Challenges to improving case management of childhood pneumonia at health facilities in resource-limited settings

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Abstract Effective case management is an important strategy to reduce pneumonia-related morbidity and mortality in children. Guidelines based on sound evidence are available but are used variably. This review outlines current guidelines for childhood pneumonia management in the setting where most child pneumonia deaths occur and identifies challenges for improved management in a variety of settings and different "at-risk" groups. These include appropriate choice of antibiotic, clinical overlap with other conditions, prompt and appropriate referral for inpatient care, and management of treatment failure. Management of neonates, and of HIV-infected or severely malnourished children is more complicated. The influence of co-morbidities on pneumonia outcome means that pneumonia case management must be integrated within strategies to improve overall paediatric care. The greatest potential for reducing pneumonia-related deaths in health facilities is wider implementation of the current guidelines built around a few core activities: training, antibiotics and oxygen. This requires investment in human resources and in equipment for the optimal management of hypoxaemia. It is important to provide data from a variety of epidemiological settings for formal cost-effectiveness analyses. Improvements in the quality of case management of pneumonia can be a vehicle for overall improvements in child health-care practices.

Bulletin of the World Health Organization 2008;86:349–355.

Une traduction en français de ce résumé figure à la fin de l'article. *Al final del artículo se facilita una traducción al español.* الترجمة العربية لهذه الخلاصة في نهاية النص الكامل لهذه المقالة.

Introduction

Pneumonia is the leading cause of death in children worldwide and the great majority of these deaths occur in resource-limited settings.[1] WHO developed a case-management strategy in the 1980s aiming to reduce pneumonia-related deaths. This was a cornerstone of the acute respiratory infection (ARI) programme and was later incorporated into the Integrated Management of Childhood Illness (IMCI) guidelines which include primary care and hospital-based case management. The basis for the case-management strategy was that:

1. Almost all ARI-related deaths were in children with pneumonia.
2. Children with pneumonia need assessment by a trained health worker.
3. Pneumonia could be distinguished from other respiratory tract infection by the use of simple clinical signs such as respiratory rate and chest indrawing.[2]
4. Many pneumonia deaths were caused by bacteria, usually *Streptococcus pneumoniae* or *Haemophilus influenzae*.[2]
5. Children with a cough but who do not have pneumonia should not receive antibiotics, reducing selection pressure for antimicrobial resistance.
6. Hypoxaemia is common and associated with increased risk of death.[3,4]

Clinical definitions of severity of pneumonia were proposed and are still used.[5] The evidence on clinical assessment and severity classification of pneumonia has been reviewed recently.[6] Studies show that clinical definitions of severity correlate with case-fatality rate.[7–9] While non-severe pneumonia is far more common than severe pneumonia, most deaths occur in children with severe pneumonia.

Effectiveness of community-based implementation of the WHO ARI case-management strategy was reviewed by meta-analysis. In communities where previously there had been no antibiotics or case-management strategy, the strategy reduced pneumonia-specific mortality by 35–40%.[10] The provision of training in case management in the hospital setting also improved outcomes and reduced unnecessary antibiotic use.[11] Implementation of the case-management strategy remains a challenge in resource-limited settings.

This review aims: (1) to highlight challenges and uncertainties relating to current case-management guidelines in a variety of settings; and (2) to address the issue of implementation in resource-limited settings. The review

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doi:10.2471/BLT.07.048512
(*Submitted: 11 October 2007 – Revised version received: 16 January 2008 – Accepted: 1 February 2008*)

will focus on case management after presentation to a health facility, the management of childhood pneumonia outside this context being the focus of another review in this issue of the *Bulletin*.[12]

Methods

Information for this review involved a search of PubMed and authors' personal archives of references. Keywords for the search included "child", "pneumonia", "case management", "hypoxia", "implementation", "cost-effectiveness" and "programmes." The most recent reviews, including Cochrane reviews of topics, were referenced wherever possible rather than original articles due to such a large subject matter. Over 200 references were retrieved, with most focusing on efficacy of treatment strategies and relatively few on programme implementation.

Current issues for case management

The relative importance of the issues listed below will vary between regions.

Clinical overlap

It is important to make the correct diagnosis. The case-management strategy assumes that the presentation of fever and cough with fast breathing means that the child has pneumonia and requires an antibiotic. This simple clinical definition can overlap with that of other diseases that do not require an antibiotic.

Studies of non-severe pneumonia from Asia report that a large proportion of antibiotic treatment failure for pneumonia has been in children with wheeze.[13,14] WHO now recommends a trial of rapid-acting bronchodilator in children with wheeze and fast breathing before making a diagnosis of pneumonia even though nebulizers are not available to health workers in the community.[15] Further, infants with wheeze usually have viral bronchiolitis and so bronchodilators are often ineffective.[16] A separate management algorithm is needed for children with wheeze. Teaching health workers what constitutes an effective response to bronchodilators will be important for diagnosis and further management.

Clinical presentation and appropriate management is more complicated in regions that are endemic for HIV, malnutrition, tuberculosis or malaria. *Plasmodium falciparum* malaria can sometimes cause cough and fast breathing and can be rapidly fatal in children if untreated.[17,18] For this reason, any febrile child in a high-risk area should be treated with an effective antimalarial whatever the alternative or comorbid conditions. Such guidance is appropriate for health workers who direct outpatient management with no laboratory support. Overlap between conditions and the common presence of comorbidities in the sickest children emphasizes the need for integrated strategies for case management.[5]

Referral for inpatient management

Clinical deterioration due to pneumonia is often rapid, especially among young infants. Septicaemia and hypoxaemia are likely to be the major mechanisms leading to deterioration and death. The health facility for initial presentation of even the sickest child is usually a primary health-care centre with limited options for case management. Accurate recognition of the child with severe pneumonia, supported by a mechanism that allows prompt referral to a facility for parenteral antibiotics and oxygen, is critical but currently inadequate in resource-limited settings. Inadequate referral had a significant independent effect on poor outcomes in Mexican children with pneumonia.[19]

Antibiotic choice and duration

Antibiotics are required to treat pneumonia. WHO recently revised recommendations on the basis of evidence from studies comparing antibiotic treatment for pneumonia[15] and provided guidelines for management of children with pneumonia and HIV in resource-limited settings.[20] The evidence from these studies was recently reviewed.[6,21]

Important issues regarding antibiotics and pneumonia are listed:

1. "Treatment failure" has been used as an endpoint in trials assessing the clinical effectiveness of antibiotics, but the term has a variety of definitions.
2. What proportion of children with fast breathing will benefit from antibiotic therapy in populations where respiratory viruses cause most cases of non-severe pneumonia and an increasing proportion of severe pneumonia? A recent study from Pakistan reported radiological evidence of pneumonia in only 14% of children with WHO-defined non-severe pneumonia.[22]
3. In vitro intermediate resistance of *S. pneumoniae* to penicillin is common worldwide and more broad-spectrum antibiotics such as cephalosporins are increasingly available and preferred as first-line therapy as they are perceived to be more effective.[6] However, intermediate resistance of pneumococcus may not affect response to recommended high dosages of penicillin for pneumonia.[23]
4. Health workers often do not make a distinction between severe and very severe pneumonia and tend to treat all hospitalized children according to the guidelines for very severe pneumonia.[24]
5. Increasing global coverage of effective vaccines against *H. influenzae* type b (Hib) and pneumococcus means that these bacteria are becoming, or are likely to become, less important causes of pneumonia.[25,26]
6. Nontyphoidal salmonellae are a common isolate from children with features of severe pneumonia in tropical Africa but are not well covered by current recommendations.[9,27]
7. Pulmonary tuberculosis is increasingly recognized as a common cause of acute pneumonia especially in children in tuberculosis-endemic countries.[8,28] It is difficult to confirm diagnosis and so to differentiate from bacterial or viral pneumonia. Therefore it is hard to estimate the real burden.
8. HIV-infected children and severely malnourished children with severe pneumonia should receive broad-spectrum antibiotics but the most effective duration of antibiotics in these children is unknown.
9. *Pneumocystis jiroveci* pneumonia is common and often fatal in HIV-infected infants but treatment response is poor in resource-limited settings.[8,29]

Management of hypoxaemia

Hypoxaemia occurs in around 20% of children presenting to health facilities with pneumonia, although there are marked geographical differences in prevalence.[30] Hypoxaemia is associated with a marked increased risk of mortality

from pneumonia.[3,4] There is still some debate about the definition of hypoxaemia, particularly as altitude increases,[4] but it is generally considered that oxygen saturation of arterial haemoglobin measured by pulse oximetry (SpO_2) <90% at sea-level represents hypoxaemia requiring treatment.[5,28] Detecting hypoxaemia presents another challenge. Many studies have demonstrated variability in the predictive value of clinical signs.[31] Pulse oximetry is the optimal approach to determining the need for and response to oxygen therapy and is the "standard of care" in higher income countries. The technique is robust and can be readily used in resource-limited settings but is moderately expensive.[32]

Value of micronutrients

Vitamin A is well established as an effective treatment for measles, significantly reducing pneumonia and the case-fatality rate.[33] The value of zinc in children with severe pneumonia is less certain and may depend upon the prevalence of zinc deficiency in the community. A randomized controlled trial (RCT) in Bangladeshi children with severe pneumonia found that daily zinc was associated with a shorter duration of severe pneumonia, hypoxia and hospital stay compared to placebo, while a similar study in India did not find any effect.[34,35]

Management of treatment failure

It is important to define or standardize treatment failure for the purpose of RCTs that compare therapeutic efficacy and for assessment of guidelines. Recent studies have used various definitions of treatment failure, based on failure to improve on different clinical criteria, measured 2–5 days after beginning treatment,[6,8] and revising current WHO case definitions of treatment failure can substantially reduce observed treatment failure rates.[36] In clinical practice, most clinicians would expect that a child with pneumonia would show some evidence of clinical improvement on antibiotics by 48 hours at the latest – and if not would consider a change of antibiotics or an alternative diagnosis. However, what comprises "some evidence of clinical improvement" remains the critical issue.

There are many risk factors for treatment failure and some of the more common are young age, viral pneumonia, wheeze, poor adherence to treatment, immunosuppression (e.g. HIV or malnutrition), development of empyema, prior antibiotic use, antibiotic resistance or alternative diagnosis (e.g. malaria, foreign body). Most of the treatment failures and deaths are in infants and this high-risk group could be categorized separately. It is important to distinguish between "benign" treatment failure such as due to viral infection and "true" treatment failure indicating worsening pneumonia or developing complications. It may be more helpful to use objective signs of clinical severity and pulse oximetry rather than persistence of tachypnoea.[37]

Management of "at-risk" groups

Neonatal pneumonia

Pneumonia is common in young infants (< 2 months) and is always classified as severe as they are at higher risk of hypoxaemia, apnoea and mortality than older children with pneumonia. Neonatal pneumonia is responsible for a large proportion of pneumonia deaths but is more difficult to define, as clinical presentation is even less specific than in children.[38] There is clinical overlap with "neonatal sepsis" and with non-infective conditions causing respiratory distress. Important pathogens identified from limited studies in developing countries include streptococci and a wide range of Gram-negative bacteria such as *Escherichia coli* or *Klebsiella* spp.[38,39] The current recommendation of penicillin or ampicillin plus gentamicin is appropriate. A major case-management problem for neonatal pneumonia is the difficulty of providing adequate supportive care such as hydration, nutrition and oxygen in resource-limited settings.

HIV-related pneumonia

HIV prevalence is now greater than 50% in children hospitalized with very severe pneumonia in some settings in sub-Saharan Africa.[8,29] HIV-related pneumonia has been reviewed recently.[29] Studies provide consistent data but are mainly from large urban-based referral hospitals. Incidence of pneumonia, including bacterial pneumonia, is much higher for HIV-infected children than for HIV-uninfected children. The common causes of bacterial pneumonia are similar but the range of bacterial pathogens is wider. Opportunistic infections such as *P. jiroveci* and cytomegalovirus are common and associated with poor outcome. Pulmonary tuberculosis is common in HIV-infected infants and children presenting with severe pneumonia in tuberculosis-endemic regions.[40] Mixed infections and treatment failure are common.[8] Case-fatality rates are reported to be 3–8 times higher than in HIV-uninfected children even when current guidelines are applied.[8,29] This emphasizes the potential of prevention of mother-to-child transmission, co-trimoxazole preventive therapy and antiretroviral therapy to reduce the burden and case-fatality of pneumonia in HIV-endemic countries.[29] Improved survival means that an increasing proportion of pneumonia presents in school-aged children and guidance is needed for case-management of children aged 5–15 years, both HIV-infected and uninfected.

Severely malnourished children

Many of the issues already outlined for neonates and HIV-infected children apply to severely malnourished children. Pneumonia is more common and more fatal than in well nourished children and is caused by a wider range of bacteria and opportunistic pathogens.[41] Clinical presentation is less specific and overlaps with septicaemia.[42] There are also difficult management issues regarding supportive care, especially nutrition. Cover for Gram-negative bacilli is included in first-line antibiotics for severely malnourished children with pneumonia, and pulmonary tuberculosis should be considered if they do not respond. HIV testing should be routine.

Implementation

For the purposes of training and implementation, it is important to achieve consensus and to define "best practice" based on available evidence. Summarizing and presenting this evidence and suggesting standards is a major role of WHO. Most critical to success, however, and more challenging, is transforming policy (or guidelines) into widespread practice. The most effective intervention to reduce pneumonia-related deaths for the majority would be improved access to early care where simple, appropriate interventions are provided, including referral where necessary. To do this requires adequate health worker numbers, training and

support, and ready availability of antibiotics and oxygen.[43,44]

The impact of training in ARI case-management was first described by Qazi et al. in Pakistan.[11] In addition to reducing ARI-related case-fatality, there was a marked reduction in antibiotic use for outpatient management over the study period. However, it is not only the quality of training that matters but also the coverage. Many children with pneumonia seek care from private practitioners or health workers who have not undergone training in case management.[1] Effective practice must be promoted in all sectors and from the community level upwards. There also needs to be political will and involvement of leading health professionals. There are many other issues that may need to be addressed such as integration into present service delivery, health-seeking behaviour, barriers to accessing health services, quality and extent of training, health-care worker retention, supervision, secure antibiotic supply, continued supervision and in-service training, maintenance and repair of equipment and clinical audit.[32,44] A comprehensive strategy in Malawi, an HIV-endemic country with an established ARI programme, markedly reduced pneumonia-related case-fatality at district hospitals.[45] Implementation of an effective oxygen system in Papua New Guinea reduced severe pneumonia mortality in one hospital by 40%[3] and, when this was extended to five other hospitals, there was an overall pneumonia case-fatality rate reduction of 35% (unpublished data, T Duke).

Adequate equipment and "best practice"

The issue of hypoxaemia identification and management raises important issues. What should be considered minimal "best practice" in resource-limited settings where most children with pneumonia die? When resources are limited, what are the most cost-effective interventions to prioritize for pneumonia management? These questions reflect fundamental moral and ethical issues encompassed in a child's right to health in a global setting where the average amount of money spent on management of an equivalent episode of illness may vary more than 100-fold between high- and low-income countries.[46]

Data from district hospitals illustrate that there is much that can be done to improve the quality of care of pneumonia and other common illnesses in district-level hospitals in developing countries. Evidence-based practice, training, support and equipment are often neglected in low-income settings, but can be achieved at low cost.[24,30,47,48] A survey of 21 hospitals in seven less-developed countries found inadequate knowledge and practice for managing pneumonia among 56% of doctors and nurses.[48] Of 14 district hospitals in Kenya, none had an oxygen saturation monitor and 11 had an inadequate oxygen supply.[24] In five hospitals in Papua New Guinea, oxygen was not available on the day of admission for 22% of 1300 children (range between hospitals 3–38%) with the worst situation in remote rural district hospitals.[30] Oxygen is even less available in primary health care clinics than in hospitals in developing countries but is often required for sick children while awaiting referral and during transport to a district hospital. In Kenya, government primary health-care clinics are not routinely provided with oxygen (unpublished observation, M English).

It is possible to provide oxygen systems in resource-limited settings but the challenge is to incorporate and sustain oxygen technology into clinical care. Oxygen concentrators were successfully introduced into small hospitals in Egypt and the importance of support for training and maintenance was highlighted.[49] More recently, pulse oximeters and oxygen concentrators were introduced into hospitals in Papua New Guinea, improving outcomes using a multidisciplinary approach to provide technical and training support. In Papua New Guinea, in the first 2.5 years, 5 of 15 concentrators and 2 oximeters malfunctioned but all were easily repaired.[32]

Importance of cost and implementation data

It is expensive to treat children with pneumonia especially as inpatients.[50,51] In Pakistan, the average cost to treat a child with pneumonia as an outpatient was estimated by activity-based costing as US$ 13.44, representing 82% of annual health expenditure per person at the time. In comparison, inpatient costs were estimated as US$ 71 and US$ 235 for pneumonia and severe pneumonia respectively.[50] These are consistent with estimates from Africa and south-east Asia.[51] This emphasizes the potential of studies that compare effectiveness of oral to parenteral antibiotics or shorter-course therapy to that currently recommended. Parenteral antibiotics that require only once-daily administration such as gentamicin or ceftriaxone are less costly in terms of equipment and staff-time than those requiring multiple injections. Potential cost savings for the patient and health system are also substantial when unnecessary antibiotic use is reduced.[11] In Pakistan, antibiotics constitute the highest proportion of cost incurred for a family in childhood pneumonia management.

Cost-effectiveness has been compared to other child-survival strategies.[51] It was estimated that case management of pneumonia, together with oral rehydration therapy and measles immunization, achieved the largest health gains by an individual intervention. The average cost-effectiveness ratio was US$ 47 and US$ 70 per DALY (disability-adjusted life year) averted for sub-Saharan Africa and south-east Asia respectively. Cost-effectiveness data will become increasingly important to help prioritize future case-management strategies, including human resource costs. Oxygen therapy is potentially a costly intervention. The proportion of children presenting to health facilities with hypoxaemia varies widely and is influenced by referral patterns and admission criteria, level of health facility, age and altitude. The demand for oxygen therefore varies widely between institutions, a fact rarely considered in facility resource planning.

There is a need for more data not just to measure cost-effectiveness but also potential cost-savings. It has already been stated that more rational use of antibiotics may lead to substantial cost-savings for families. Although moderately expensive, oximetry may be cost-effective, not just because of improved outcomes compared to the use of clinical signs,[3] but also because of potential cost savings by more rational use of oxygen. Interventions that aim to improve the management of children with pneumonia should be encouraged to collect and publish comprehensive

data relating to cost and behaviour change as well as outcome.

There is also a need for more research on health systems and implementation, to address the provision of available interventions more effectively to the children who need them most. A model for setting research priorities has been developed to shift the emphasis from the generation of new knowledge and publication to potential public health outcomes.[52] It is recognized that implementation research is methodologically challenging but measuring the impact of delivery at different levels of health facilities and cost will provide the important data needed for political support.

Conclusion

This review has highlighted issues relating to pneumonia management at health facilities that require further evidence to improve effectiveness of case-management guidelines in different settings. This is a particular challenge in regions of high case-fatality rate where bacterial pneumonia is common in young infants and where comorbidities such as HIV infection and malnutrition are common. Even in these settings, implementation of current guidelines can substantially reduce pneumonia-related mortality because many health facilities still lack the basic needs for effective case management: evidence-based training, facilitated referral, antibiotics and oxygen. ■

Acknowledgements

Steven Graham recently worked for the Malawi-Liverpool-Wellcome Trust Programme of Tropical Clinical Research and the Department of Paediatrics, College of Medicine, University of Malawi, Blantyre, Malawi, from where he gained much of the experience relating to this review. He was supported by a Wellcome Trust-funded core grant 074124/Z/04/Z.

Competing interests: None declared.

Résumé

Difficultés pour améliorer la prise en charge des cas de pneumonie chez l'enfant dans les établissements de soins des pays à ressources limitées

La prise en charge efficace des cas joue un rôle important dans la réduction de la morbidité et de la mortalité dues à la pneumonie. Des recommandations reposant sur des éléments factuels solides sont disponibles, mais sont appliquées diversement. Le présent article expose dans leurs grandes lignes les recommandations actuelles pour la prise en charge de la pneumonie chez l'enfant dans les pays où interviennent la plupart des décès d'enfants par pneumonie et identifie les difficultés pour améliorer cette prise en charge dans divers pays et chez différents groupes « à risque ». Ces recommandations concernent notamment le choix d'un antibiotique adapté, le recouvrement clinique avec d'autres pathologies, l'orientation rapide et appropriée vers des soins hospitaliers et la prise en charge des échecs thérapeutiques. La prise en charge des nouveau-nés et des enfants infectés par le VIH ou gravement dénutris est plus complexe. L'influence des comorbidités sur l'issue de la pneumonie implique que la prise en charge de cette maladie doit s'intégrer dans des stratégies d'amélioration des soins pédiatriques en général. Le plus fort potentiel de réduction de la mortalité par pneumonie dans les établissements de soins réside dans l'élargissement de l'application des recommandations actuelles, élaborées autour de quelques interventions centrales : formation, antibiotiques et oxygène. Cet élargissement nécessite des investissements en ressources humaines et en équipements pour une prise en charge optimale de l'hypoxémie. Il est important de fournir des données provenant de divers contextes épidémiologiques pour établir des analyses coût/efficacité formelles. L'amélioration en termes de qualité de la prise en charge de la pneumonie pourrait servir de moteur à des améliorations globales des pratiques de soins pédiatriques.

Resumen

Retos para mejorar el manejo de los casos de neumonía en la niñez en los centros sanitarios en los entornos con recursos limitados

Un manejo de casos eficaz constituye una estrategia importante para reducir la morbilidad y la mortalidad por neumonía en la niñez. Las directrices basadas en la evidencia de que se dispone se utilizan en diversa medida. En el presente análisis se describen las directrices actuales para el tratamiento de la neumonía en la niñez en las circunstancias que rodean la mayoría de las muertes por neumonía en la infancia y se señalan los retos que deben superarse para mejorar el tratamiento en diversos contextos y diferentes grupos en riesgo. Entre ellos cabe citar la elección apropiada del antibiótico, el solapamiento clínico con otras dolencias, la derivación rápida y apropiada para dispensar atención hospitalaria, y el manejo de los casos de fracaso terapéutico. El tratamiento de los recién nacidos y de los niños infectados por el VIH o malnutridos es más complicado. Dada la influencia de posibles comorbilidades en la evolución de la neumonía, el tratamiento de los casos de esa enfermedad debe integrarse en estrategias orientadas a mejorar la atención pediátrica en general. Las mayores posibilidades de reducir las defunciones relacionadas con la neumonía en los centros de salud son las que se derivan de una más amplia aplicación de las directrices actuales centradas en unas cuantas actividades básicas: capacitación, antibióticos y oxígeno. Eso exige invertir en recursos humanos y en equipo para manejar óptimamente la hipoxemia. Es importante aportar datos procedentes de diversos entornos epidemiológicos para poder realizar análisis formales de costo-eficacia. Las mejoras de la calidad del tratamiento de casos de neumonía pueden brindar la ocasión para introducir otras mejoras más generales en las prácticas de salud infantil.

ملخص

التحدِّيات التي تواجه تحسين معالجة الأطفال المصابين بالالتهاب الرئوي في المرافق الصحية في المواقع المحدودة الموارد

نُعد المعالجة الفعَّالة لحالات الالتهاب الرئوي استراتيجية هامة في الحد من الوفيات والمراضة ذات الصلة بالالتهاب الرئوي بين الأطفال. وتتوافر في هذا الصدد دلائل إرشادية مرتكزة على بيِّنات سليمة، ولكن تتفاوت درجة الاستفادة منها. وتقدِّم هذه الدراسة نبذة عامة عن الدلائل الإرشادية المتاحة حالياً لمعالجة الالتهاب الرئوي لدى الأطفال في الأماكن التي تحدث فيها معظم وفيات الأطفال بسبب هذا المرض، كما تحدد الدراسة التحدِّيات التي تواجه تحسين سُبُل المعالجة في أماكن مختلفة وبين مجموعات مختلفة معرَّضة للمخاطر. وتشمل هذه الدلائل الإرشادية الاختيار السليم للمضادات الحيوية، والتشابه السريري مع حالات أخرى، والإحالة الفورية والمناسبة لتلقِّي الرعاية داخل المستشفيات، وتدبير حالات فشل المعالجة. وتتسم معالجة الولدان والأطفال المصابين بفيروس الإيدز أو بسوء التغذية الوخيم بمزيد من التعقد. ويتضح من تأثير المراضة المشتركة على حصيلة الإصابة بالالتهاب الرئوي، ضرورة إدماج معالجة حالات الالتهاب الرئوي في استراتيجيات مناسبة لتحسين الرعاية الشاملة للطفولة. وتتمثَّل أكبر الإمكانيات للحد من الوفيات ذات الصلة بالالتهاب الرئوي، التي تحدث في المرافق الصحية، في توسيع نطاق تنفيذ الدلائل الإرشادية الحالية التي تركز على عدد قليل من الأنشطة الرئيسية، وهي: التدريب، والمضادات الحيوية، والأكسجين. ويستلزم هذا الأمر الاستثمار في الموارد البشرية وفي المعدات، من أجل تحقيق المعالجة المثلى لنقص تأكسج الدم. ومن المهم توفير البيانات من مواقع وبائية متنوعة، لإجراء تحاليل رسمية للمردودية. ومن الممكن أن يكون تحسين جودة معالجة حالات الالتهاب الرئوي وسيلة للتحسين الشامل لممارسات الرعاية الصحية للأطفال.

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