Reviews/Analyses

Potential interventions for the prevention of childhood pneumonia in developing countries: a systematic review

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This article describes the background and framework for a systematic review of potential interventions for preventing pneumonia among under-5-year-olds in developing countries. Twenty-eight intervention areas are identified in six groups — immunization, case management/chemoprophylaxis of high-risk children, improving nutrition, reducing environmental pollution, reducing transmission of pathogens, and improving child care practices. Calculation of the potential impacts is illustrated and the expected outcomes are also described.

Introduction

Acute respiratory infections (ARI) are the leading cause of death among young children in developing countries. In the global burden of disease study (*1*), carried out for the World Bank's *World Development Report 1993*, 2 654 000 deaths out of the 12 443 000 deaths that occurred in 1990 in the developing world among children less than 5 years of age were attributed to acute lower respiratory infections (ALRI), which had not been associated with measles, pertussis or HIV, and 58 000 to acute upper respiratory infections (AURI, mosly otitis media). All deaths in the first week of life were categorized as perinatal and not included in these estimates. However, at least 10% of perinatal deaths (240 000) would be due to ALRI. In addition, a recent literature review (*2*) suggests that 67% of measles deaths, 83% of pertussis deaths, and at least 25% of HIV deaths are due to an ALRI. These proportions suggest that approximately 578 000 measles deaths, 230 000 pertussis deaths, and 14 000 HIV deaths are associated with an ARI, making a total estimate of 3 774 000 ARI or ARI-associated deaths among young children in developing countries in 1990 (Fig. 1). Thus ARIs are associated with or cause 30.3% of all deaths in this age group. The vast majority of ARI deaths are due to pneumonia.

The central objective of WHO's Programme for the Control of Acute Respiratory Infections is to reduce the severity of and mortality from pneumonia in young children.[a] Currently global efforts at mortality control focus on case management and improving the coverage of measles and pertussis immunization. Case-management intervention studies have demonstrated the substantial impact which can be achieved by treating children with inexpensive oral antibiotics if they have a cough and fast breathing (*3*).[b] ARI case management, particularly when combined within integrated management of the sick

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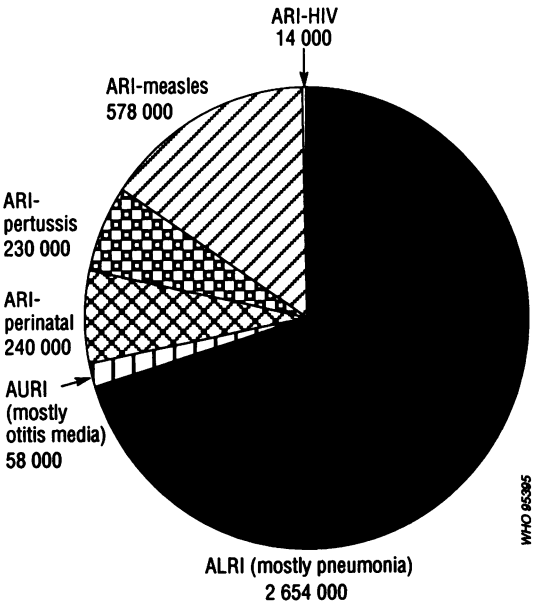
[a] WHO Programme for the Control of Acute Respiratory Infections. *Sixth programme report, 1992–1993.* Unpublished document WHO/ARI/94.33, 1994.

[b] WHO Programme for the Control of Acute Respiratory Infections. *Case management of acute respiratory infections in children: intervention studies.* Unpublished document WHO/ARI/88.2, 1988.

Fig. 1. **Distribution of 3 774 000 deaths from acute respiratory infections (ARI) or conditions associated with ARI among under-5-year-olds in 1990 in developing countries.** ALRI, acute lower respiratory infection; AURI, acute upper respiratory infection.



child, can be a highly cost-effective strategy for reducing mortality (*4*). Global efforts to immunize children against two serious acute respiratory infections, measles and pertussis, have already averted a substantial number of deaths. Preventive strategies can complement the case-management strategy at a number of levels. By reducing the incidence they would reduce the demand on curative services and may limit the use of antibiotics. Even if their effects on incidence are small, strategies that reduce the severity of pneumonia when it occurs could reduce the nutritional costs of infection (*5*), decrease the risks of residual pulmonary damage (*6*), and reduce case-fatality rates. An approach to ARI control incorporating preventive strategies is therefore expected to have a broader and more sustainable effect on pneumonia morbidity and mortality, and on overall child health, than can be expected from a strategy based only on case management.

Interventions for ARI control

A systematic and comprehensive review was carried out by the WHO programme and the London School of Hygiene and Tropical Medicine in order to identify interventions that are likely to be effective for the prevention of childhood pneumonia. The review was overseen by an international expert advisory committee which met in WHO, Geneva, in March 1992, March 1993 and June 1994.

Three different clusters of preventive strategies were considered; immunization, case management/chemoprophylaxis of high-risk children, and strategies based on the modification of risk factors that place a child at increased risk of pneumonia incidence and/or case fatality. The last cluster was further subdivided into four categories: improving nutrition, reducing environmental pollution, reducing transmission of pathogens, and improving childcare practices. A total of 28 potential intervention areas were then identified among the resulting six intervention groups, as shown in Fig. 2. Each intervention area has an associated risk category, defined as either exposure to a risk factor, or as membership of a high-risk group, or as not immunized by a vaccine, depending on the particular preventive strategy cluster to which it belongs.

Separate reviews were commissioned from international experts in each of the 28 intervention areas. A detailed review was also carried out to describe the etiology of acute lower respiratory infections among young children in developing countries, as essential background for the reviews relating to vaccines.

For each intervention area a standard series of questions were asked:

- By considering the underlying biological mechanisms, and by reviewing the epidemiological evidence, can a plausible case be made for a causal link between the risk category associated with the intervention area and an increased incidence of pneumonia and/or case fatality?
- If a causal link is possible:
  - How widespread is the associated risk category?
  - By how much does belonging to the risk category increase the incidence of pneumonia morbidity or mortality—in other words, what is the associated relative risk?
  - By how much might it be plausible to decrease the prevalence of the risk category?

Answers to these questions were then used to estimate the proportion of all pneumonia deaths that might be averted by an intervention to reduce the prevalence of the risk category.

Calculation of potential impacts

The calculation of the potential impact on pneumonia deaths achievable by an intervention is illustrated

in Fig. 3. A hypothetical situation is depicted, in which 400 (40%) of 1000 children are in the risk category. The 600 children not in the risk category experience a mortality rate of 50/1000, which means that 30 of them will die, while the 400 children in the risk category are at a threefold risk of dying, giving a mortality rate of 150/1000 which translates into 60 deaths in this group. If the latter group were not at increased risk there would only be 20 deaths, giving an excess of 40 deaths occurring because of the presence of the risk category. Thus if it were possible to eliminate the risk category, the total number of deaths would be reduced from 90 by 40, in other words by 40/90 = 44%. Thus the etiologic fraction associated with the risk category in this hypothetical example is 44%.

Suppose now that an intervention has taken place which reduced the prevalence of the risk category from 40% to 20%. The right hand side of Fig. 3 shows that there would then be a total of 70 deaths. As the size of the risk category has been halved by the intervention, the number of excess deaths has also been halved. The intervention has therefore prevented 20 of the pre-intervention total of 90 deaths. That is, the impact of the intervention would be 20/90 = 22%.

From this calculation it can be seen that the potential impact of an intervention depends crucially on three factors. The pre-intervention prevalence of the risk category, together with the relative risk associated with the risk category, determines the percentage of the total deaths attributable to the risk category. This percentage, known as the etiologic fraction, is the impact that would be achieved by a totally successful intervention which managed to eliminate the risk category. It is a theoretical maximum that is unlikely to be realized in practice. The actual impact will equal the etiologic fraction multiplied by the percentage reduction in prevalence of the risk category that the intervention achieved. In the hypothetical example in Fig. 3, this was 50%.

Fig. 4 shows how the potential impact of an intervention increases independently with the pre-intervention prevalence of the risk category, with the size of the associated relative risk, and with the reduction in risk-category prevalence achieved by the intervention. Estimates of these three factors were derived from the detailed reviews carried out, and used to model the range of potential impacts that might be achievable within a given intervention area.

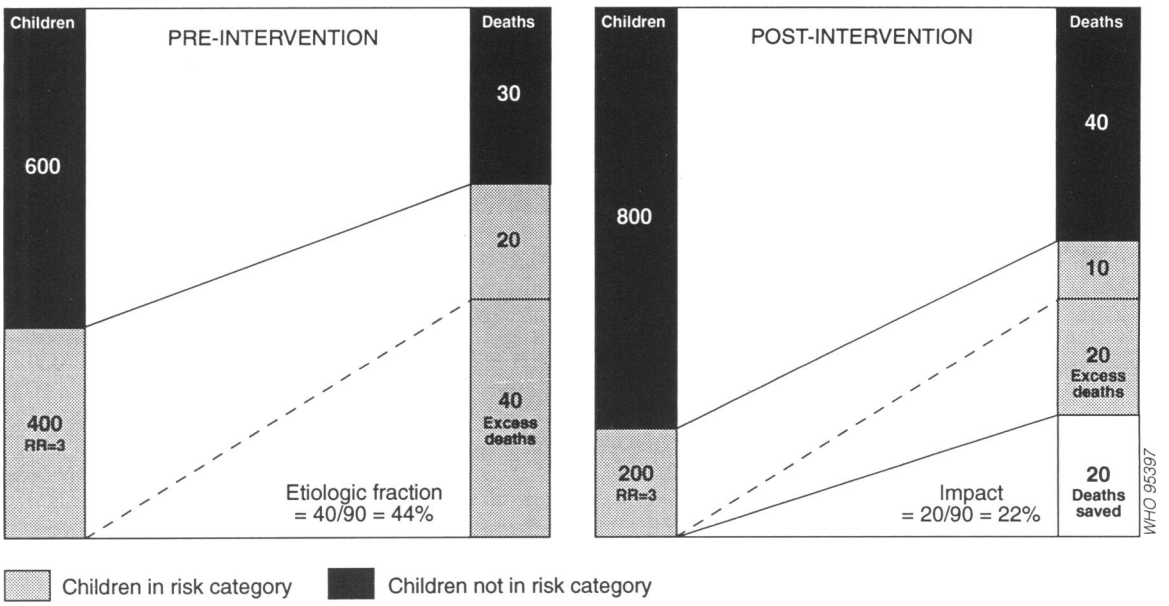
In carrying out this modelling, it was also essential to take into account that not all risk categories operate uniformly throughout the first five years of childhood, and also that pneumonia deaths are not evenly spread throughout this age range. Consider, for example, low birth weight. The detailed review suggested that a low-birth-weight baby was at 6.4 times the risk of death from pneumonia during the

Fig. 2. **Potential intervention areas for reducing pneumonia morbidity or mortality among under-5-year-olds.**

Immunization	**Improving nutrition**	**Reducing environmental pollution**
INCREASED COVERAGE *Measles* *Pertussis* NEW VACCINES *Pneumococcus* H. influenzae B *Respiratory syncytial virus* *Other viral vaccines*	*Breast-feeding* *Low birth weight* *Malnutrition* *Vitamin A* *Severe anaemia* *Other micronutrients* *(zinc, copper, vitamin D)*	*Indoor air pollution* *Environmental tobacco smoke* *Outdoor air pollution*
Case management and chemoprophylaxis	**Reducing transmission of pathogens**	**Improving childcare practices**
Severely malnourished children *High risk neonates* *Acute upper respiratory infection* *Helminths* *Wheezing*	*Crowding* *Direct transmission* *HIV*	*Care-seeking* *Avoiding chilling* *Other childcare practices* *Maternal education* *Child spacing*

WHO 95396

Fig. 3. **Example showing calculation of potential impact of an intervention, assuming pre-intervention prevalence of risk category = 40%; relative risk (RR) associated with risk category = 3; baseline mortality rate = 50/1000; and the intervention reduces the prevalence of risk category by 50% to 20%.**



first 6 months of life compared to a baby born with adequate birth weight, and at 2.9-fold increased risk for the next 6 months. There was no evidence to suggest that the increased risk of death associated with low birth weight persisted at older ages. Thus, the potential impact of an intervention is further limited by the percentage of the total childhood pneumonia deaths that occur in the age groups over which the risk category that it addresses has an influence.

Fig. 4. **Percentage impact on pneumonia deaths according to the pre-intervention prevalence of risk category, assuming relative risks (RR) of 3 and 4 and reductions in prevalence of 40% and 20%.**

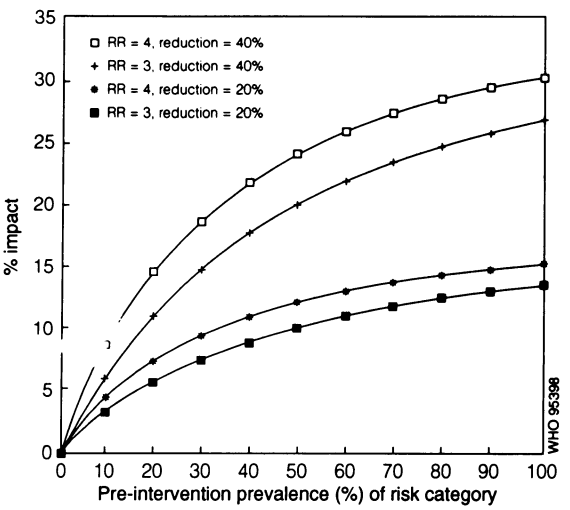


Table 1 shows the age distribution of pneumonia deaths by age used for the modelling. Its derivation is described in detail in the etiology review (*2*). It can be seen that 75% of pneumonia deaths occur during the first year of life, 58% of them within the first 6 months. This contrasts sharply with the pattern for diarrhoea deaths, where the comparable figures are 50% and 36% respectively. This means that other factors being equal, interventions will tend to be associated with a greater potential impact the earlier in life they exert an influence.

Table 1: **Percentage distribution of childhood pneumonia and diarrhoea deaths, by age group**

Age (months)	Pneumonia (%)	Diarrhoea (%)
0	22	9
1–5	36	27
6–11	17	14
12–17	9	15
18–59	16	35

Expected outcomes

The purpose of modelling the potential impacts achievable in different intervention areas is not to yield precise estimates, but to divide intervention areas into the following broad categories:

- high effectiveness, potential impact >10%;
- medium effectiveness, potential impact 5–10%;
- low effectiveness, potential impact <5%;
- no impact likely;
- insufficient evidence to assess potential impact;
- inconclusive evidence—doubts exist about causality, and evidence is inconclusive/contradictory concerning an increased relative risk.

Thus, the modelling will be used as a planning guide to systematically compare the potential impacts of preventive approaches to the control of childhood pneumonia, with the impact achievable with the case-management strategy, and to identify those intervention areas worthy of attention to assess whether feasible, cost-effective intervention strategies either exist or could be developed.

Two detailed reviews have already been published, on vitamin A (*7*) and on routine administration of antibiotics for upper respiratory infections (*8*). Several more papers will be published over the coming months summarizing the main conclusions of the review, and presenting detailed results in the different intervention groupings. These will be published in different journals, depending on the intervention area discussed, in order to reach as wide an audience as possible. The common title used for the series is "Potential interventions for the prevention of childhood pneumonia in developing countries".

It is expected that the results of this systematic review will influence policy formulation for ARI control strategies. A similar review, carried out by Feachem and his colleagues (*9*) for diarrhoeal disease control policies, was instrumental in causing, for example, breast-feeding promotion to become a standard part of diarrhoeal disease control activities. In summary, it is hoped that this systematic review will focus attention on a few preventive strategies, which, if implemented alongside standard case management, could substantially improve the achievements of ARI control programmes.

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Résumé

Etude systématique des possibilités de prévention de la pneumonie infantile dans les pays en développement

Cet article décrit le cadre de travail adopté par le programme OMS de lutte contre les infections respiratoires aiguës et la London School of Hygiene and Tropical Medicine lors d'une étude systématique des possibilités d'interventions efficaces et réalisables à un coût abordable en vue de la prévention de la pneumonie infantile. Vingt-huit interventions, classées en six groupes, ont été retenues: vaccination, prise en charge/chimioprophylaxie des enfants à haut risque, amélioration de la nutrition, réduction de la pollution de l'environnement, réduction de la transmission des agents pathogènes, et amélioration des soins pédiatriques.

Pour chaque intervention, les questions suivantes ont été posées:

- Compte tenu des mécanismes biologiques sous-jacents et de la situation épidémiologique observée, peut-on considérer comme plausible un lien de cause à effet entre la catégorie de risque associée à l'intervention et une augmentation de l'incidence de la pneumonie et/ou du taux de létalité?

Si un tel lien est possible:

- Jusqu'à quel point le risque associé à l'intervention est-il répandu?
- Dans quelle mesure le fait d'appartenir à une catégorie de risque augmente-t-il l'incidence de la morbidité ou de la mortalité due à la pneumonie? En d'autres termes, quel est le risque relatif associé?
- Dans quelle mesure est-il possible de réduire la prévalence de la catégorie de risque?

Les réponses à ces questions ont ensuite servi à établir un modèle pour évaluer l'impact potentiel des différents types d'interventions. Les résultats seront utilisés comme guide pour com-

parer systématiquement l'impact potentiel des différentes approches de la prévention de la pneumonie infantile à celui d'une stratégie fondée sur la prise en charge des cas, et pour identifier les interventions intéressantes afin de déterminer si elles peuvent servir de base à des stratégies réalistes et d'un bon rapport coût/efficacité.

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