies accounted for about three-quarters of cases. Both incidence and aetiology estimates are likely substantially underestimated due to multiple epidemiological and microbiological factors. Despite some initial studies showing promising impact of the Hib conjugate vaccine, further research on both Hib and pneumococcal vaccine impact as well as serotype distribution of pneumococcal meningitis is needed to inform vaccine policymaking and implementation.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings reported in this paper. The corresponding author (SKM) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Authors' contributions

MA and SKM conceived and designed the study. MA and BC independently conducted the literature review, screened articles, and abstracted data. MA and KWJ independently performed all the statistical analyses. All authors interpreted the findings. MA and BC drafted the article and all authors critically revised the article. SKM supervised the study and is the guarantor.

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Conflicts of interest

The authors report no conflict of interest concerning the materials or methods used in this study or the findings reported in this paper.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.07.037.

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