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Burden of acute infections (except respiratory and diarrheal) and its risk factors among under-five children in India: A systematic review and meta-analysis

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Abstract

Context—Acute infections of eyes, ears, skin, and others are a common cause of morbidity in under-five children. The overall burden of other infections and their risk factors is not known.

Evidence Acquisition—Available literature was searched comprehensively using PubMed for acute infections (except acute respiratory and diarrheal diseases) using the relevant medical subject heading terms. Extracted articles were independently reviewed against inclusion/exclusion criteria and rated for quality. 10 articles were abstracted and reviewed to identify the reported prevalence and risk factors for acute infections among children.

Results—The pooled prevalence of infections (not including acute respiratory and diarrhea) between 2002 and 2013 was 18.42 (95% confidence interval: 9.30–30.62), with reported range of 3.7–50.8%. The significantly positively associated factors reported in single studies were young age of the child, malnutrition, poor breastfeeding, low socio-economic status, animal rearing near household and mothers' illiteracy for independent morbidities.

Conclusion—The evidence on risk factors including breastfeeding, vaccination, age, and sex that predispose under-five Indian children to different infections is inconclusive. There is a need to conduct more studies on acute infections other than acute respiratory and diarrhea, to establish their determinants in Indian children.

Keywords

Ear infection; Eye infection; India; Meta-analysis; Prevalence; Risk factors; Skin infection; Systematic review; Under-five children

A large proportion of children aged under-5 years are affected by acute morbidities globally. Indian children share about a quarter of this burden annually [1]. Most of the attention are focused on pneumonia and diarrhea, which are the major killers of young children [2];

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nevertheless, other infections also cause the huge burden of morbidity that frequently goes unreported, leading to gross underestimation. Nearly 30% of children under the age of 3 years suffer from fever [3], whereas the exact burden of other infections including those of ear, eyes, and skin are unknown.

The Integrated Management of Neonatal and Childhood Illnesses Program has stressed on the appropriate syndromic management of fevers and ear infections which reinstate the gravity of prevalence as well as the diagnostic difficulties of these health problems in Indian children. While the World Health Organization has focused its attention on eye health of children in developing countries [4] including India, there are no programs for skin and other minor infections. The growing emphasis being placed on identification of these morbidities is evident from the recent WHO document that reviewed the available literature on children from developing countries [5]. The review, that identified pyoderma and scabies as major skin diseases of childhood, commented on the scarcity of pertinent literature and infective conditions being the primary reason for visit to a health facility, as also the unknown nature of cost of treatment. The global burden of disease Study 2010 to estimated 15 categories of skin disease attributing to the global diseases burden in 187 countries [6], while underlining the importance of understanding the local burden of disease for setting achievable goals for controlling them.

Many Indian practices are known to be risk factors for multiple infections in childhood [7], which coupled with socio-demographic factors often, complicate the common infections or cause co-morbidities. The purpose of this review is to identify the burden of childhood infections in India and the associated risk factors to generate evidence for preventive action.

METHODS

Search Strategy

Articles with original data on risk factors associated with infections (not including acute respiratory and diarrheal) among children younger than 5 years in India were sought. Outcomes of interest were any infection (other than acute respiratory and diarrheal) and its risk factors in children. Separate systematic reviews and meta-analyses were undertaken to describe the burden and risk factors of acute respiratory and diarrheal diseases among children.

PubMed was searched systematically to identify articles published from 2000 to 2014. The following algorithm containing medical subject heading (MeSH) terms combined with text words was used: “Child, preschool” (MeSH terms) AND “morbidity” (MeSH terms) AND “India” (MeSH terms) AND “epidemiologic factors” (MeSH terms) AND “bacterial infections” (MeSH terms) OR “skin diseases, bacterial” (MeSH terms) OR “eye infections, bacterial” (MeSH terms) OR “ear infections” (MeSH terms).

Selection Criteria and Data Extraction

The eligibility criteria for inclusion were studies whose full text was available in English, reporting the prevalence of infections such as those of eye and skin as outcomes, and describing the association of risk factors in relation to childhood morbidities on Indian

children 5 years of age and younger. Systematic reviews, review articles, meta-analyses, editorials, case reports, withdrawn publications, studies published before 2000, studies among children older than 5 years of age, and studies from outside India were excluded.

Study Selection

The search identified 404 articles potentially involving childhood infections. 18 articles were on bacterial skin disease while remaining referenced other infections. By reviewing the titles and abstracts, reviewers identified 46 articles of relevance. If the abstract indicated that the study fulfilled the eligibility criteria or the abstract did not provide sufficient information for selection decision, the reviewers assessed the full texts of articles for eligibility. Supplementary Tables 1, wherever necessary, were also reviewed for additional information. 10 articles on other bacterial infections in children <5 years old were included in review after reading the full text of the articles (Fig. 1). It was decided to include all articles together for meta-analysis since the number of individual articles describing a single condition was too small to be meta-analyzed. All the articles were independently reviewed by two authors (EG and PS) and rated for quality.

Data Extraction

Relevant data were extracted from selected studies using a data collection form that were designed before the implementation of the search strategy. The form yielded information on identifying study author, year of publication, study design, geographic origin and study setting, patient samplings, information on the frequency of the reported outcomes and association of risk factors with common infections during childhood. If there was a discrepancy in data extraction between two independent reviewers, it was resolved by an independent senior epidemiologist (CHB).

Statistical Analysis

Comprehensive meta-analysis software (Version 2.2 Englewood, NJ, Biostat Inc.,) [8] and Stats Direct (Version 2.7.8) software was used to analyze the data. We used the reported percentage prevalence and sample size for each of the included studies to calculate the standard error (SE) of prevalence using the formula $\sqrt{[p\times(1-p)/n]}$, where p is the proportion of prevalence and n is the reported sample size. Pooling of the prevalence of childhood infections and selected risk factors was done using Der Simonian and Laird method (random effects model). Random effects model was used to address the wide variation in independent studies. We calculated urban and rural pooled estimate for the prevalence of childhood infections weighted by population size in each study place. The pooled estimate for overall prevalence of all, as well as selected childhood infections in India was calculated using regional population size weights, along with the values of I^2 (p value) that provides a measure of % residual variation due to heterogeneity and Cochran Q (degrees of freedom, d.f.) that describes the percentage of total variation across studies due to heterogeneity, and τ^2 (SE) that provides an estimate of between-study variance in a random effects model of meta-analysis. The mean percentage (%) prevalence and the 95% confidence intervals (CIs) have been reported in the pooled analysis depicted using Forest plots (Supplementary Table 1).

Quality of Methodology Rating

We devised a composite quality construct of the methodology using the STROBE statement [9] for observational studies that provided an estimate of the strength of evidence drawn from these studies. The authors adopted a simplified rating procedure by assigning one point to each relevant methodology point on the checklist (Supplementary Table 1), adding up to a maximum of ten points, while ignoring the other sections. Articles were rated as follows: 1–4 points, Poor; 5–7, Fair; and 8–10, Good quality articles. We also studied if stated objectives of the paper matched the reporting of outcomes within the paper. If not so, an article was rated poor even if it was methodologically robust according to the quality construct. The quality scores, however, were not incorporated in the meta-analysis weights.

RESULTS

10 studies met the criteria to be included in this review. The quality rating and characteristics of the studies are shown in Table 1. The outcomes included eye, ear and skin infections, fever, sepsis, *Helicobacter pylori* infection, and *Staphylococcus aureus* carriage among healthy children (Table 2).

Burden of Disease

The pooled prevalence of infections (not including respiratory and diarrhea) among children aged <5 years between 2002 and 2013 was 18.42% (95% CI: 9.30–30.62; I^2 : 98.46%, $p<0.0001$) (Fig. 2). The rural and urban difference in prevalence was large, with children from rural area showing a higher prevalence of infections (Table 3). $p<0.0001$ for the I^2 values derived suggest gross heterogeneity in the literature included in meta-analysis for calculating rural, urban, and combined pooled prevalence.

The pooled prevalence of eye infections (30.61%) was the highest followed by skin infections (26.48%), eye infections (12.91%), and sepsis (8.14%) (Table 4). On systematic review, the prevalence of skin, eye, and other infections (excluding acute respiratory infections and diarrhea) was reported to be 3.7 [13]–50.8% [18], with 1.7 episodes per child year being contributed by infections of ears and skin [14].

Risk Factors of Infections

Since none of the included studies reported any risk factors in common except young age, meta-analysis of risk factors could not be performed. Age 1–2 years [16] and 3–5 months [14] reported in two studies was analyzed together to yield a point estimate of 1.24 (95% CI: 0.99–1.55, $p<0.05$). The I^2 (p) and τ^2 (SE) were 0.00 (0.53) and 0.00 (0.04), respectively, indicating minimal variation due to heterogeneity across and between the two studies in random effects model.

Three studies included in this review have studied ear infection as the outcome of interest [11,12,14] and reported age of child 3–5 months, cold season, female sex, tobacco based occupation in household, presence of nasal symptoms and passive smoking to be significantly and positively associated. Single studies on skin infection and sepsis [13], eye infection [18], nasal infection [10], and fever [16], respectively, reported inappropriate

breastfeeding; animal pens near household, unclean face and absence of latrine; attending school and large family; and age 1–2 years at maximum risk compared with 2–3 and 3–4 years to be positively associated. Four studies [12,17,19] did not report any association with risk factors (Table 2).

DISCUSSION

The eye infections were found to be the most common infection of childhood on meta-analysis, closely followed by skin infections, whereas ear infection and sepsis were less prevalent. The pooled prevalence of infections is largely consistent with other independent studies [20–22]. The rural and urban differences signify the presence of a large number of risk factors in the rural areas. This systematic review helped us to identify overcrowding, low socio-economic status, and insanitary living conditions to be positively associated with most childhood diseases. These risk factors exert compounded effect in the presence of addictions among the elders at home [23–24]. This, however, does not imply generalized applicability since we derived a number of inconsistent findings from our review of single studies. The review also did not yield definite information on the role of vaccination, personal hygiene, good postnatal care, and breastfeeding in protecting children from infection. Studies have reported a wide array of infections that include hepatitis, measles, chicken pox, and fevers linked to adverse home environment and poor economic conditions [25].

Girl children are more prone to infections at home since they are often malnourished [26,27], not well fed [27], do not attend school and help in household chores [28] predisposing them to overcrowding and indoor air pollution [29]. Boys, on the other hand, are commonly affected at school mostly by viral, parasitic, or fungal infections as a result of crowded classrooms [30]. Studies from small Indian towns showed a higher prevalence of common disorders among girls [26,30], and these infections were associated with poor housing conditions and domestic risk factors [31]. The Indian school health program, aimed at early identification of common childhood diseases, is not conducted routinely (especially in rural areas) possibly giving rise to secondary attacks and chronic diseases which are transmitted to fellow children and family members [32].

Infections of the ears, eyes, and skin affect a large number of under-five children in India. However, our search identified few good quality studies for these infections. The determinants for these infections have been reported to be mostly of poor environmental origin, including overcrowding and poor housing and sanitation [33,34]; the current review findings are concordant provided large family size is taken as a surrogate for overcrowding. The major risk factors for acquiring common skin diseases in developing countries have been identified as hot and humid climate, poor personal hygiene, low use of water, overcrowding and simultaneous presence of other skin disorders such as scabies, insect bites, and traumatic sores [5,32,33]. We did not find any studies that reported the aforesaid risk factors, except one reporting unclean face [18], which may be considered a proxy indicator for low water use leading to trachoma. We did not find studies that explored the role of different biomarkers [35] for predicting infections among children. This presents the opportunity to test and implement the multiple exposures multiple effects model [36]

suggested by the WHO under global initiative on children's environmental Health indicators to study risk factors in multiple settings across the country.

The gaps in the present review are the association of disease with specific strains of infectious agent, role of vaccination and immunization status of children [37,38] role of nutritional deficiencies among children [7,27], certain environmental exposures during intrauterine life [39], role of home environment [40], and association with co-morbidities. Countries that have included pneumococcal vaccination in their immunization programs have been able to demonstrate a clear reduction in ear infection rates and related respiratory illness [41]. These need to be addressed in research as there is an acute dearth of studies on these aspects as determinants of childhood infections in the country.

Strengths/Limitations

Independent literature search and rating of the methodological quality of the included studies are the strengths of this review. We included only peer-reviewed, original research journal articles that were published in English and indexed in PubMed, thereby further insisting on the quality of included studies. However, our quality scoring could not differentiate between low reporting and low methodological quality. Few studies on the prevalence of common morbidities among under-five children were found outside PubMed, which could not be included for meta-analysis. This may have influenced the high prevalence of the conditions reported in this systematic review while under-representation of other infections which could not be included.

CONCLUSION

Infections of the eye, followed by skin infections were found to be the most common infections affecting Indian under-five children. Rural children are affected more than their urban counterparts due to the presence of multiple risk factors. More evidence is warranted to establish the role of immunization, malnutrition, and association of co-morbidities with other common childhood infections.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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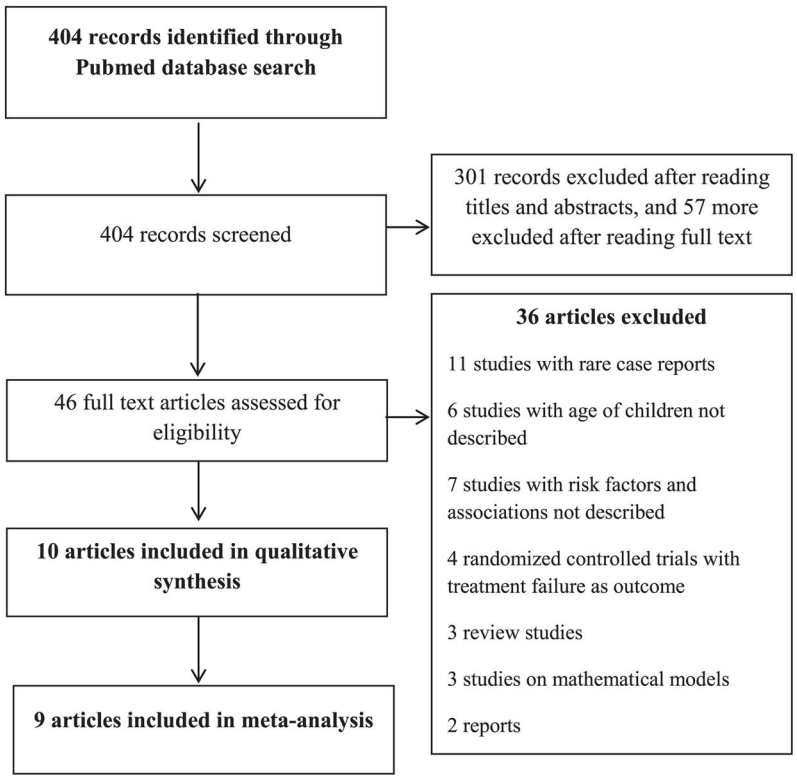

Figure 1.

PRISMA diagram showing selection of studies for inclusion in systematic review of risk factors of acute infectious morbidities among under- five children in India

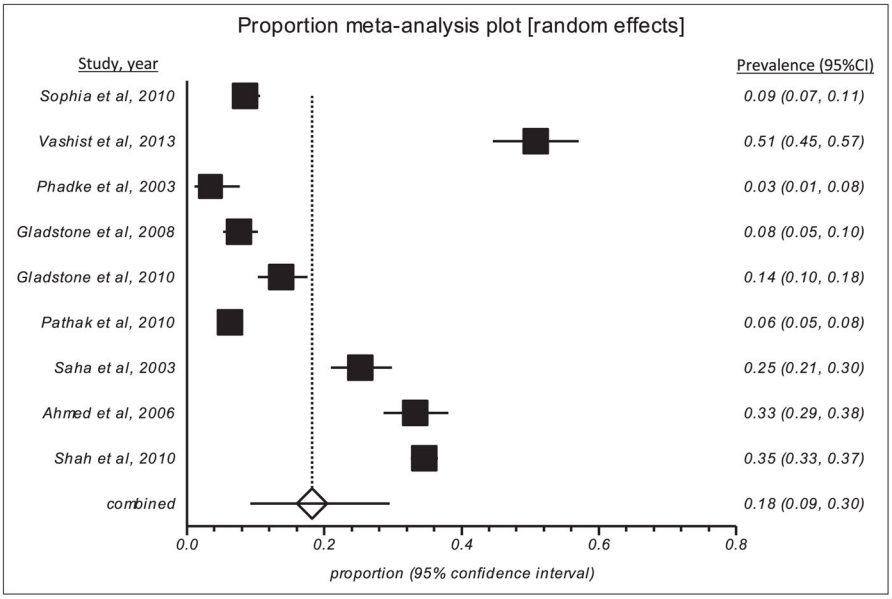

Figure 2.
Pooled prevalence of ear, skin and other infections in Indian children

Table 1

Characteristics of the included studies

Authors	Year	Study design	Setting	Quality
Pathak A et al. [10]	2010	Prospective, period prevalence (hospital based)	Ujjain, Madhya Pradesh	Good
Sophia A et al. [11]	2010	Case control design	Vellore, Tamil Nadu	Good
Gladstone BP et al. [12]	2010	Cohort	Vellore, Tamil Nadu	Poor
Phadke MA et al. [13]	2003	Observational (case control)	Pune, Maharashtra	Good
Gladstone BP et al. [14]	2008	Cohort study	Vellore, Tamil Nadu	Good
Mohile M et al. [15]	2002	Cross sectional Hospital based	New Delhi	Poor
Saha MR et al. [16]	2003	Hospital based retrospective	Kolkata, West Bengal	Poor
Ahmed KS et al.[17]	2006	Cross sectional	Hyderabad, Andhra Pradesh	Fair
Vashist P et al. [18]	2013	Surveillance study	Car Nicobar, Andaman & Nicobar Islands	Fair
Shah AS et al. [19]	2010	Prospective, surveillance	Bangalore, Karnataka	Poor

1–4: Poor, 5–7: Fair, 8–10: Good

Table 2

Summary of studies enumerating risk factors of infections other than diarrhea and acute respiratory in children

Authors (year)	Place	No. of participants	Age (months)	Outcome	Burden reported (%)	Risk factors	Test of association	Strength of association	Confidence interval, p value
Phadke MA et al. (2003) [13]	Urban	148	<60	Sepsis	18.5	Breast fed	OR	Ref.	-
				Skin infection	3.70	Replacement feeding	OR	0.093	0.062–0.136
Gladstone BP et al. (2008) [14]	Urban	452	<60	Ear infection	17.4	Age 0–2 months	Rate ratio	Ref.	-
						Age 3–5 months	Rate ratio	1.1	1.0–1.7 (p=0.05)
						Hot/dry season (Mar–Aug)	Rate ratio	Ref.	-
						Cold/wet season (Sep–Feb)	Rate ratio	1.1	1.1–1.2 (p<0.001)
						Male	Rate ratio	Ref.	-
						Female	Rate ratio	0.9	0.8–1.0 (p=0.02)
						No beedi work	Rate ratio	Ref.	-
						Beedi work in household	Rate ratio	1.2	1.1–1.4 (p<0.001)
Mohile M et al. (2002) [15]	Urban	70	<28 days	Conjunctivitis	-	Delivered by caesarian section due to Premature rupture of membranes			p=0.89
Gladstone BP et al. (2010) [12]	Urban	373	0–36	Eye, ear, skin, localized infections	13.9	None			
Pathak A et al. (2010) [10]	Urban slum	1562	1–59	Nasal carriage of *S. aureus*	6.3 (95 CI=5.07–7.47)	Child not attending school	Adj OR	Ref.	-
						Child attending preschool	Adj OR	4.26	2.25–8.03
						Child attending school	Adj OR	3.02	1.27–7.1
						Family size <4	Adj OR	Ref.	8–1.0
						Family size more than 10 members	Adj OR	2.76	6–7.15
Sophia A et al. (2010) [11]	Rural	800	>11	Otitis media	8.6	Persistent rhinorrhea absent	OR	Ref.	-
						Persistent rhinorrhoes present	OR	7.56	2.73–20.92
						Snoring absent	Adj. OR	Ref.	-
						Snoring present	Adj. OR	4.89	1.32–18.1
						Seasonal rhinitis absent	OR	Ref.	-
						Seasonal rhinitis present	OR	5.93	1.33–26.5
						Passive smoking absent	Adj. OR	Ref.	-
						Passive smoking present	Adj. OR	3.29	1.05–10.3
Saha MR et al. (2003) [16]	Urban slum	388	0–59	Typhoid	25.51	Age between 2–3 years	ANOVA		p<0.01
						Age between 1–2 years	ANOVA		p<0.05
						Age between 3–4 years	ANOVA		p<0.05

Authors (year)	Place	No. of participants	Age (months)	Outcome	Burden reported (%)	Risk factors	Test of association	Strength of association	Confidence interval, p value
Ahmed KS et al. (2006) [17]	Urban	400	0–59	H.pylori infection	33.3				
Vashist P et al. (2013) [18]	Rural	258	0–59	Trachoma	50.8	Presence of animal pens near households			p=0.04
						Unclean face			
						Absence of functional latrine			
Shah AS et al. (2010) [19]	Urban	2219	0–60	Sepsis	34.6				

OR: Odds ratio

Table 3

Point estimates for infections (not including respiratory and diarrhoea) among under- five children in India

Place	Pooled prevalence (95% CI)	I^2 (95% CI)	p value
Rural (n=2)	26.81 (0.33–73.55)	99.48 (99.10–99.70)	<0.0001
Urban (n=8)	16.03 (6.66–28.46)	99.11 (98.93–99.33)	<0.0001
Overall	18.42 (9.30–30.62)	98.46 (97.90–98.87)	<0.0001

CI: Confidence interval

Table 4

Pooled prevalence for infections (not including respiratory and diarrhoea) among under- five children in India

Infection type (no. of studies)	Pooled prevalence (95% CI)	I^2 (95% CI)	Cochran Q (d.f.)	p value
Sepsis (n=2)	8.14 (1.12–20.71)	93.9 (78.01–97.95)	14.86 (1)	0.0001
Ear infection (n=3)	12.91 (7.89–18.94)	90.8 (71.2–95.3)	21.77 (2)	<0.0001
Skin infection (n=2)	26.48 (12.40–43.59)	94.74 (83.93–98.28)	18.95 (1)	<0.0001
Eye infection (n=2)	30.61 (3.26–69.98)	99.04 (98.11–99.51)	104.20 (1)	<0.0001

CI: Confidence interval