Childhood Pneumonia and Diarrhoea 2

Interventions to address deaths from childhood pneumonia and diarrhoea equitably: what works and at what cost?

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Global mortality in children younger than 5 years has fallen substantially in the past two decades from more than 12 million in 1990, to 6·9 million in 2011, but progress is inconsistent between countries. Pneumonia and diarrhoea are the two leading causes of death in this age group and have overlapping risk factors. Several interventions can effectively address these problems, but are not available to those in need. We systematically reviewed evidence showing the effectiveness of various potential preventive and therapeutic interventions against childhood diarrhoea and pneumonia, and relevant delivery strategies. We used the Lives Saved Tool model to assess the effect on mortality when these interventions are applied. We estimate that if implemented at present annual rates of increase in each of the 75 Countdown countries, these interventions and packages of care could save 54% of diarrhoea and 51% of pneumonia deaths by 2025 at a cost of US$3·8 billion. However, if coverage of these key evidence-based interventions were scaled up to at least 80%, and that for immunisations to at least 90%, 95% of diarrhoea and 67% of pneumonia deaths in children younger than 5 years could be eliminated by 2025 at a cost of $6·715 billion. New delivery platforms could promote equitable access and community platforms are important catalysts in this respect. Furthermore, several of these interventions could reduce morbidity and overall burden of disease, with possible benefits for developmental outcomes.

Published **Online**
April 12, 2013
http://dx.doi.org/10.1016/S0140-6736(13)60648-0

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

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Introduction

Although global mortality in children younger than 5 years has substantially reduced in the past two decades from more than 12 million deaths in 1990, to 6·9 million in 2011,[1] improvements have been inconsistent worldwide. Whereas some countries and regions have reduced child mortality by more than half,[2] progress in others has been much slower. Half of all deaths worldwide in children younger than 5 years are concentrated in only five countries: India, Nigeria, the Democratic Republic of the Congo, Pakistan, and China.[1] In the past decade, the number of child deaths decreased by 2 million worldwide, with reductions in deaths due to pneumonia and diarrhoea contributing to 40% of the overall reduction.[3] Notwithstanding this success, pneumonia diseases still account for 1·3 million deaths and diarrhoeal diseases for 0·7 million deaths, and both are major causes of post-neonatal child deaths.[2,3] Pneumonia is the largest cause of child deaths worldwide. Corresponding reductions in burden of disease and morbidity have been much slower than those for global child mortality. Incidence of diarrhoea has fallen from 3·4 episodes to 2·9 episodes per child-year, and that of pneumonia from 0·29 episodes to 0·23 episodes per child-year between 1990 and 2010.[4] Despite such decreases, these disorders are two of the most common reasons for health service attendance and hospital admission, with an estimated 1731 (uncertainty range 1376–2033) million episodes of childhood diarrhoea (uncertainty range 26·6–42·4 million severe episodes) and 120 (60·83–277·03) million episodes of pneumonia (10·03–40·04 million severe episodes) in 2011.[5,6]

Pneumonia and diarrhoea deaths are closely associated, with overlapping risk factors such as those related to poverty, undernutrition, poor hygiene, and deprived home environments making children more likely to develop these diseases. Improvements in socioeconomic development with corresponding increases in maternal education, falling fertility rates, and improved living conditions (with reduced crowding) are important contributors to

Key messages

- Worldwide, pneumonia and diarrhoeal diseases are the two major killers of children younger than 5 years
- Each year, 1·3 million children die from pneumonia and 700 000 from diarrhoea
- Preventive and therapeutic interventions exist that could have a role in reducing the morbidity and mortality burden due to diarrhoea and pneumonia, especially in children younger than 5 years
- Few interventions with wide range of outcomes have been assessed at a sufficient scale
- Interventions with maximum effect include breastfeeding, oral rehydration solution, and community case management
- Despite persistent burden, childhood diarrhoea and pneumonia deaths are avoidable and 15 interventions delivered at scale can prevent most of these avoidable deaths
- Estimates modelled with the Lives Saved Tool show that if the interventions are scaled up by 80% in the 75 Countdown countries, they could save 95% of diarrhoeal and 67% of pneumonia deaths in children younger than 5 years by 2025
- Scaling up of diarrhoea and pneumonia interventions would cost US$6·715 billion, only $2·9 billion more than present levels of spending; costs needed for lives saved calculated on the basis of estimates of projected spending based on historic trend
- Scaling up of these interventions could also ensure equitable delivery of care
- The cost-effectiveness of these interventions in national health systems needs urgent assessment
- With an increasing number of countries deploying community health-worker programmes to reach unreached populations, real opportunities exist to scale-up community advocacy and education programmes and early case detection and management strategies

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reductions in child mortality.[7] However, to reduce childhood pneumonia and diarrhoea, interventions are needed that directly lower disease transmission and severity, and promote access to life-saving treatment once a child becomes sick. Previous reviews[8–11] have shown that increases in coverage with present evidence-based interventions could greatly reduce child mortality and deaths from diarrhoea and pneumonia. However, little consensus exists about approaches to scale up coverage and about delivery strategies to reduce disparities and provide equitable access to marginalised populations.[12]

In this Series paper, we systematically review evidence for the effectiveness of various potential health interventions on morbidity and mortality due to diarrhoea and pneumonia in line with guidelines from the Child Health Epidemiology Reference Group.[13] We used a standardised method with criteria from the Child Health and Nutrition Research Initiative (CHNRI) to identify priority areas for research and future interventions. We modelled the potential effect of delivery of these interventions to the 75 high-burden countries that are part of the Countdown to 2015 initiative and assessed the result of scaling-up of interventions on diarrhoea and pneumonia mortality across poverty quintiles in three countries (Bangladesh, Pakistan, and Ethiopia).

See **Online** for appendix

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

For more on **Countdown to 2015** see http://www.countdown2015mnch.org/

Interventions reviewed and the conceptual framework

We used a conceptual framework to assess preventive and case management interventions for diarrhoea and pneumonia, including preventive and therapeutic interventions common to both disorders (figure 1). We selected these interventions from several previous reports that identified their benefits and effects.[9,14–26] We specifically reviewed the interventions to identify data for their effectiveness on diarrhoea or pneumonia, or both; incidence; and morbidity or mortality. Systematic reviews of potential interventions were undertaken by teams of researchers in Karachi, Pakistan; Baltimore, USA; and Toronto, Canada, and were done with standard methodologies. Reviews were done in line with Lives Saved Tool (LiST) methods,[13] employing Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria (appendix). Researchers did 26 reviews for various interventions, consisting of 15 new reviews done to generate estimates of effect, and assessment of 11 existing reviews for possible updates.

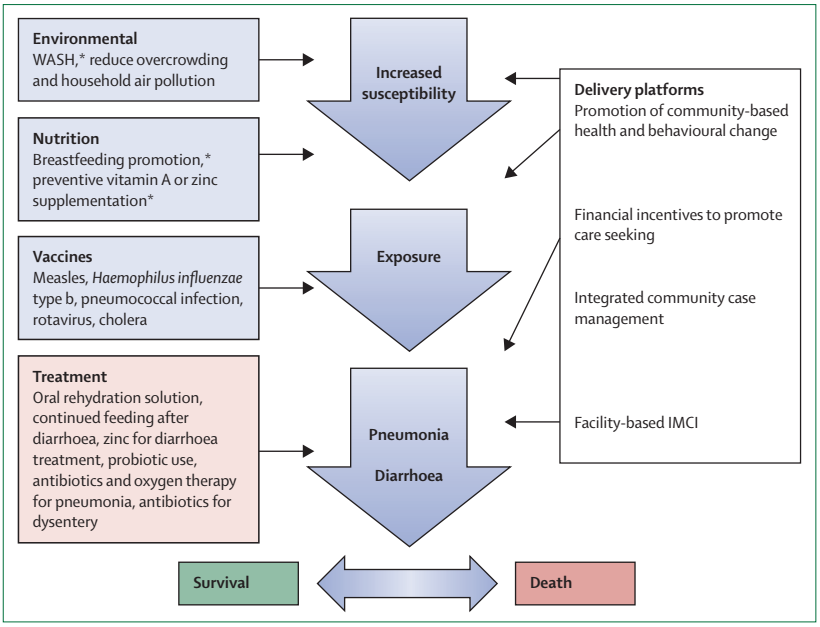

***Figure 1*: Conceptual framework of the effect of interventions for diarrhoea and pneumonia**
WASH=water, sanitation, and hygiene. IMCI=Integrated Management of Childhood Illness. *Interventions common to both diarrhoea and pneumonia.

Interventions for both diarrhoea and pneumonia

Strategies to promote breastfeeding

Table 1 summarises the available evidence and effect estimates for interventions to prevent and manage diarrhoea and pneumonia. Breast milk provides various immunological, psychological, social, economic, and environmental benefits, and is therefore recommended as the best feeding option for newborn babies and young infants in developing countries, even in HIV-infected populations.[31] Lamberti and colleagues[27] reviewed 18 studies from developing countries reporting the effect of breastfeeding on diarrhoea morbidity and mortality. The investigators estimated that not breastfeeding was associated with a 165% increase in diarrhoea incidence in 0–5-month-olds and a 32% increase in 6–11-month-olds. Not breastfeeding was also associated with a 47% increase in diarrhoea-related mortality in 6–11-month-olds and a 157% increase in 12–23-month-olds. Overall, not breast feeding was associated with a 566% increase in all-cause mortality in children aged 6–11 months, and a 223% increase in mortality in those aged 12–23 months.

We assessed the effect of various educational and promotional strategies on rates of exclusive, predominant, partial, and no breastfeeding.[28] Rates of exclusive breastfeeding increased significantly because of breastfeeding promotional interventions; rates of not breastfeeding reduced significantly. The effects reported for rates of predominant and partial breastfeeding were not significant. After 6 months, educational interventions had no significant effect, but did increase rates of partial breastfeeding by 19%. Subgroup analyses suggested that combined individual and group counselling was more effective than either technique alone. Overall, in developing countries, facility and combined facility-based and community-based interventions led to greater improvements in breastfeeding rates, with greater effects of breastfeeding promotion and support interventions, than routine care.

	Evidence reviewed	Effect estimates
Breastfeeding and the risk for morbidity and mortality	Existing review of 18 studies from developing countries[27]	Not breast feeding was associated with a 165% (RR 2·65, 95% CI 1·72–4·07) increase in diarrhoea incidence in babies aged 0–5 months, a 32% (1·32, 1·06–1·63) increase in those aged 6–11 month, and a 32% (1·32, 1·06-1·63) increase in those aged 12–23 months. No breastfeeding is also associated with a 47% (1·47, 0·67–3·25) increase in diarrhoea mortality in babies aged 6–11 months, and a 157% (2·57, 1·10–6·01) increase in those aged 12–23 months
Breastfeeding education and effects on breastfeeding rates	New review of 110 randomised trials and quasi-experimental studies[28]	Significant increases were reported in rates of exclusive breastfeeding as a result of promotional interventions: 43% at 1 day, 30% at 0–1 months, and 90% at 1–6 months. Rates of no breastfeeding decreased by 32% at 1 day, 30% at 0–1 month, and 18% for 1–6 months. Effects on rates of predominant and partial breastfeeding were not significant. After 6 months, educational interventions had no significant effect except to increase rates of partial breastfeeding by 19%
Water, sanitation, and hygiene interventions	Existing review of randomised trials and quasi-experimental and observational studies[29]	Risk reductions for diarrhoea of 48% with hand washing with soap, 17% with improved water quality, and 36% with excreta disposal
Preventive zinc supplementation	Existing review of 18 randomised trials from developing countries[30]	Preventive zinc supplementation resulted in an 18% (RR 0·82, 95% CI 0·64–1·05) non-significant reduction in diarrhoea-related mortality and a 9% non-significant reduction in all-cause mortality (0·91, 0·82–1·01). Preventive supplementation resulted in a 15% (0·85, 0·65–1·11) non-significant reduction in ALRI-related mortality

RR=relative risk. ALRI=acute lower respiratory infection.

Table 1: **Interventions common to both childhood diarrhoea and pneumonia**

Strategies for improved water provision, use, sanitation, and hygiene promotion

Consensus exists about the importance of improved water supply and excreta disposal for prevention of diseases, especially diarrhoeal diseases. Waddington and colleagues[32] assessed the effectiveness of these interventions and concluded that those for water quality (protection or treatment of water at source or point of use) were more effective than those to improve water supply (improved source of water or improved distribution, or both). Interventions for water quality were associated with a 42% relative reduction in diarrhoea morbidity in children, whereas those for water supply had no significant effects. Overall, sanitation interventions led to an estimated 37% reduction in childhood diarrhoea morbidity and hygiene interventions to a 31% reduction. Subgroup analysis suggests that provision of soap was more effective than education only. Cairncross and colleagues[29] estimated the effect of water, sanitation, and hygiene strategies and estimated risk reductions for diarrhoea of 48% for hand washing with soap, 17% with improved water quality, and 36% with excreta disposal. Although the investigators regarded much of the evidence to be of poor quality, the findings were consistent enough to support the provision of water supply, sanitation, and hygiene for all.

Preventive zinc supplementation

About 17·3% of the world's population is zinc deficient and this deficiency is most prevalent in children younger than 5 years in developing countries.[33] Yakoob and colleagues[30] assessed 18 studies from developing countries and showed that preventive zinc supplementation was associated with a non-significant reduction of 9% in all-cause mortality (table 1). Zinc alone resulted in a non-significant reduction of 18% in diarrheoa mortality and of 15% in pneumonia mortality. Preventive zinc supplementation was associated with a 13% reduction in the incidence of diarrhoea (relative risk [RR] 0·87, 95% CI 0·81–0·94) and a 19% reduction in pneumonia morbidity (0·81, 0·73–0·90).

Diarrhoea-specific interventions

Preventive interventions

Table 2 summarises the evidence and effect estimates for interventions to prevent and manage diarrhoea. Rotavirus is the most common cause of severe dehydrating diarrhoea in infants worldwide.[5] In their review of six studies assessing the effectiveness of new rotavirus vaccines, Munos and colleagues[34] estimated that use of these vaccines was associated with a 74% reduction in very severe rotavirus infections, a 61% reduction in severe infections, and reduced rotavirus-related hospital admission in young children by 47%. These summary effects do not show the reduced effectiveness of the vaccine in different geographic settings, with studies reporting 54% effectiveness in Malawi,[40] and even lower efficacy (43%) in Mali.[41]

Although case management with oral rehydration therapy has substantially improved case-fatality rates for cholera, the infection can still kill rapidly, especially in outbreak settings.[42] Old-generation injectable cholera vaccines have been abandoned since the 1970s because of their restricted effectiveness and local side-effects. We identified 12 studies, all from developing countries, which assessed the efficacy and effectiveness of oral cholera vaccine.[35] We estimated that this vaccine reduced risk of cholera infection in children younger than 5 years by 52%. Such evidence for the effectiveness of oral cholera vaccines makes them good candidates for cholera control in endemic areas. Research shows that because of herd protection, even moderate coverage levels of

	Evidence reviewed	Effect estimates
Preventive interventions		
Rotavirus vaccine	Existing review of six randomised trials and quasi-experimental studies[34]	Rotavirus vaccines were 74% (95% CI 35–90) effective against very severe rotavirus infection and 61% (38–75) against severe infection. Effectiveness against hospital admission for rotavirus was 47% (22–64)
Cholera vaccine	New review of 12 randomised trials and quasi-experimental studies[35]	Cholera vaccine was 52% (RR 0·48, 95% CI 0·35–0·64) effective against cholera infection. Vibriocidal antibodies increased by 124% (2·24, 1·32–3·80). Relative risk of one or more adverse events was 1·42 (1·06–1·89)
Therapeutic interventions		
ORS and recommended home fluids	Existing review of 205 studies mostly from developing countries[36]	Use of ORS reduced diarrhoea mortality by 69% (51–80) and treatment failure by 0·2% (0·1–0·2). Evidence for the benefit of recommended home fluids was insufficient
Zinc	Existing review of 13 randomised trials from developing countries[37]	Zinc administration for diarrhoea management significantly reduced all-cause mortality by 46% (RR 0·54, 95% CI 0·32–0·88) and hospital admission by 23% (0·77, 0·69–0·85). Zinc treatment resulted in a non-significant reduction in diarrhoea mortality by 66% (0·34, 0·04–1·37) and diarrhoea prevalence by 19% (0·81, 0·53–1·04) Zinc administration for diarrhoea management resulted in a 28% reduction in pneumonia-specific mortality (RR 0·72, 95% CI 0·23–2·09), a 50% reduction in hospital admissions for pneumonia (0·50, 0·18–1·39), and an observed 23% reduction in pneumonia prevalence (0·77, 0·47–1·25)
Feeding strategies and improved dietary management of diarrhoea	New review of 29 randomised trials from developing countries[38]	In acute diarrhoea, lactose-free diets significantly reduced the duration of diarrhoea compared with lactose-containing diets (SMD −0·36, 95% CI −0·62 to −0·10). Treatment failure was also significantly reduced (RR 0·53, 0·40–0·70). Weight gain did not have any significant effect (SMD 0·05, −0·22 to 0·33)
Antibiotics for treatment of shigella	New review of four randomised trials from developing countries[39]	Antibiotic treatment of shigella reduced clinical failure by 82% (RR 0·18, 0·10–0·33), whereas bacteriological failure decreased by 96% (0·04, 0·01–0·12)
Antibiotics for treatment for cholera	New review of two randomised trials[39]	Findings showed a 63% (RR 0·37, 95% CI 0·19–0·71) reduction in clinical failure and a 75% (0·25, 0·12–0·53) reduction in bacteriological failure
Antibiotics for treatment for cryptosporidiosis	New review of three randomised trials[39]	Findings showed a 52% (RR 0·48, 0·30–0·75) reduction in rates of clinical failure, a 38% (0·62, 0·46–0·83) reduction in parasitological failure, and a 76% (0·24, 0·04–1·45) non-significant reduction in all-cause mortality

RR=relative risk. ORS=oral rehydration solution. SMD=standardised mean difference.

***Table 2*: Interventions for the prevention and management of diarrhoea**

targeted populations with killed oral cholera vaccine could lead to almost complete control of cholera;[43,44] however, this control would not prevent outbreaks in other populations.

Therapeutic interventions

Because the immediate cause of death in most cases of diarrhoea is dehydration, deaths are almost entirely preventable if dehydration is prevented or treated. In a review of the efficacy and effectiveness of oral rehydration solution and recommended home fluids, Munos and colleagues[36] assessed 205 studies, mostly from developing countries. Use of oral rehydration solution reduced diarrhoea specific mortality by 69% and rates of treatment failure by 0·2% (table 2). Since 2004, WHO and UNICEF have recommended zinc for the treatment of diarrhoea. Walker and colleagues[37] reviewed 13 studies from developing countries of zinc supplementation for diarrhoea and concluded that zinc administration was associated with a significant reduction of 46% in all-cause mortality and of 23% in diarrhoea-related hospital admissions. The effects on prevalence of diarrhoea and mortality were not significant. Several of the large studies of zinc treatment for diarrhoea were also associated with reported benefits for pneumonia mortality, hospital admission, and prevalence, albeit not significantly.

Current WHO guidelines for the management and treatment of diarrhoea in children strongly recommend continued feeding alongside administration of oral rehydration solution and zinc therapy. However, some debate surrounds what the optimum diet or dietary ingredients are to hasten recovery and maintain nutritional status in children with diarrhoea. We did an extensive review[38] of all studies of feeding strategies and food-based interventions in children younger than 5 years with diarrhoea in low-income and middle-income countries. Although illness duration was shorter and risk of treatment failure 47% lower in children with acute diarrhoea who consumed lactose-free rather than lactose-containing liquid feeds, we noted no effect of lactose avoidance on stool output or weight gain. Pooled analyses of trials comparing commercial preparations or specialised ingredients to foods available in the home showed no beneficial effects in either acute or persistent diarrhoea, suggesting that locally available ingredients can be used to manage childhood diarrhoea at least as effectively as can commercial preparations or specialised ingredients. Moreover, when we restricted this analysis to lactose-free diets only, weight gain in acute diarrhoea was higher in children who consumed foods available in the home.

Antibiotics are used to treat some forms of bacterial diarrhoea, especially dysentery. A review by Traa and colleagues[45] assessed the effectiveness of WHO-recommended antibiotics—ciprofloxacin, ceftriaxone, and pivmecillinam—for the treatment of dysentery, and concluded that antibiotics are effective in reducing the

clinical and bacteriological signs and symptoms of this disorder and can thus be expected to decrease diarrhoea mortality attributable to dysentery by more than 99%. We assessed the effectiveness of WHO-recommended antibiotics in diarrhoea in relation to cholera, shigella, and cryptosporidium infections.[39] The mainstay of treatment in cholera is rehydration; WHO recommends antibiotics for severe cases. We identified two[46,47] randomised trials from developing countries and showed that antibiotic management of cholera resulted in a 63% reduction in rates of clinical failure and a 75% reduction in rates of bacteriological failure.[39]

A range of antibiotics are used to treat shigella dysentery, dependent on variations in resistance patterns by region. We analysed four studies[48–51] from developing countries, which showed that antibiotic management of shigella resulted in an 82% reduction in rates of clinical failure and a 96% reduction in rates of bacteriological failure.[39] Cryptosporidium can cause life-threatening disease in people with AIDS and contributes greatly to morbidity in children in developing countries. We systematically analysed three studies[52–54] from developing countries. Antibiotics for treatment of cryptosporidiosis reduced mortality by 76%, rates of clinical failure by 52%, and rates of parasitological failure by 38%.[39] None of these studies assessed the effect of a given treatment regimen on emergence of antibiotic resistance over time; however, the investigators noted that use of nalidixic acid for treatment of shigellosis could be associated with rapid emergence of quinolone resistance.[55]

Pneumonia-specific interventions

Preventive interventions

Table 3 summarises the evidence and effect estimates for interventions to prevent and manage pneumonia. Several effective vaccines are available for prevention of various causes of pneumonia. In regions where measles is a substantial cause of childhood morbidity and mortality, measles vaccination is an important intervention that can also affect risk of subsequent complications, including secondary bacterial infections and diarrhoea. Sudfeld and colleagues[56] proposed that measles vaccination was 85% effective for prevention of measles in children younger than 1 year.

We assessed the effectiveness of *Haemophilus influenzae* type b and pneumococcal conjugate vaccines.[57] For prevention of invasive *H influenzae* type b and pneumonia, we identified six studies from developing countries yielding estimates of an 18% non-significant reduction in radiologically confirmed pneumonia, a 6% reduction in severe pneumonia, and a 7% non-significant reduction in pneumonia-specific mortality. We reviewed six studies from developing countries for the prevention of invasive pneumococcal disease and pneumonia with pneumococcal conjugate vaccines, which were associated overall with a 29% significant reduction in radiologically confirmed pneumonia, an 11% reduction in severe pneumonia, and an 18% non-significant reduction in pneumonia-specific mortality.[57] Large-scale use of these vaccines is associated with important positive effects related to herd immunity and population benefits, and negative indirect effects related to serotype replacement and emergence of resistant strains. The magnitude and importance of these indirect effects is likely to vary by setting.

Therapeutic interventions

Treatment with appropriate antibiotics and supportive management in neonatal nurseries is the cornerstone of management of neonatal sepsis and pneumonia, with strong biological plausibility that such treatment saves lives. A review[60] of community-based management of neonatal pneumonia showed a 27% reduction in all-cause neonatal mortality and a 42% reduction in pneumonia-specific mortality. Zaidi and colleagues[57] estimated the effect of provision of oral or injectable antibiotics at home or in first-level facilities, and of in-patient hospital care on neonatal mortality from pneumonia and sepsis. Results suggested a 25% reduction in all-cause neonatal mortality and a 42% reduction in neonatal pneumonia mortality. Similar studies in older infants and children younger than 5 years have focused on choice and duration of antibiotic treatment for pneumonia in various settings.[61–63]

Information is scarce about the effect of low-cost pulse oximetry and oxygenation systems. A large multihospital quasi-experimental study[59] in Papua New Guinea with an intervention of hypoxaemia detection by pulse oximetry, together with oxygen therapy with an assured oxygen supply from oxygen concentrators, resulted in a 35% significant reduction in mortality from severe pneumonia in patients admitted to hospital.

Delivery platforms

Community-based promotion and case management

Although evidence shows the efficacy and effectiveness of many interventions, these interventions are not accessible to people in need; hence, focus on delivery strategies has increased. One of the main contributors to the delay in meeting the targets of Millennium Development Goal 4 is the paucity of trained human resource professionals in first-level health services, and the reduced awareness of and accessibility to services for those living in large socioeconomically, geographically deprived, ethnically marginalised populations. One method of community-based case management is to provide these amenities through community health workers with home visitation and community-based sessions for education and promotion of care seeking. These approaches have been assessed for both newborn babies and children aged 1–59 months.

Lassi and colleagues[64,65] estimated that community-based packaged interventions delivered by community health workers significantly increase levels of care-seeking behaviour for neonatal morbidy by 52%. The role

	Evidence reviewed	Effect estimates
Preventive interventions		
Measles vaccine	Existing review of five randomised and quasi-randomised trials[56]	Measles vaccines was 85% (95% CI 83–87) effective in prevention of disease before age 1 year
Hib vaccine	Existing review of four randomised trials and two case-control studies from developing countries[57]	Hib vaccines resulted in a 6% (RR 0·94, 95% CI 0·89–0·99) significant reduction in severe pneumonia, an 18% (0·82, 0·67–1·02) non-significant reduction in radiologically confirmed pneumonia, and a 7% (0·93, 0·81–1·07) reduction in pneumonia mortality
Pneumococcal conjugate vaccine	Six randomised trials from developing countries[57]	Pneumococcal vaccines resulted in a 29% (RR 0·71, 95% CI 0·58–0·87) significant reduction in radiologically confirmed pneumonia, an 11% (0·89, 0·81–0·98) reduction in severe pneumonia, and an 18% (0·82, 0·44–1·52) non-significant reduction in pneumonia mortality
Therapeutic interventions		
Antibiotics for the treatment and management of neonatal pneumonia	Existing review of four quasi-experimental studies[58]	Oral or injectable antibiotics at home or in first-level facilities, and in-patient hospital care, resulted in a 25% (RR 0·75, 0·64–0·89) reduction in all-cause neonatal mortality and a 42% (0·58, 0·41–0·82) reduction in neonatal pneumonia mortality
Oxygen systems	One quasi-experimental study from Papua New Guinea[59]	Detection of hypoxaemia by pulse oximetry together with oxygen therapy with an assured oxygen supply from oxygen concentrators resulted in a 35% (RR 0·65, 0·52–0·78) significant reduction in severe pneumonia mortality

Hib=*Haemophilus influenzae* type b. RR=relative risk.

Table 3: **Interventions for the prevention and management of pneumonia**

of these health workers has also been assessed in various settings in large-scale programmes in which their presence improved immunisation uptake and care seeking for childhood illnesses.[66] We estimated the effect of community-based delivery strategies with community health workers on the coverage and uptake of essential commodities for diarrhoea and pneumonia: oral rehydration solution, zinc therapy for diarrhoea, and antibiotics for pneumonia.[67] We also assessed the effect of these interventions on care-seeking behaviour and on potentially harmful practices, such as prescription of unnecessary antibiotics for diarrhoea. Theodoratou and colleagues[68] estimated that community case management of pneumonia could result in a 70% reduction in pneumonia mortality in children younger than 5 years. We updated the previous estimate and also estimated the effect of case management on diarrhoea mortality. We included 26 studies and estimated that community-based interventions are associated with a 160% significant increase in use of oral rehydration solution (RR 2·60, 95% CI 1·59–4·27) and an 80% increase in use of zinc in diarrhoea.[67] Furthermore, findings showed a 13% (1·13, 1·08–1·18) increase in care-seeking for pneumonia, and a 9% (1·09, 1·06–1·11) increase in that for diarrhoea. We noted a 75% significant decline (0·25, 0·12–0·51) in inappropriate use of antibiotics for diarrhoea, and a 40% (0·60, 0·51–0·70) reduction in rates of treatment failure for pneumonia. Community case management for pneumonia by community health workers was associated with a 32% (0·68, 0·53–0·88) reduction in pneumonia-specific mortality, whereas evidence for diarrhoea-related mortality was weak.[67]

Reduction of financial barriers

Financial incentives are becoming widely used as policy strategies to alleviate poverty, to promote care seeking, and to improve the health of populations. Additionally, such incentives have been recommended as an important strategy to reduce barriers to access to health care.[69] An extensive review was undertaken to identify relevant studies reporting the effect of financial incentives on coverage of health interventions and behaviours targeting children younger than 5 years.[12] Investigators assessed the effect of financial incentive programmes on five categories of intervention: breastfeeding practices, immunisation coverage, diarrhoea management, health-care use, and other preventive strategies. Findings showed that financial incentives could promote increased coverage of several important child health interventions, but the quality of available evidence was low. Of all financial incentive programmes, more pronounced effects seem to be achieved by those that directly removed user fees for access to health services. Some indication of effect was also reported for programmes that conditioned financial incentives on the basis of participation in health education and attendance to health-care visits.

Emerging interventions for diarrhoea and pneumonia

Research priorities to develop and deliver interventions

We undertook a systematic analysis of various emerging interventions for diarrhoea and pneumonia on the basis of priorities emerging from the global research priority review process.[70,71] Preventive interventions assessed were reductions in levels of household air pollution,[72,73] and vaccines for *Shigella*[43,74–77] and enterotoxigenic *Escherichia coli*.[43] Therapeutic interventions were probiotics for diarrhoea[78] and antiemetics for gastroenteritis.[79] The appendix summarises the evidence for some of these interventions, which are promising, but not yet recommended for inclusion in programmes.

We undertook two expert panel methods to assess the feasibility and effectiveness of ten emerging health interventions for childhood diarrhoea and 23 for

Panel: Research priorities to prevent childhood diarrhoea and pneumonia mortality

We undertook two expert panel methods to assess feasibility and potential effectiveness of ten emerging health interventions against childhood diarrhoea and 23 against pneumonia (see appendix for the list of interventions for both illnesses). For each method we assembled a group of 20 leading international experts from international agencies, industry, basic science, and public health research, who took part in a Child Health and Nutrition Research Initiative (CHNRI) priority setting process. The experts used nine different criteria relevant to successful development and implementation of emerging interventions. They assessed the likelihood of answerability (in an ethical way), affordable cost of development and implementation of the intervention, efficacy and effectiveness against the disease, deliverability, sustainability, maximum effect on mortality reduction, acceptability to health workers, acceptability to end users, and positive effect on equity. Further details about the modified CHNRI framework, the criteria used, and the process of the expert opinion exercise have been published elsewhere.[82]

For pneumonia interventions, when the scores against all nine criteria were analysed, the experts showed mostly collective optimism towards improvement of low-cost pneumococcal conjugate vaccines, development of non-liquid and mucosal antibiotic paediatric formulations, and development of common-protein pneumococcal vaccines. The second level of priority was assigned to improvements in existing vaccines (eg, measles or *Haemophilius influenzae* type b) to enable needle-free delivery and heat stability. This assignment was followed by assessments of maternal immunisation, improved use of oxygen systems, and the development of combination vaccines and vaccines against major viral pathogens. The fourth level of priority was assigned to improved point-of-care diagnostic techniques. The lowest scores were assigned to passive immunisation, action on risk factors such as indoor air pollution or poor sanitation, or development of vaccines against neonatal bacterial pathogens that cause sepsis. The method suggested that most of the emerging interventions are still not feasible.

Pneumococcal conjugate vaccines, which were still regarded as an emerging intervention because of low uptake in low-income and middle-income countries at the time, achieved scores of more than 80% for all criteria apart from low product cost, which became the main point of discussion once they were introduced. By comparison, common protein pneumococcal vaccines are still hindered by concerns about answerability (although answerability is getting closer to 80%), and about all criteria related to their future cost. Other interventions have quite different score profiles. For example, antirespiratory syncytial virus vaccine for use in infants showed no feasibility for all criteria apart from acceptance for health workers, whereas monoclonal antibodies for passive immunisation against respiratory syncytial virus was completely unfeasible for product cost, affordability, and sustainability concerns; however, product development cost was considered to be feasible. Introduction of oxygen systems was considered answerable and there were no major cost concerns, but these systems were not deemed sustainable, sufficiently acceptable, or equitable. By comparison, common protein vaccines for influenza were considered sustainable, acceptable, and equitable, but concerns remained about answerability and costs of development. Emerging point-of-care diagnostic techniques were restricted with suboptimum levels of access to care, care-seeking behaviour, and the availability of first-line and second-line antibiotics.

The top ten research areas in the delivery categories for both the diarrhea and pneumonia process are:

1. Identify the barriers to increases in coverage and ensure that hard to reach populations have access to effective interventions—ie, oral rehydration solution, zinc, *Haemophilius influenza* type b and pneumococcal vaccines, WHO's seven-point plan, and WHO's strategy for acute respiratory infection
2. Identify contextual or cultural factors that positively or negatively affect care-seeking behaviour and which factors most effectively drive care-seeking behaviour
3. Investigate the effectiveness of culture-appropriate health education and public health messages on changes in health-seeking behaviour, hospital admission, and mortality, and which communication strategies are best to spread knowledge and generate care-seeking behaviour
4. Identify the main barriers to increase demand for and compliance with vaccination schedules for available vaccines in different contexts and settings
5. Identify the added effect of integrated Community Case Management or Integrated Management of Childhood Illness on early and equitable administration of appropriate treatment for acute diarrhoea and for pneumonia
6. Identify the best indicators for measurement of uptake of interventions and effectiveness of communication strategies
7. Identify the effect on child health outcomes of interventions to support mothers, for example to reduce maternal depression, strengthen maternal coping, and develop problem-solving skills for child health
8. Identify the capacity of health systems worldwide to correctly diagnose and manage childhood pneumonia, and the obstacles to correct diagnosis and case management in developing countries
9. Identify how trained health workers can be effectively trained and sustained and whether they can be trained to adequately assess, recognise danger signs, refer, and treat acute respiratory infections, including safe and effective administration of antibiotics
10. Identify the effectiveness of a community-led approach to total sanitation

pneumonia (appendix). We undertook a method to develop research priorities in line with the CHNRI[80–82] with various experts worldwide.[83] For diarrhoea, we expanded on previous methods[84,85] by identifying priorities to reduce morbidity and mortality caused by childhood diarrhoea in the next 15–20 years.[83] For pneumonia, we used a research method to define priorities to reduce mortality caused by childhood pneumonia by 2015,[86] including health policy and systems research. The panel shows the highest ranked research questions in these two areas. In these areas, research priorities including identification of barriers to health-care access—eg, implementation barriers to increase coverage of existing, effective interventions—and identification of drivers of care-seeking behaviour, ranked highly. Respondents prioritised assessment of the effect of Integrated Community Case Management and Integrated Management of Childhood Illness (IMCI) on early and equitable administration of appropriate treatment. Furthermore, prioritisation process for pneumonia identified the need to establish whether community health workers or community volunteers could be trained to adequately assess, recognise danger signs of, refer, or treat acute respiratory infections effectively.

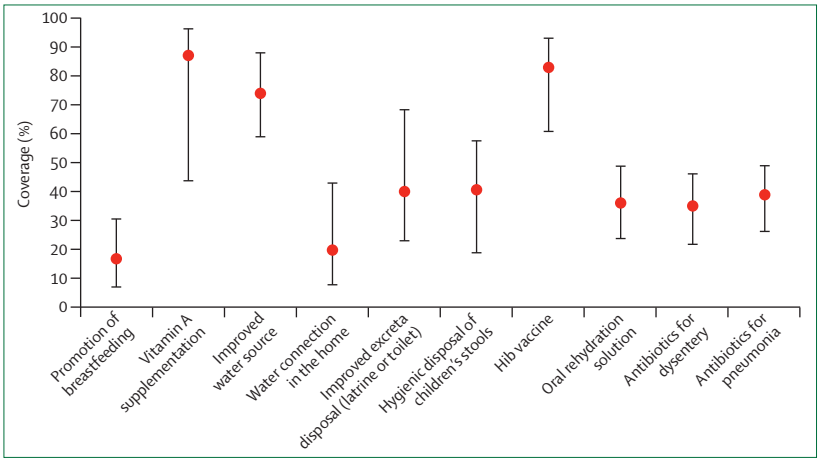

***Figure 2*: Coverage of interventions in 75 Countdown countries by quartiles**
Figure shows medians and IQRs. Hib=*Haemophilus influenzae* type b.

	Estimated deaths (2011)	Deaths averted (2025 *vs* 2011)	
		Historical trends (2025)	Ambitious scale-up (2025)
All deaths			
Children aged <5 years	7 038 418	1 821 329 (26%)	2 378 492 (34%)
Neonatal deaths	2 918 004	787 783 (11%)	874 217 (12%)
Infants aged 1–59 months	4 120 414	1 033 546 (15%)	1 504 275 (21%)
Diarrhoea deaths			
Children aged <5 years	711 569	382 415 (54%)	673 743 (95%)
Neonatal deaths	49 902	16 016 (2%)	35 174 (5%)
Infants aged 1–59 months	661 667	366 399 (51%)	638 569 (90%)
Pneumonia deaths			
Children aged <5 years	988 578	499 859 (51%)	662 495 (67%)
Neonatal deaths	326 308	150 143 (15%)	224 501 (23%)
Infants aged 1–59 months	662 270	349 716 (35%)	437 994 (44%)

Results are based on implementation of 15 interventions: improved water source, hand washing with soap, improved sanitation, hygienic disposal of children's stools, breastfeeding promotion, *Haemophilus influenzae* type b vaccine, pneumococcal vaccine, rotavirus vaccine, vitamin A supplementation, zinc supplementation, oral rehydration solution, zinc for diarrhoea treatment, antibiotics for dysentery, oral antibiotics for pneumonia, and case management.

***Table 4*: Diarrhoea and pneumonia deaths averted in the 75 high-burden Countdown countries between 2011 and 2025 with the historical trends and ambitious scale-up approaches**

LiST modelling effects on mortality outcomes for 75 Countdown countries

We selected a set of interventions from those reviewed for modelling on the basis of their proven benefits and availability in public-health programmes. We used LiST to model the potential effect of introduction of these interventions with a standard sequential introduction in health systems of the 75 high-burden Countdown countries. LiST estimates the effect of increases in intervention coverage on deaths from one or more causes, or in reduction of the prevalence of a risk factor (appendix). We modelled the effect of increased coverage of individual interventions from present levels for each country (figure 2) on child mortality. We used two approaches—historical trends and ambitious scale-up—to project coverage trends and scaling up of various interventions identified to 2025.

With the first approach (historic trends), we assessed the pragmatic trends of increased coverage on the basis of historical rates of change for the individual interventions in each country to predict the coverage of specific interventions to 2025 if trends continued unchanged. In the second approach (ambitious scale-up) we used a predefined target coverage level of 80% for all interventions except vitamin A supplementation and vaccines, for which we used a 90% target coverage. Table 4 shows the effect of these two approaches on diarrhoea and pneumonia deaths by 2025. The data show that based on country-specific historic trends 54% of diarrhoea and 51% of pneumonia deaths in children younger than 5 years can be averted by implementation of these interventions by 2025. However, ambitious scaling up of interventions would eliminate almost all diarrhoea deaths, but only two-thirds of pneumonia deaths, which shows the continued need to develop and implement more effective interventions to prevent and treat pneumonia (figure 3).

We also assessed the potential effect of individual interventions on lives saved by scaling up interventions to reach 90% coverage for vaccines and vitamin A, and 80% coverage for all other interventions and projected lives saved due to diarrhoea and pneumonia up to 2025. The analysis showed that water, sanitation, and hygiene interventions could prevent almost 0·5 million child deaths due to diarrhoea and pneumonia by 2025; almost the same number as that shown for the projected effect of *H influenzae* type b, pneumococcal, and rotavirus vaccines. Similar effects are noted in scaling up of community case management in children younger than 5 years (figure 4,

appendix). These findings have policy relevance and suggest that countries should consider a range of best buys to address childhood diarrhoea and pneumonia.

Cost analysis

Table 5 shows results of our cost analysis with LiST of interventions and packages in 2025 for the 75 Countdown countries. The costs are based on four components: personnel and labour, drugs and supplies, other direct costs, and indirect costs. We obtained assumptions about time needed for an intervention and costs for drugs and supplies from the One Health Model[87] developed by the UN. Costs shown for daily zinc supplementation are for 6–36 months. For breastfeeding, there was difficulty in translation of breastfeeding prevalence to breastfeeding promotion for our costing analysis; therefore, breastfeeding costs for the trend scenario were done by hand with country-specific unit costs, prevalence, and births. For scaling up of low-cost latrines, we estimated costs for all households, not just those with children younger than 5 years, and for *H influenzae* type b vaccine we used the present cost of pentavalent vaccine for our estimates (US$2·95 per dose; appendix).

On the basis of estimates of historic trend coverage, $3·8 billion dollars would be needed to avert 882 274 deaths due to diarrhoea and pneumonia, and for the ambitious scale-up plan, $6·715 billion dollars would be needed—an extra $2·914 billion to save an additional 557 163 lives. Drugs and supplies are the main cost items. The cost breakdown by intervention showed that for some interventions (oral rehydration solution and antibiotic treatment of dysentery), our analysis indicates cost savings because the number of diarrhoea cases has fallen substantially in most places, whereas for other interventions the costs increase because initial coverage levels are low and any increase in use results in a net increase in cost (appendix).

Equitable delivery of interventions and effect

A major limitation in previous strategies used to establish outcomes has been relatively little emphasis on reducing of inequities and targeting. We assessed the effect of interventions across equity strata for three countries (Pakistan, Bangladesh, and Ethiopia). We estimated the potential effect and cost-effectiveness of targeting of the same set of interventions to address neonatal mortality and mortality in children younger than 5 years within wealth quintiles. We computed all inputs except cause of death for the two wealth quintiles by reanalysing the most recent Demographic and Health Survey for the country (appendix). We estimated the effect of interventions on lives saved for the two quintiles of socioeconomic status: poorest (Q1) and poorer (Q2). The effect of various evidence-based interventions is greatest in the poorest quintiles (figure 5, appendix). Scaling up of these interventions would not only reduce the overall burden of childhood mortality but would also greatly reduce the discrepancies in provision of health care across various strata of socioeconomic status. To assess the effect of reaching the poorest individuals through community-based platforms, we assessed the benefit of three strategies (breastfeeding promotion, scale up of interventions for zinc or oral rehydration solution, and case management of pneumonia) deploying community health workers in these strata. Our model showed that if 90% coverage were achieved for these three interventions, 64% of diarrhoea deaths and 74% of pneumonia deaths could be averted in the poorest quintiles in the three countries assessed. This finding shows that community-based platforms deploying community health workers could not only reduce overall burden, but also ensure equitable delivery of these interventions to those who need them most (appendix).

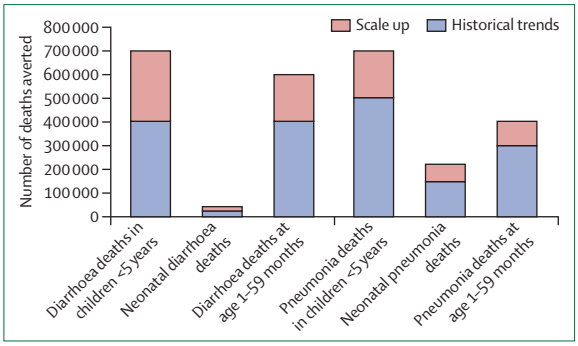

***Figure 3*: Additional effect of the ambitious scale-up approach on diarrhoea and pneumonia deaths averted for the 75 Countdown countries up to 2025**

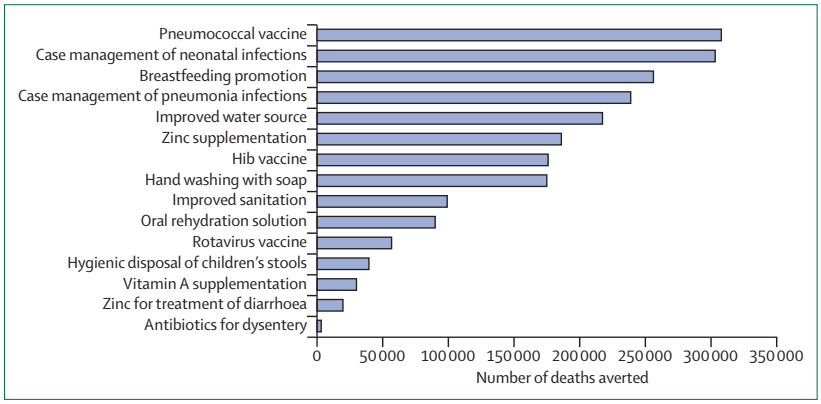

***Figure 4*: Sequential effect of individual interventions on deaths due to diarrhoea and pneumonia**
Haemophilus influenzae type b.

Discussion

Our findings are in line with those from previous reviews and studies, emphasising that effective interventions exist to address childhood diarrhoea and pneumonia, which are still major killers of children younger than 5 years worldwide. We refined and updated the evidence for a range of preventive, promotive, and therapeutic interventions, and by application of these estimates to the LiST model, reaffirmed that these interventions

	Historical trends					Scale-up strategy				
	Personnel and labour	Intervention costs	Other direct costs	Indirect	Total	Personnel and labour	Intervention costs	Other direct costs	Indirect costs	Total
Water, sanitation, and hygiene*†	$253·3	$1410·7	..	..	$1664·1	$404·2	$1678·3	..	..	$2082·4
Nutrition‡	$108·6	$2·5	$4·4	$15·1	$130·6	$368·9	$1785·4	$49·3	$171·0	$2374·7
Vaccines§	$45·3	$1623·7	$35·9	$124·6	$1829·5	$52·1	$1938·9	$42·1	$146·1	$2179·2
Case management¶	$41·5	$107·1	$6·4	$22·0	$177·1	$–0·5	$65·6	$3·2	$10·7	$79·1
Total	$448·7	$3144·1	$46·7	$161·8	$3801·3	$824·7	$5468·2	$94·7	$327·8	$6715·4

*Includes $4 per year per household for latrines, hand washing, and hygienic disposal of excreta. No costs are included for the improved water supply or piped water. †Water connection in the home, improved water source, improved sanitation (use of latrines or toilets), hygienic disposal of children's excreta, and hand washing with soap. ‡Breastfeeding promotion, and supplementation of vitamin A and zinc. §*Haemophilus influenzae* type b, pneumococcal, and rotavirus vaccines. ¶Oral rehydration solution, zinc for treatment of diarrhoea, antibiotics for dysentery, case management, and oral antibiotics.

***Table 5*: Estimated incremental costs (US$ million) by packages in 2025 for the 75 Countdown countries**

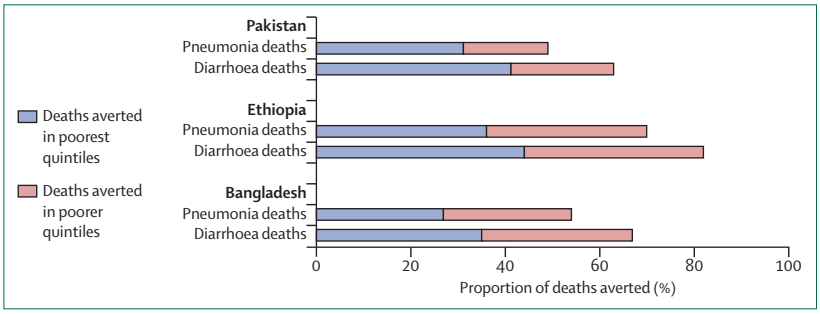

***Figure 5*: Equity analysis for Bangladesh, Ethiopia, and Pakistan**

could potentially eliminate diarrhoea deaths and prevent almost two-thirds of childhood pneumonia deaths by 2025 if implemented at scale. Many of these interventions would clearly affect morbidity and other outcomes, although our present models do not allow for assessment of effect on disease incidence and adverse outcomes contributing to overall disability.

Most the interventions exist within present health systems, although their coverage and availability to poor and marginalised populations varies greatly. Strategies for scaling up and emerging evidence of delivery platforms for key interventions have received relatively little focus. In addition to structural changes needed to reduce environmental pollution and provide safe water and sanitation, many of the risks associated with development of diarrhoea and pneumonia also need behavioural change at the household level. Our analysis emphasised the importance of focus on delivery strategies that target the poor, and hence a balance of demand creation and service delivery is needed to address these issues.

Our data show that key nutrition interventions for prevention of childhood diarrhoea and pneumonia have received scant attention, which is shown by poor rates of exclusive breastfeeding worldwide, especially in low-income and middle-income countries. Several reasons exist for this finding, including low awareness of the benefits of exclusive breastfeeding. In many low-income and middle-income countries there is no enabling environment for exclusive breastfeeding. Few laws are in place to protect the employment and work conditions that allow mothers to practise exclusive breastfeeding for the first 6 months after childbirth and implementation of the International Code on Marketing of Breast Milk Substitutes is insufficient. The same situation applies for interventions to address intrauterine growth retardation, a recognised risk factor for neonatal mortality and childhood illnesses including diarrhoea and pneumonia. In view of the global burden of low birthweight, which encompasses both prematurity and intrauterine growth retardation, this problem is a crucial risk factor that must receive greater attention.

The remarkably low coverage of oral rehydration solution for diarrhoeal episodes, and the almost negligible use of zinc for the management of diarrhoea, emphasises the fundamental challenges faced in public health. About four decades after findings showed the effectiveness of oral rehydration solution in population settings,[88] global coverage rates are negligible. Even a decade after WHO and UNICEF released recommendations for treatment of diarrhoea with improved oral rehydration solution and zinc, global uptake of zinc for the treatment of diarrhoea is abysmally low. Our findings show that several opportunities exist for scaling up the use of these interventions with community health-worker programmes, free distribution, social marketing, and co-packaging of zinc and oral rehydration solution, which can increase coverage by several times.[89] Promising indications show that such scaling up is beginning to happen and is being recommended as a strategy to reduce inequities in child survival in high-burden countries.[90]

The forthcoming Decade of Vaccines initiative offers a unique possibility that reductions in diarrhoea and pneumonia burden can be achieved with some of the new effective vaccines for pneumonia and diarrhoea through global financing and country-support mechanisms.[91] Our estimates show that 27% of childhood diarrhoea and pneumonia deaths can be averted by deployment of three key vaccines: *H influenzae* type b, pneumococcal conjugate, and rotavirus vaccines. A 90% improvement in coverage of a package of life-saving childhood vaccines in 72 countries eligible for support from the GAVI Alliance between 2011 and 2020 would prevent the deaths of roughly 6·4 million children

younger than 5 years, corresponding to $231 billion (uncertainty range $116–$614 billion) in the value of statistical lives saved.[91] The maximum benefits accrued from pneumococcal and *H influenzae* type b vaccines, contributing $105 billion ($52–$270 billion) from scale up of pneumonia and rotavirus vaccines contributed $54 billion ($27–$138 billion) to these estimates.[91]

Despite persistent burden, childhood deaths from diarrhoea and pneumonia are avoidable and 15 interventions delivered at scale can save most of these avoidable deaths. In some of the high-burden countries with existing inequities in intervention coverage and a high burden of mortality in poor populations, strategies exist that can reach these individuals and reduce the disproportionate burden of diarrhoea and pneumonia mortality therein. With an increasing number of countries deploying community health-worker programmes to reach the unreached, real opportunities exist to scale up community advocacy and education programmes and early case detection and management strategies. The new vaccines for *H influenzae* type b, pneumococcal pneumonia, and rotavirus diarrhoea could save at least 0·5 million lives in the next decade. Nevertheless, major gaps remain in implementation and strategies for scaling up. Operational research needs to be done urgently to establish the best strategies to improve community uptake of the best practices and encourage household-level behaviour change. Furthermore, the best delivery channels need to be identified to reach marginalised and disenfranchised populations, especially the urban poor. In view of the need to optimise treatment strategies and reduce inappropriate use of antibiotics, the balance of antibiotic access and excess[92] must be defined and research to address the benefits and population-level safety of programmes for Integrated Community Case Management should be done. Major advances in improvement of practical aspects of point-of-use water purification, low-cost sanitary facilities, and improved housing and living conditions offer an opportunity to address some of the fundamental challenges in reducing diarrhoea and pneumonia burden, but these methods need cost-effectiveness analyses.

Contributors

ZAB conceptualised the review of interventions and led the process, supported by JKD and REB. The following members contributed to specific reviews: LL to community case management, strategies for oral rehydration solution, and financial platforms; MG to feeding practices in diarrhoea and financial platforms; DB and KW to financial platforms; RAS to cholera vaccines, antiemetics, antibiotics for cholera and shigella, and community case management; and ZL to community case management. KW and AZ led the Child Health and Nutrition Research Initiative (CHNRI) method for setting of research priorities, overseen by ZAB. HC and IR contributed to the review of strategies to prevent and treat pneumonia. ZAB wrote the first draft of the review with substantial input from JKD. NW and AR contributed to the lives saved estimates in the Lives Saved Tool (LiST). IF and NW contributed estimates for costs with LiST.

***The Lancet* Diarrhoea and Pneumonia Interventions Study Group**

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Conflicts of interest

We declare that we have no conflicts of interests.

Acknowledgments

Funding was provided by an unrestricted grant from the Bill & Melinda Gates Foundation to Aga Khan University and to collaborating universities and institutions (Bloomberg School of Public Health, Johns Hopkins University, Boston; University School of Public Health and Program for Global Pediatric Research, Hospital for Sick Children, Toronto). The funding source had no role or control over the content and process of development of these papers, or in drafting of the report. The views expressed in this report are solely those of the authors. We thank Yvonne Tam (Johns Hopkins University) for assisting with LiST modelling, Margaret Manley (Program for Global Pediatric Research, Toronto), and Asghar Ali (Aga Khan University, Karachi) for administrative support.

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