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# Childhood Pneumonia and Diarrhoea 1



## Global burden of childhood pneumonia and diarrhoea

Christa L Fischer Walker\*, Igor Rudan\*, Li Liu, Harish Nair, Evropi Theodoratou, Zulfiqar A Bhutta, Katherine L O'Brien, Harry Campbell†, Robert E Black†

Diarrhoea and pneumonia are the leading infectious causes of childhood morbidity and mortality. We comprehensively reviewed the epidemiology of childhood diarrhoea and pneumonia in 2010–11 to inform the planning of integrated control programmes for both illnesses. We estimated that, in 2010, there were 1·731 billion episodes of diarrhoea (36 million of which progressed to severe episodes) and 120 million episodes of pneumonia (14 million of which progressed to severe episodes) in children younger than 5 years. We estimated that, in 2011, 700 000 episodes of diarrhoea and 1·3 million of pneumonia led to death. A high proportion of deaths occurs in the first 2 years of life in both diseases—72% for diarrhoea and 81% for pneumonia. The epidemiology of childhood diarrhoea and that of pneumonia overlap, which might be partly because of shared risk factors, such as undernutrition, suboptimum breastfeeding, and zinc deficiency. Rotavirus is the most common cause of vaccine-preventable severe diarrhoea (associated with 28% of cases), and *Streptococcus pneumoniae* (18·3%) of vaccine-preventable severe pneumonia. Morbidity and mortality from childhood pneumonia and diarrhoea are falling, but action is needed globally and at country level to accelerate the reduction.

### Introduction

Acute diarrhoeal and respiratory infections are the most frequent childhood illnesses and causes of attendance at health services in low-income and middle-income countries. Severe diarrhoea and pneumonia are among the most common reasons for hospital admission in children in low-income and middle-income countries. Despite large reductions in child mortality between 2000 and 2010 (both all-cause mortality, and that specifically associated with diarrhoea and pneumonia), these diseases remain major causes of avoidable deaths and account for about 30% of all child deaths worldwide.<sup>1,2</sup> Thus, achievement of the fourth Millennium Development Goal and the longer-term target<sup>3</sup> of reduction of child mortality to 20 deaths or fewer per 1000 livebirths in all countries by 2035 will necessitate substantial decreases in mortality from the two illnesses.<sup>4</sup> In this first paper in the Series, we review the epidemiological profile of childhood diarrhoea and pneumonia and present data jointly to inform the planning of integrated control programmes for both illnesses. We bring together previously reported data to compare and contrast the diseases and present new estimates of severe disease, report updated mortality estimates for 2011 (including the estimated number of deaths, by age), and establish how many severe cases and deaths could have been prevented by vaccination.

### Search strategy and selection criteria

We searched PubMed, Embase, Global Health, Scopus, Web of Knowledge, and the WHO Regional Databases with combinations of key terms and medical subject headings, including “diarrhea”, “pneumonia”, “respiratory tract infection”, “children”, “childhood”, “neonates”, “neonatal”, “age-group 0–4 years”, “epidemiology”, “incidence”, “prevalence”, “morbidity”, “mortality”, “case-fatality”, “severity”, “sepsis”, “sequelae”, and “etiology”,

and terms for specific risk factors and specific pathogens to identify pertinent reviews. We did not restrict our search by language of publication. We brought together 24 separate systematic reviews to identify all sources of information about incidence (overall and severe cases only), mortality, sequelae, age and sex distribution, and causes of, and risk factors for, diarrhoea and pneumonia in children younger than 5 years. When recent (ie,

### Key messages

- Diarrhoea and pneumonia remain the leading infectious causes of death in children younger than 5 years, and caused an estimated 700 000 and 1·3 million deaths, respectively, in 2011
- 72% of deaths associated with diarrhoea and 81% of those associated with pneumonia happen in the first 2 years of life, suggesting that an increased emphasis on prevention and treatment in neonates and children younger than 2 years is crucial
- The global burden of incidence and severe disease for both diarrhoea and pneumonia is highest in southeast Asia and Africa
- Nearly a third of episodes of severe diarrhoea are preventable by vaccination (ie, against rotavirus and cholera), whereas vaccine-preventable pneumonias (ie, those caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and the influenza virus) account for at least a third of severe episodes and two-thirds of deaths
- Nearly three-quarters of diarrhoea mortality and pneumonia mortality are concentrated in 15 high-burden countries, yet data sources from these countries are scant
- Undernutrition is a key shared risk factor for morbidity and mortality associated with diarrhoea and pneumonia, and interventions to improve nutrition should be prioritised

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\*These authors contributed equally

†These authors contributed equally

This is the first in a **Series** of four papers about childhood pneumonia and diarrhoea

Department of International Health, Johns Hopkins

Bloomberg School of Public Health, Baltimore, MD, USA (C L Fischer Walker PhD,

L Liu PhD, Prof K L O'Brien MD, Prof R E Black MD); Centre for Population Health Sciences and Global Health Academy, University of Edinburgh

Medical School, Edinburgh, UK (Prof I Rudan PhD, H Nair PhD, E Theodoratou PhD,

Prof H Campbell MD); Public Health Foundation of India, New Delhi, India (H Nair); and Aga Khan University, Karachi, Pakistan (Prof Z A Bhutta PhD)

Correspondence to:

Prof Robert E Black, Department of International Health, Johns Hopkins Bloomberg School of Public Health, 615 N Wolfe Street, Baltimore, MD 21205, USA [rblack@jhsph.edu](mailto:rblack@jhsph.edu)

between Jan 1, 2008, and Dec 31, 2012) reviews had been published, we used published results, but when relevant reviews had not been published or needed updating, we did new systematic reviews in accordance with standard Child Health Epidemiology Reference Group (a technical reference group that was created to provide independent estimates of the main causes of childhood morbidity and mortality) guidelines for systematic reviews.<sup>5,6</sup> The appendix contains further details about our methods, including case definitions of the 24 reviews used.

We estimated the number of cases of diarrhoea and pneumonia (including the number of severe cases) that occurred in 2010, and deaths that occurred in 2011, globally and for each WHO region. We made the same burden estimates for the 15 countries with the greatest absolute numbers of combined deaths from childhood diarrhoea and pneumonia.

For low-income and middle-income countries, we estimated country-level diarrhoea incidence with the expectation-maximisation algorithm, which incorporated age-specific study data and overall variations in incidence by region.<sup>7</sup> For high-income countries, we calculated a median diarrhoea incidence on the basis of studies that met our previously published inclusion and exclusion criteria.<sup>8</sup> We then generated population-weighted regional and global estimates on the basis of country-level incidence and the population of children younger than 5 years in 2010.

For pneumonia, we identified 35 cohort studies, from which we derived a median global estimate of incidence (and an IQR). With this so-called global envelope defined, we then used information about the prevalence of five major risk factors for incidence at country level to estimate country-level incidence, which we summed to derive regional estimates.<sup>9,10</sup> We identified a subset of community-based prospective studies that included data for the proportion of cases of pneumonia that presented as severe. We used the median proportion from these studies to estimate the number of severe cases of diarrhoea and pneumonia. Severe diarrhoea was defined as disease with moderate or severe dehydration, whereas severe pneumonia was that which was judged by a doctor to necessitate hospital admission.<sup>11,12</sup> Estimates of mortality from childhood diarrhoea and pneumonia for 2010–11 based on country-level results that were aggregated for regional and global mortality have been published (appendix).<sup>1,2</sup>

For diarrhoea incidence by age, we abstracted age-specific incidence and used the expectation-maximisation method to generate regional and global rates.<sup>8</sup> The distribution of pneumonia incidence by age was based on a subset of prospective community-based studies.<sup>8,10</sup> Median incidences in older age groups (ie, age 1–4 years) were derived in relation to incidence in the first year of life (appendix). Methods to investigate the burden of sequelae from pneumonia and diarrhoea have been published.<sup>13–15</sup> Mortality by age was based on age-specific

data from verbal autopsy studies with published age-specific data available.<sup>1</sup>

The comparative analysis of yearly reductions in mortality was based on a two-dimensional plot of country-specific diarrhoea rates on corresponding pneumonia rates for all countries in 2010 (dataset and model presented previously<sup>1</sup>). The same dataset based on country-level estimates was also used for a regression of the proportional contribution of diarrhoea and pneumonia to overall child mortality in 74 Countdown countries in 2010 (appendix).

We also present the contribution of vaccine-preventable causes of diarrhoea and pneumonia to severe morbidity and mortality (appendix). For diarrhoea, we systematically reviewed all studies that provided a breakdown of causes of severe episodes; proportions of disease caused by rotavirus and *Vibrio cholerae*, the two vaccine-preventable diarrhoea pathogens, were applied to regional envelopes of severe cases and deaths. For pneumonia, we did an updated meta-analysis of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b vaccine trials (methods<sup>16,17</sup> as per that done in 2000), and adjusted the derived proportions attributable to those pathogens for the pneumococcal and *H influenzae* type b vaccination rollout during the past 10 years.<sup>18</sup> We made no adjustments for the effects of the HIV/AIDS pandemic, because the relation between HIV/AIDS and severe morbidity and mortality from pneumonia is not sufficiently understood. Additionally, we used adjusted published estimates of influenza to provide a causative range for severe episodes and deaths from pneumonia,<sup>19</sup> but did not include a review of the burden of respiratory syncytial virus because an effective vaccine is not available.

We did a systematic review of published reviews of risk factors for childhood pneumonia and diarrhoea and retained risk factors that met the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria level 1 or 2 in favour of a definite effect.

## Data for action on childhood pneumonia and diarrhoea

### Global and regional burden

Table 1 shows the number of episodes, severe episodes, and deaths by WHO regions and globally. We estimate that 2% of diarrhoea episodes and 12% of pneumonia episodes progress to severe disease. Our results suggest a worldwide case-fatality ratio from severe diarrhoea of 2.0% (uncertainty range 1.4–4.4) and from severe pneumonia of 8.9% (3.1–12.5). In 2011, the number of deaths from the two diseases fell to 1.97 million (0.71 million associated with diarrhoea and 1.26 million with pneumonia).

The incidence of diarrhoea does not differ substantially between regions, but incidence and case-fatality ratios are much higher in low-income than in middle-income and high-income countries. Pneumonia incidence is more variable between regions than is diarrhoea incidence; adjusted for immunisation against *H influenzae* type b and *S pneumoniae*, it was lowest in the European region and highest in the African and southeast Asian regions.

For the Child Health Epidemiology Reference Group see <http://www.cherg.org>

See Online for appendix

For the WHO regions see <http://www.who.int/about/regions/en/index.html>

	Population aged 0–4 years (2010)	Diarrhoea				Pneumonia					
		Incidence* (2.1–5.0)	Total episodes (×10 <sup>6</sup> ) (282.2–669.2)	Total severe episodes (×10 <sup>6</sup> ) (7.1–11.3)	Total deaths (×10 <sup>3</sup> ) (195.8–564.7)	Change in mortality from 2010 (%)	Incidence* (0.14–0.63)	Total episodes (×10 <sup>6</sup> ) (18.2–84.4)	Total severe episodes (×10 <sup>6</sup> ) (2.98–12.03)	Total deaths (×10 <sup>3</sup> ) (437.8–627.3)	Change in mortality from 2010 (%)
African region	133 340 762	3.3 (2.1–5.0)	437.6 (282.2–669.2)	9.6 (7.1–11.3)	353.3 (195.8–564.7)	-17.1	0.27 (0.14–0.63)	36.4 (18.2–84.4)	4.17 (2.98–12.03)	540.6 (437.8–627.3)	-10.5
American region	76 995 700	3.2 (2.6–3.8)	248.1 (199.6–289.2)	4.8 (3.6–5.7)	11.0 (8.2–23.9)	-3.0	0.08 (0.04–0.18)	6.4 (3.3–14.5)	0.78 (0.57–2.18)	23.9 (22.6–35.6)	-15.7
Eastern Mediterranean region	72 151 965	2.9 (1.6–4.2)	208.8 (114.1–300.8)	4.3 (3.2–5.0)	96.6 (64.2–153.3)	-24.2	0.23 (0.11–0.53)	16.4 (8.2–38.0)	1.88 (1.35–5.42)	168.4 (147.3–217.1)	-16.5
European region	54 605 243	2.8 (2.3–3.3)	154.3 (127.1–177.7)	2.5 (1.9–3.0)	6.3 (4.2–10.8)	-1.7	0.03 (0.02–0.04)	1.6 (1.3–2.1)	0.41 (0.32–0.72)	18.1 (14.7–23.4)	-6.3
Southeast Asian region	179 956 087	2.4 (1.5–3.3)	427.4 (262.6–589.0)	9.3 (6.9–10.9)	227.7 (186.9–292.8)	-1.2	0.26 (0.13–0.61)	47.4 (23.7–109.8)	5.44 (3.81–15.63)	443.8 (336.7–534.2)	-3.8
Western Pacific region	116 411 580	2.2 (1.3–2.5)	256.3 (151.7–290.6)	5.5 (4.0–6.4)	16.9 (6.0–23.7)	-27.8	0.11 (0.05–0.24)	12.2 (6.2–28.2)	1.43 (1.01–4.06)	61.9 (50.7–78.0)	-17.2
World	633 461 337	2.7 (2.1–3.2)	1731.3 (1375.7–2032.8)	36.1 (26.6–42.4)	711.8 (491.1–1049.3)	-11.1	0.19 (0.10–0.44)	120.4 (60.8–277.0)	14.11 (10.03–40.04)	1256.8 (1053.2–1482.9)	-10.0

We calculated deaths on the basis of total number of deaths estimates for 2011;<sup>2</sup> proportionate mortality for diarrhoea and pneumonia were as reported for 2010.<sup>1</sup> Data in parentheses are uncertainty ranges. \*Incidence=episodes per child-year.

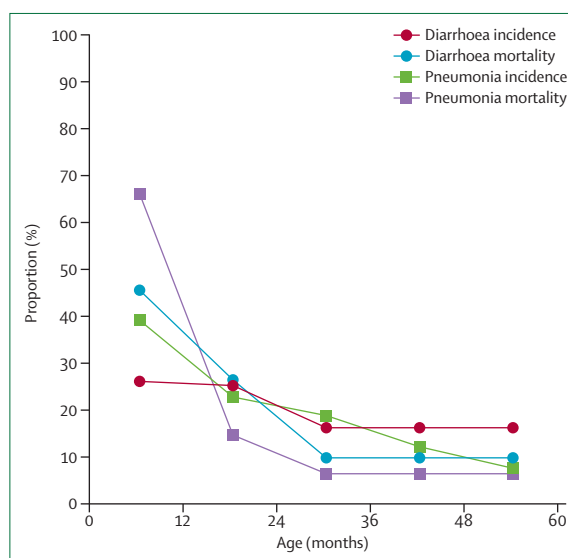
**Table 1: Global and regional burden of diarrhoea and pneumonia per year in children aged 0–4 years, by WHO region**

The greatest proportions of severe episodes of diarrhoea and pneumonia were in the southeast Asian (26% and 39%, respectively) and African regions (26% and 30%, respectively). The highest numbers of childhood deaths were in sub-Saharan Africa, where 50% of deaths from diarrhoea and 43% of deaths from pneumonia occurred in 2011.

15 countries—namely, Afghanistan, Angola, Burkina Faso, China, Democratic Republic of the Congo, Ethiopia, India, Indonesia, Kenya, Mali, Niger, Nigeria, Pakistan, Tanzania, and Uganda—account for 53% of total episodes of diarrhoea and 56% of severe episodes, and 65% of total episodes of pneumonia and 64% of severe episodes (appendix). In 2011, 74% of the total burden of diarrhoea and pneumonia mortality in children younger than 5 years was in these 15 countries. Thus, as outcomes become more severe, more of the global burden is concentrated in the highest burden countries.

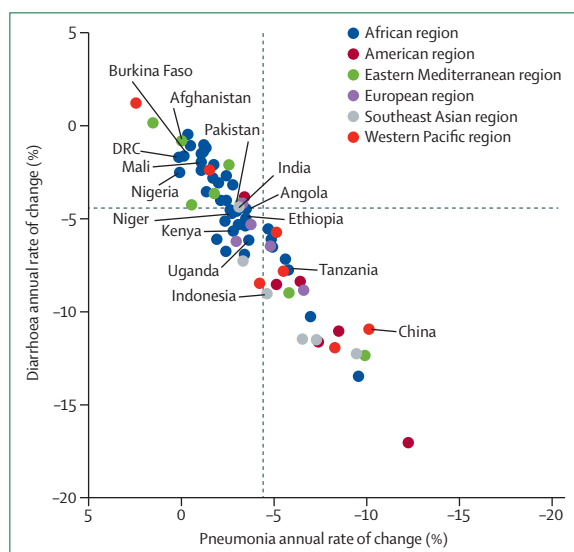
### Burden by age and sex

Incidence of, and mortality from, diarrhoea and pneumonia vary by age (figure 1). The burden of disease is mainly in younger age groups; 72% of deaths from diarrhoea and 81% of deaths from pneumonia happen in children younger than 2 years. Pneumonia incidence falls less rapidly with age than does mortality from the



**Figure 1: Distribution of cases of, and deaths from, diarrhoea and pneumonia in children aged 0–4 years**

disease. Diarrhoea incidence peaks at age 6–11 months and then decreases with age;<sup>8</sup> proportionate mortality is highest from age 0–11 months, the ages at which the risk of disease and severe disease also peak.



**Figure 2: Annual rates of change in diarrhoea-specific and pneumonia-specific mortality between 2000 and 2010**

74 Countdown to 2015 countries<sup>49</sup> are shown; the 15 countries with the highest burdens are labelled. Dotted lines show target annual rates of change to achieve the fourth Millennium Development Goal. DRC=Democratic Republic of the Congo.

Few data are available for sex differences in incidence and mortality. We identified 23 studies with information about sex with respect to the incidence of diarrhoea,<sup>20–42</sup> seven<sup>24,29–31,36,37,39</sup> of which showed significantly more cases in boys than in girls. The other studies did not show significant differences between the sexes. 11 community-based studies had sex-specific data for pneumonia incidence, which was higher in boys than in girls (median odds ratio 1.3 [IQR 1.2–1.4]; unpublished); the largest differences were noted in south Asia.<sup>12</sup>

### Long-term sequelae

For an otherwise healthy child, a single episode of diarrhoea is typically self-limiting and has no long-term sequelae. However, for children in low-income and middle-income countries, several episodes per year can lead to nutritional deficits and long-term consequences. A pooled analysis of nine studies that assessed morbidity and anthropometry showed that the odds of growth stunting by age 2 years increased by 1.13 (95% CI 1.07–1.19) for every five episodes of diarrhoea.<sup>13</sup> The proportion of stunting that could be attributed to five or more episodes of diarrhoea before 2 years of age was 25% (8–38). Stunting is an important sequela because it is indicative of long-term nutritional deficit and is associated with decreased cognitive function.<sup>43</sup> Repeated episodes of diarrhoea can thus lead to cognitive deficits via stunting, but not independently as some researchers have postulated.<sup>44</sup> Guillain-Barré syndrome, haemolytic uraemic syndrome, and reactive arthritis are rarely noted and are attributable only to selected pathogens (unpublished).<sup>15,45</sup>

A systematic review<sup>14</sup> of pneumonia sequelae showed that the risk of at least one long-term major sequela was 5.5% (95% CI 2.8–8.3) in non-severe pneumonia and 13.6% (6.2–21.1) in severe pneumonia treated in hospital. The most common sequela was reduction in lung volume. Bronchiectasis was reported after 0.9% (0.7–8.7) of cases of severe pneumonia. The risk of major sequelae was higher in children younger than 2 years (13.4% [4.5–22.3]) than in those aged 2–4 years. These findings are consistent with large population-based studies of children in the early 1990s,<sup>46–48</sup> which showed a 6–7% increased risk of reduced lung capacity after childhood pneumonia. These studies suggested that risk was highest in the first year of life, presumably because of damage to lung parenchyma and bronchioles in an early stage of lung development, which is postulated to impair lung growth and reduce vital capacity and forced expiratory volume.<sup>14</sup> The link between childhood pneumonia and obstructive lung disease is not yet clear.<sup>14</sup>

### Temporal patterns in mortality

Rates of mortality from diarrhoea and pneumonia are highly correlated, and changes in mortality with time are similar for both diseases within the same country (figure 2). The yearly rate of change varies substantially between countries, with China reaching 12% for both diseases, whereas other countries have rates that are much less than the fourth Millennium Development Goal target rate of 4.4%. More than ten countries have rates of decline for diarrhoea that are needed to achieve the target of the fourth Millennium Development Goal, but are unable to achieve the same rates for pneumonia (figure 2 [lower left quadrant]). Conversely, no countries achieved the target rates for pneumonia but not for diarrhoea.

### Vaccine-preventable causes

Table 2 presents a breakdown of the global and regional burden of severe episodes of, and deaths from, diarrhoea and pneumonia that are caused by vaccine-preventable pathogens. A full review of the causes of diarrhoea and pneumonia is beyond the scope of this Series paper and will be published elsewhere.<sup>50</sup> The most common cause of severe and fatal diarrhoea worldwide is rotavirus (associated with 28% of severe cases and 28% of fatal cases); the data analysed here are from before the rotavirus vaccine was available, and thus this proportion might be slightly lower in 2011 in the Americas and a few other countries where the vaccine is used (unpublished). *V cholerae* causes roughly 1% of severe diarrhoea worldwide, but is endemic in south Asia and some countries in sub-Saharan Africa. The global estimate of cases of severe diarrhoea associated with *V cholerae*, which is based on available data from a global model, differs slightly from that based on regional estimates derived from a subset of regional data (table 2). Because regional estimates are less certain (and thus have wider CIs) than are estimates produced

from a global model, we use the global figure for the pathogen-specific global burden of severe diarrhoea and mortality. The outbreak of cholera that began in October, 2010, in Haiti is not included in these estimates, which are for endemic disease only.<sup>51</sup>

Many other viruses (including norovirus, astrovirus, and adenovirus), bacteria (the most common of which are pathogenic *Escherichia coli*, *Shigella*, *Campylobacter*, and *Salmonella*) and parasites (including *Giardia lamblia*, *Entamoeba histolytica*, and *Cryptosporidium*) cause severe diarrhoea but cannot be prevented by vaccines. *G lamblia* and *E histolytica* do not typically cause severe dehydrating diarrhoea, but *Cryptosporidium* spp can in some circumstances.

Important vaccine-preventable causes of severe pneumonia are *S pneumoniae* (which causes at least 18% of severe episodes and 33% of deaths worldwide), the influenza virus (7% of severe episodes and 11% of deaths), and *H influenzae* type b (4% of severe episodes and 16% of deaths). The contribution of *H influenzae* type b is falling quite rapidly because of widespread vaccination in many low-income and middle-income countries. A vaccine against respiratory syncytial virus is in development.<sup>50</sup> Other causes of severe pneumonia that are not preventable by vaccination include *Staphylococcus aureus* (which often causes very severe presentations), non-typhoidal *Salmonella* spp in regions of Africa where malaria is endemic,<sup>52,53</sup>

	African region	American region	Eastern Mediterranean region	European region	Southeast Asian region	Western Pacific region	World
<b>Severe diarrhoea episodes</b>							
Rotavirus:							
Episodes (×10 <sup>3</sup> )	2557 (1901–3026)	1129 (833–1330)	1344 (990–1576)	660 (488–781)	2382 (1753–2790)	1781 (1312–2090)	9853 (7277–11593)
Proportion of all severe episodes (%)	26.8%	23.4%	31.3%	25.9%	25.5%	32.6%	27.3%
<i>Vibrio cholerae</i> :							
Episodes (×10 <sup>3</sup> )	38 (28–45)	..	..	..	416 (306–488)	2 (2–3)	456 (336–536)
Proportion of all severe episodes (%)	0.4%	..	..	..	4.5%	0.04%	1.3%
<b>Diarrhoea deaths</b>							
Rotavirus:							
Deaths (×10 <sup>3</sup> )	95 (52.5–151.3)	2.6 (1.9–5.6)	30.2 (20.1–48.0)	1.6 (1.1–2.8)	58.1 (47.7–74.7)	5.5 (2.0–7.7)	192.7 (133.1–284.4)
Proportion of diarrhoea deaths (%)	26.8%	23.4%	31.3%	25.9%	25.5%	32.6%	27.1%
<i>V cholerae</i> :							
Deaths (×10 <sup>3</sup> )	1.4 (0.8–2.3)	..	..	..	10.2 (8.4–13.2)	0.1 (0.02–0.1)	11.7 (7.9–16.8)
Proportion of diarrhoea deaths (%)	0.4%	..	..	..	4.5%	0.04%	1.6%
<b>Severe pneumonia episodes</b>							
<i>Streptococcus pneumoniae</i> :							
Episodes (×10 <sup>3</sup> )	774 (453–1069)	127 (74–175)	349 (204–482)	70 (41–97)	1001 (585–1382)	263 (154–363)	2585 (1511–3568)
Proportion of all severe episodes (%)	18.6%	16.4%	18.6%	16.9%	18.4%	18.4%	18.3%
<i>Haemophilus influenzae</i> :							
Episodes (×10 <sup>3</sup> )	130 (0–312)	14 (0–34)	52 (0–124)	15 (0–35)	291 (0–698)	72 (0–172)	574 (0–1376)
Proportion of all severe episodes (%)	3.1%	1.9%	2.8%	3.6%	5.4%	5.0%	4.1%
Influenza							
Episodes (×10 <sup>3</sup> )	172 (86–307)	84 (56–126)	155 (57–500)	52 (33–76)	273 (78–1094)	246 (105–597)	982 (414–2699)
Proportion of all severe episodes (%)	4.1%	10.8%	8.3%	12.6%	5.0%	17.2%	7.0%
<b>Pneumonia deaths</b>							
<i>S pneumoniae</i> :							
Deaths (×10 <sup>3</sup> )	177 (94–245)	7 (4–10)	55 (29–77)	6 (3–8)	146 (77–202)	20 (11–28)	411 (218–569)
Proportion of pneumonia deaths (%)	32.7%	29.1%	32.9%	30.8%	33.0%	32.8%	32.7%
<i>H influenzae</i> :							
Deaths (×10 <sup>3</sup> )	70 (9–125)	2 (0–4)	19 (3–35)	3 (0–5)	92 (13–156)	12 (2–21)	197 (27–345)
Proportion of pneumonia deaths (%)	12.9%	9.2%	11.3%	14.3%	20.7%	19.6%	15.7%
Influenza:							
Deaths (×10 <sup>3</sup> )	60 (16–71)	3 (1–4)	19 (5–22)	0 (0–1)	49 (13–58)	7 (2–8)	137 (38–163)
Proportion of pneumonia deaths (%)	11.1%	10.7%	11.1%	5.7%	11.1%	11.0%	10.9%

Data in parentheses are uncertainty estimates.

**Table 2: Contribution of specific pathogens to severe episodes of, and deaths from, childhood diarrhoea and pneumonia, by WHO region**



*Klebsiella pneumoniae* (especially in malnourished children and neonates), *Mycoplasma pneumoniae*, *Chlamydia pneumoniae* (in children older than 3 years), *Mycobacterium tuberculosis* (especially in HIV-positive children) and, less frequently, respiratory viruses, such as parainfluenza viruses 1–3, human metapneumovirus, adenovirus, coronavirus, and bocavirus, often in conjunction with bacterial co-infections.

*Bordetella pertussis*, which causes pertussis, an acute respiratory infection, can cause severe pneumonia, particularly in the first 6 months of life. Although immunisation has greatly reduced its importance, the true burden of pertussis pneumonia is largely unknown because few valid surveillance or research data are available (as a result of difficulties in obtaining laboratory diagnoses, the restricted availability of microbiological

#### Panel 1: Changes in causes of diarrhoea and pneumonia with age and HIV/AIDS infection

Pathogen-specific incidences of diarrhoea vary by age, yet few data are available for generation of age-specific estimates by enteropathogen. In pathogen-endemic areas, infants receive passive protection from transplacental and breastmilk antibodies for the first 6 months of life. Additionally, exclusively breastfed infants are exposed less to many pathogens than are infants who are not breastfed or receive mixed feedings. After passive immunity wanes, the child's first exposure to a pathogen often results in severe disease; subsequent illnesses tend to be milder and less likely to result in severe dehydration, admission to hospital, and death. For example, symptomatic rotavirus disease is less common in the first than in the second 6 months of life.<sup>55</sup> The highest rates of severe disease occur at age 6–24 months. Rates of illness then fall as children age because the first infection induces at least partial active immunity, which protects against subsequent illnesses. In view of the high number of enteric pathogens, children won't be immune to all after first infection, so exposures to new organisms or pathogen strains induce illness in older children.

The causes of life-threatening invasive bacterial infections in the neonatal period, when clinical syndromes of pneumonia, meningitis, and sepsis are practically indistinguishable, are uncertain. Most data from developing countries are reported from unrepresentative hospital-based studies, which have little relevance in home-birth settings (where most children are born in many countries).<sup>56–59</sup> Some data from community-based studies in developing countries suggest that Gram-negative rods are the major cause in early neonates (0–6 days), in whom such rods might cause as many as three of every four infections. *Klebsiella* spp and *Staphylococcus aureus*, but also *Escherichia coli* and group B streptococci are thought to be the leading causes in the early neonatal period, when most deaths occur. In the late neonatal and postneonatal periods, Gram-positive cocci (primarily *Streptococcus* spp) cause about two of every three infections. In the early neonatal period, any of these infections might be environmentally acquired because of unhygienic delivery practices in low-income settings rather than perinatally acquired, which might explain the predominance of Gram-negative infections in home-born infants.<sup>56–59</sup> However, even hospital-born babies in developing countries have a three times greater to 20 times greater risk of neonatal infections because of poor infection-control practices.<sup>56–59</sup> *Klebsiella pneumoniae*, other Gram-negative rods (*E coli*, *Pseudomonas* spp, *Acinetobacter* spp), and *S aureus* are the major pathogens isolated from the bloodstream in hospital settings in the

neonatal period, and about 70% of these blood isolates might be untreatable in low-income settings.<sup>56–59</sup> As children grow older, the causes of clinical pneumonia are mainly respiratory syncytial virus, influenza virus, *Streptococcus pneumoniae*, and *Haemophilus influenzae*.

Chronic diarrhoea is part of the clinical syndrome of AIDS; it occurs in roughly 50% of children younger than 5 years who have AIDS in high-income countries and nearly all of those in low-income and middle-income countries. Individuals who are infected with HIV and not yet immunodeficient are susceptible to the same microbial causes of diarrhoea as are HIV-negative individuals. Additionally, as the immune system fails, generally when patients have fewer than 200 CD4 cells per  $\mu\text{L}$ , such individuals are also susceptible to many opportunistic pathogens, such as *Mycobacterium tuberculosis*, the *Mycobacterium avium* complex, cryptosporidium, microsporidia, and cytomegalovirus. HIV can directly affect the intestinal mucosa, resulting in enteropathy with diarrhoea due to changed intestinal functions.<sup>60</sup> Infection with *Clostridium difficile* is common in patients exposed to antimicrobials and hospital settings.

Children infected with HIV have a greatly increased risk of pneumonia, particularly bacterial pneumonia (*S pneumoniae* and *H influenzae*).<sup>61</sup> In addition to the causes of pneumonia listed in table 2, *Pneumocystis jirovecii*, *M tuberculosis*, cytomegalovirus, and Gram-negative infections are important causes of severe pneumonia in HIV-positive children in the postneonatal period. Of these pathogens, *P jirovecii* and cytomegalovirus pneumonia occur mainly in infants aged 2–6 months. Infections with more than one pathogen or antibiotic-resistant bacteria are more common in HIV-positive than in HIV-negative children, and lead to higher case-fatality ratios.<sup>62,63</sup> In areas where tuberculosis is endemic, *M tuberculosis* is an important cause of pneumonia in HIV-positive children and can present as acute severe pneumonia. Chronic lung disease is common (although no accurate estimates are available) in HIV-positive children and is due to bacterial pneumonias responding poorly to treatment, tuberculosis, bronchiectasis, lymphoid interstitial pneumonia, or opportunistic fungal infections.<sup>61,63,64</sup> Little information is available about the effect of HIV infection on neonatal pneumonia. As antiretroviral therapy and co-trimoxazole prophylaxis become more widely used and lead to improved survival of HIV-positive children, severe pneumonia and chronic lung disease can be expected to become more common in older children.

facilities in many countries, and inadequate disease surveillance), but has probably decreased as a result of successful immunisation programmes.<sup>54</sup>

The causes of diarrhoea and pneumonia vary by age, and differ particularly in neonates (panel 1) and with disease severity.<sup>65</sup> The HIV/AIDS pandemic has also changed the risk for both diseases and the range of causes in countries with high prevalences of HIV infection.

### Risk factors

Table 3 shows the effect sizes for specific confirmed biological risk factors for diarrhoea and pneumonia. Because identification of individual risk relations is complex when several risk factors exist, we present results from multivariable analyses whenever possible. Diarrhoea and pneumonia share many risk factors, such as not exclusively breastfeeding infants younger than 6 months, undernutrition, and zinc deficiency. Vitamin A deficiency increases the risk of severe diarrhoea and thus diarrhoea mortality (relative risk [RR] 1.5, 95% CI 1.3–1.8),<sup>66</sup> but is not an important risk factor for the incidence of diarrhoea or pneumonia, or for pneumonia-related mortality.<sup>66</sup> Other factors, such as intrauterine

growth restriction and prematurity, are risk factors for all-cause neonatal mortality, but cause-specific data are not available and thus risk relations cannot be quantified.<sup>67</sup> Risk relations between specific water and sanitation risk factors (ie, unwashed hands and poor water quality) and diarrhoea morbidity and mortality have been shown, but for some outcomes, such as inappropriate excreta disposal, poor availability of evidence permits only rough estimates of risk.<sup>68,69</sup>

Crowding and exposure to indoor air pollution increase pneumonia incidence, but are not associated with increased risk for diarrhoea morbidity or mortality. Various definitions and outcomes were used in studies of crowding,<sup>70–73</sup> but effects on pneumonia were consistently moderate. Exposure to indoor air pollution from solid fuel combustion increases the incidence of pneumonia by 80% (95% CI 43–125). In a small group of studies,<sup>74</sup> exposure to indoor air pollution (various definitions of risk were used) was associated with increased risk of severe pneumonia and pneumonia mortality; additional studies are needed before a combined analysis can be done to produce a risk estimate. In a randomised controlled trial<sup>75</sup> in rural Guatemala, participants who were given wood stoves with chimneys had

	Diarrhoea		Pneumonia	
	Morbidity	Mortality	Morbidity	Mortality
Not exclusively breastfeeding (0–5 months; vs exclusive breastfeeding)				
Partially breastfed	RR 1.7 (95% CI 1.0–2.8)*	RR 4.6 (95% CI 1.8–11.8)*	..	RR 2.5 (95% CI 1.0–6.0)*
Not breastfed	RR 2.7 (95% CI 1.7–4.1)*	RR 10.5 (95% CI 2.8–39.6)*	..	RR 15.0 (95% CI 0.7–332.7)*
No breastfeeding (6–23 months; vs receives any breastmilk)				
	RR 1.3 (95% CI 1.1–1.6)†	RR 2.2 (95% CI 1.1–4.2)*	..	..
Underweight (vs >–2 WAZ for morbidity and >–1 WAZ for mortality)				
–2 to <–1 WAZ	..	OR 2.1 (95% CI 1.6–2.7)§	..	OR 1.2 (95% CI 0.7–1.9)§
–3 to <–2 WAZ	RR 1.2 (95% CI 1.1–1.4)‡	OR 3.4 (95% CI 2.7–4.4)§	RR 1.9 (95% CI 1.1–3.3)‡	OR 1.3 (95% CI 0.9–2.0)§
Less than <–3 WAZ	..	OR 9.5 (95% CI 5.5–16.5)§	..	OR 6.4 (95% CI 3.9–10.4)§
Stunting (vs >–1 HAZ)				
–2 to <–1 HAZ	..	OR 1.2 (95% CI 0.9–1.7) §	..	OR 1.0 (95% CI 0.6–1.6) §
–3 to <–2 HAZ	..	OR 1.6 (95% CI 1.1–2.5) §	..	OR 1.3 (95% CI 0.9–2.1) §
<–3 HAZ	..	OR 4.6 (95% CI 2.7–8.1) §	..	OR 3.2 (95% CI 1.5–6.7) §
Wasting§ (vs >–WHZ)				
–2 to <–1 WHZ	..	OR 1.2 (95% CI 0.7–1.9)§	..	OR 1.6 (95% CI 1.1–2.4)§
–3 to <–2 WHZ	..	OR 2.9 (95% CI 1.8–4.5)§	..	OR 4.2 (95% CI 3.2–5.5)§
<–3 WHZ	..	OR 6.3 (95% CI 2.7–14.7)§	..	OR 8.7 (95% CI 4.8–15.6)§
Vitamin A deficiency (vs not deficient)				
	..	RR 1.5 (95% CI 1.3–1.8)¶	..	..
Zinc deficiency (vs not deficient)				
	RR 1.2 (95% CI 1.1–1.2)	RR 1.2 (95% CI 1.0–1.6)	RR 1.2 (95% CI 1.2–1.4)	RR 1.2 (95% CI 0.9–1.5)

A referenced version of this table is in the appendix. RR=relative risk. WAZ=weight-for age z-score. OR=odds ratio. HAZ=height-for-age z-score. WHZ=weight-for-height z-score. \*Mix of cohort, observational, and case-control studies. Adjusted risk relations from individual studies used when available. †Mix of cohort, observational, and case-control studies. Adjusted risk relations from individual studies used when available. Data only available for ages 6–11 months for this risk relation. ‡Mix of cohort, observational and case-control studies; analysis done with unadjusted risk estimates. §Prospective datasets adjusted for socioeconomic and non-nutritional determinants of mortality. ¶Meta-analysis of observed risk reductions from supplementation trials. ||Meta-analysis of observed risk reductions from randomised controlled trials.

**Table 3: Risk factors with direct biological links to diarrhoea and pneumonia**



non-significant reductions in the incidence of pneumonia compared with those who continued to use open fires (RR 0.84, 95% CI 0.63–1.13); however, in an exposure–response analysis the reduction was significant (0.82, 0.70–0.98).

Diarrhoea and pneumonia have each been investigated as independent risk factors for increasing the risk of simultaneous or sequential infection with each other. Schmidt and colleagues<sup>76</sup> assessed the effect of cumulative time ill with diarrhoea on subsequent respiratory infections in cohorts of children from Ghana and Brazil. In Ghanaian children, a time-to-event analysis showed that, as the daily prevalence of diarrhoea increased, the risk of a subsequent acute lower-respiratory-tract infection increased by 1.08 (95% CI 1.0–1.15) per day of diarrhoea. Yet, a similar finding was not noted in the Brazilian cohort. In neither country was the reverse relation—ie, pneumonia as a risk for diarrhoea—noted. In a similar analysis of two cohorts, one of Indian and the other of Nepali children, Fischer Walker and coworkers<sup>77</sup> reported that, as the number of days with diarrhoea increased, the incidence of acute lower-respiratory-tract infections increased. Acute lower-respiratory-tract infections were only a risk factor for diarrhoea in a stratified subgroup of infants younger than 6 months.

Measles is an established risk factor for diarrhoea. In 1983, Feachem and Koblinsky<sup>78</sup> estimated that, with moderate coverage of the measles vaccine (45–90%) in infants, the incidence of diarrhoea could be reduced by 0.6–3.8%, and, more importantly, diarrhoea mortality could be reduced by 6–26% in children younger than 5 years. Pneumonia is the most common mode of death from measles, and is associated with 56–86% of measles deaths.<sup>79</sup> The case fatality of severe pneumonia associated with measles is more than twice that of severe pneumonia without measles.<sup>80</sup> This increased mortality is largely due to the immunosuppressive and systemic effects of measles with bacterial superinfection.

## Discussion

Severe morbidity and mortality and yearly changes in mortality with time are strongly correlated for childhood diarrhoea and pneumonia. Most of the deaths from both illnesses occur in children younger than 2 years. Both diseases are associated with poverty, and child mortality from them is higher in low-income than in high-income countries and in populations in crisis situations (panel 2). Diarrhoea and pneumonia share many risk factors, and reduction of risk factors, immunisation, and case management comprise the main approaches to disease control. Thus, we assess their epidemiology in parallel and consider the implications for planning of joint programmes.

Diarrhoea and pneumonia are the most important causes of child mortality, and thus the continuing absence of reliable population-based morbidity or mortality data from countries with high disease burdens

is remarkable. Many of the available data are not nationally representative and do not come from the highest mortality stratum, and so they might underestimate the true national burden of disease,<sup>45</sup> and consequently our estimates have wide CIs. Therefore, monitoring of disease trends with time or assessment of the effect of new interventions is difficult.

Childhood pneumonia and diarrhoea were estimated to account for about 2 million child deaths in 2011 (28.5% of total mortality in children younger than 5 years), and are a high priority for child health programmes. Almost three-quarters of this mortality was in 15 high-burden countries. Most deaths from diarrhoea and pneumonia are preventable<sup>95</sup> with high coverage of existing interventions (as shown in the second paper in this Series<sup>96</sup>). 72% of deaths from diarrhoea and 81% of deaths from pneumonia occur within the first 2 years of life, which has clear implications for health policy. Programmes need to focus on interventions for children younger than 2 years—eg, on-time infant vaccination, breastfeeding and high-quality early childhood nutrition, improvement of rates of care-seeking and appropriate case management.

Mortality from both diarrhoea and pneumonia fell substantially between 2000 and 2011. The rate of reduction correlates strongly across countries. Diarrhoea deaths have decreased quicker than have those caused by pneumonia. Because no notable improvements in diarrhoea treatment practices have been implemented in the past decade,<sup>97</sup> we speculate that improvements in nutrition and general environmental and socioeconomic development have more prominent roles in diarrhoea than in pneumonia.<sup>98</sup>

Rapid reductions in mortality have not occurred in all low-income and middle-income countries. In a subgroup of countries in which rates of mortality from diarrhoea and pneumonia are falling slowly, child deaths continue to rise because of high birth rates. For example, in Burkina Faso, the estimated rates of diarrhoea and pneumonia specific mortality fell from 2000 to 2010, yet the estimated number of deaths in children younger than 5 years increased (from 13447 to 14648 for diarrhoea and 17389 to 21763 for pneumonia); we note similar trends in Afghanistan, Cameroon, Chad, Democratic Republic of the Congo, and Mali. Within regions, disparities exist between countries that have achieved rapid reductions in mortality for both diarrhoea and pneumonia and those that have not. In Cambodia, for example, diarrhoea mortality rates have been falling by 12% and pneumonia mortality rates by 8% each year from 2000 to 2010—findings which contrast with yearly decreases of 2.4% and 1.6% in Papua New Guinea. Differences in immunisation rates, breastfeeding practices, and community case management of diarrhoea and pneumonia might be important factors in these discrepancies.

We present new estimates of the incidence of severe pneumonia and diarrhoea, which imply potential burdens on hospital services in low-income and

middle-income countries. Prevention of some of these severe episodes is possible through routine and timely immunisation, especially of high-risk children, and timely community-based case management.<sup>99,100</sup> An effective health-service response to this burden of severe disease will necessitate not only development of hospital services and improved access to inpatient care, but also community approaches to management of illness before hospital care becomes necessary.

Undernutrition (including zinc deficiency) and measles are risk factors for diarrhoea and pneumonia. Reductions in underweight and measles (because of immunisation programmes) might have contributed to falls in deaths from diarrhoea and pneumonia.<sup>101</sup> Shared nutritional risk factors should be emphasised to policy and programme planners. Interventions to improve nutrition are available and should be prioritised because of the joint benefits in the reduction of morbidity and mortality. For some risk factors, such as inadequate water and sanitation, poor handwashing, indoor air pollution, and crowding, risk relations have been difficult to define, but addressing them will probably have benefits for disease reduction.

Rotavirus is the most important cause of diarrhoea mortality in children, whereas *S pneumoniae*, *H influenzae*, and influenza virus are three of the four main causes of pneumonia mortality. High coverage with highly effective vaccines against these pathogens has the potential to reduce mortality and severe morbidity substantially. Available vaccines are not 100% effective, and thus the potential effect is substantially decreased. Effective new vaccines are needed to reduce mortality from pneumonia caused by respiratory syncytial virus. A substantial change in the causative range for pneumonia would be expected with high coverage of these vaccines (both available vaccines and effective new vaccines), which could necessitate fundamental change to case management guidelines. Referrals of severe disease to hospitals would be substantially reduced for both disorders, but management of the remaining cases would be more complicated and expensive, with increased health-service costs per case. Pneumonia in neonates and in early infancy will become increasingly important.

Increasing access to high-quality treatment is a priority to reduce deaths. The Integrated Management of Childhood Illnesses<sup>102</sup> approach in health facilities has improved the quality of clinical care. Integrated Community Case Management<sup>103</sup> of pneumonia, diarrhoea, and malaria improves access to care, and community health workers can safely and effectively treat such disorders. Although improved access and expanded treatment is an important public health goal, the associated rise in antibiotic use can lead to increased antimicrobial resistance and more multidrug resistant pathogens. Replacement of the first-line antibiotics nalidixic acid with ciprofloxacin for dysentery, and

co-trimoxazole with amoxicillin for pneumonia,<sup>104</sup> shows the effect of resistance on public health policies and costs.

Reports from WHO<sup>105</sup> and the Intergovernmental Panel on Climate Change have identified changes in the incidence of diarrhoea as one of the most important future health effects of climate change.<sup>105</sup> Checkley and colleagues<sup>106</sup> reported increases in hospital admissions

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## Panel 2: Situations necessitating urgent policy responses related to diarrhoea and pneumonia in children younger than 5 years

### Refugees and emergencies

In 2011, an estimated 15.3 million people were displaced by complex humanitarian emergencies. Diarrhoea and pneumonia are important causes of child morbidity and mortality in emergency or refugee settings. Data from health information systems<sup>81</sup> in these populations show that pneumonia (defined by WHO thresholds for fast breathing) accounted for 20% of all child deaths and 17% of illness episodes, whereas diarrhoea accounted for 7% of deaths and 10% of illness episodes. Child mortality can be particularly high during the initial emergency phase of a complex humanitarian emergency, and pneumonia and diarrhoea are major avoidable causes of these deaths.<sup>82</sup> Mean incidences of pneumonia and diarrhoea in children younger than 5 years were substantially higher than those noted in these countries in non-emergency settings.<sup>83</sup> High disease risk is associated with malnutrition, crowding, and poor access to clean water and sanitation.

### Pandemic influenza

Seasonal influenza is the second most common respiratory pathogen identified in children with pneumonia and contributes substantially to hospital admission and mortality worldwide in children younger than 5 years. The first influenza pandemic of the 21st century was officially announced in April, 2009. Infection with the influenza A (H1N1) pdm09 strain resulted in much higher rates of hospital admission in young children than are reported during a normal influenza season.<sup>84,85</sup> Children younger than 5 years can be a high-risk group for pneumonia after an influenza infection—either due to primary viral pneumonia or secondary bacterial pneumonia (mainly associated with pneumococci).<sup>86,87</sup>

The 2009 influenza pandemic showed the need for improved surveillance systems to detect changes in influenza activity and underscored the importance of pneumonia control programmes (including immunisation with pneumococcal conjugate vaccine and provision of oxygen therapy in more hospital paediatric wards in low-income and middle-income countries) in pandemic influenza preparedness because pneumonia is a major cause of death from pandemic influenza in young children.

### Cholera

Cholera is one of the most devastating diarrhoeal diseases, and causes high rates of mortality and widespread social upheaval during epidemics.<sup>88</sup> It is caused by infection of the small intestine with the Gram-negative *Vibrio cholerae*.<sup>89</sup> Infection typically causes acute secretory diarrhoea with so-called rice-water stools (as much as 1 L/h), and can result in hypotensive shock and high case-fatality rates in susceptible individuals.<sup>90</sup> In endemic areas, incidence peaks in children younger than 5 years because at least partial immunity develops after illness.<sup>88,91</sup> In epidemics when *V cholerae* infects a naive population, morbidity and mortality occur at all ages.<sup>92</sup> Epidemics occur in areas with poor water and sanitation facilities, little basic infrastructure, and high population densities.<sup>93</sup> *V cholerae* O1 and O139 still cause epidemics and outbreaks have been reported in Zimbabwe, Pakistan, and Haiti since 2005. Oral cholera vaccines are effective in endemic regions where epidemics are common but are not yet widely used in emergency settings. As more data showing the benefits of vaccination are generated, the absence of widespread use, especially in settings where prevention and control are challenging, is becoming questionable.<sup>94</sup>

for diarrhoea in Peru associated with *El Niño* in 1997–98, suggesting that if ambient temperatures increase because of climate change, admissions associated with diarrhoea could be expected to rise. Pneumonia has also been postulated to be a climate-sensitive disease that is likely to be affected substantially by pronounced climate change.<sup>107</sup> Incidence in many settings is strongly associated with rainfall, and thus the predicted increased intensity rainy seasons in Asia, Africa, the western Pacific region, and parts of South America in the future will probably be associated with a raised burden of childhood pneumonia.<sup>108</sup> However, the true scale of these effects is unknown.

The 2010 Global Burden of Disease<sup>109</sup> group published estimates for morbidity and mortality by cause, age, and sex in 2012. Estimates of deaths from pneumonia and diarrhoea in children younger than 5 years are lower than are the WHO and UNICEF estimates we used, which is probably because of differences in the inclusion data, cause-of-death classification, and modelling approaches. We used the most up-to-date information about the causes of pneumonia and diarrhoea to estimate the attributable disease and death to specific pathogens against which vaccines are available. Studies that are underway (Global Enteric Disease Multicenter Study, Pneumonia Etiology Research for Child Health, Interaction of Malnutrition and Enteric Infection) will provide additional data about the pathogen-specific burden of disease for both diarrhoea and pneumonia. Although researchers worldwide eagerly await the results of these important studies, the data generated will not fill all knowledge gaps and might help us to further understand only a small aspect of these complex diseases. Research will remain important to track trends in these diseases as new interventions are introduced, sociodemographic conditions evolve, and other diseases and risk factors change, if the global burdens of childhood diarrhoea and pneumonia are to continue to fall.<sup>110</sup>

#### Contributors

CLFW and IR drafted the initial paper, and led the reviews, analyses, and preparation of the final submitted version. ZAB, HC, and REB provided technical leadership and contributed to preparation and editing. LL provided all data and analyses related to mortality. HN provided data and analysis for pneumonia incidence, severe morbidity, risk factors, and influenza. ET contributed to pneumonia modelling and estimates of vaccine effectiveness. KLO'B coordinated the revision of cause estimates for pneumonia, provided all data for estimation of the burden from *S pneumoniae* and *H influenzae*, and checked the final paper for important intellectual content.

#### Conflicts of interest

We declare that we have no conflicts of interest.

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For more on Pneumonia Etiology Research for Child Health see <http://www.jhsph.edu/research/centers-and-institutes/ivac/projects/perch/>  
For more on Interaction of Malnutrition and Enteric Infection see <http://mal-ed.fnih.org/>

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