Dr Fyezah inside the home of a patient treated successfully within the trial

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Fighting pneumonia for improving treatment efficiency

While pneumonia is a major cause of illness and death in small children of low-income countries, non-severe cases of the disease are often treated unnecessarily with antibiotics. Antibiotic treatment is not only costly, it also contributes to the global epidemic of antimicrobial resistance. **Dr Fyezah Jehan**, from Aga Khan University, is conducting a trial which, if applied in the appropriate WHO algorithm, could reduce the financial burden and harm from overtreatment of this disease.

The current World Health Organization (WHO) guidelines recommend the use of oral antibiotics for children with fast-breathing pneumonia, a mild form of the illness. The organisation's definition of pneumonia, which covers a broad spectrum of clinical signs and symptoms varying from isolated fast breathing to the presence of danger signs, is non specific. An all-encompassing definition has naturally led to an approach in treatment that involves prescribing antibiotics to cover most children with pneumonia-like symptoms who may have a bacterial infection. However, up to 65 percent of these pneumonia cases are of viral and not bacterial aetiology (underlying cause), rendering antibiotic treatment redundant and potentially harmful.

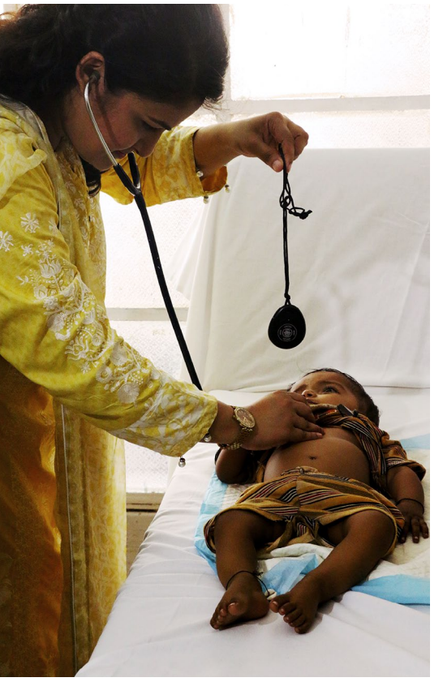
What's more, through the Expanded Program of Immunization, Hemophilus Influenza B (HiB) and pneumococcal vaccines were introduced in low-income countries that protect against two of the most common bacterial pathogens of bacterial pneumonia. This has resulted in far fewer children with lower respiratory tract infections (LRTI) having a bacterial aetiology. Considering these observations, empiric antibiotic use in all children with pneumonia has recently been called into question. The high cost of antibiotic treatments – an estimated 200 million USD in South Asia and sub-Saharan Africa alone – and the risk of antimicrobial resistance in treated children are also significant reasons to reassess the WHO guidelines and its definition of pneumonia.

HARD EVIDENCE

Amending the WHO guidelines for antibiotic prescription is no easy task. High quality trial evidence is required to build a case for change. Luckily, a study is already underway. Dr Fyezah Jehan from the Department of Paediatrics and Child Heath at Aga Khan University, Pakistan is leading a double-blind community-based randomised controlled trial of amoxicillin versus placebo for fast-breathing pneumonia in children aged 2–59 months in Karachi, Pakistan. Children in this age group with fast breathing and without any WHO-defined danger signs are randomised to receive three days of either a placebo or the antibiotic amoxicillin. Based on similar studies, a sample size of around 4000 children is required over a period of 36 months in order to produce viable results.

The primary research question is to assess whether a placebo treatment is non-inferior to ▶

High cost of antibiotic treatments … and risk of antimicrobial resistance are significant reasons to reassess WHO guidelines and its definition of fast breathing pneumonia



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Above: A child with cough and difficulty breathing being examined for pneumonia at the primary health care centre (PHC). Right: "Initiating the trial was an ethically challenging job as it required multiple layers of safety to protect the enrolled children from harm in the study" says Imran Nisar.

oral amoxicillin. Secondary to this assessment, researchers will also evaluate the proportion of children with fast-breathing pneumonia associated with pneumococcal carriage, viral carriage or both in nasopharyngeal specimens. Finally, they will investigate predictors of treatment failure with regards to viral or bacterial nasopharyngeal carriage. The study is currently being carried out in four different health care centres located in low-income communities with the aim of providing evidence to support or refute the use of antibiotics for fast-breathing pneumonia, paving the way for guideline reconsideration.

THE IMCI STRATEGY

In primary health facilities, the Integrated Management of Childhood Illness (IMCI) is an integrated approach to child health that focuses on the well-being of the whole child. The strategy promotes accurate identification of childhood illnesses in outpatient settings, ensures appropriate combined treatment of all major illnesses, strengthens the counselling of caretakers, and speeds up the referral of severely ill children.

Within the framework of the IMCI strategy and with the view to decrease death by pneumonia, WHO and UNICEF developed an IMCI algorithm to improve case management used to treat common childhood illness like pneumonia in low-income countries. Currently, it defines non-severe or fast breathing pneumonia as a respiratory rate of 50 breaths per minute or more in infants, or 40 breaths per minute in children 12–59 months of age, irrespective of wheezing and without the presence of danger signs. However, these parameters do not advocate a pneumonia diagnosis of the utmost specificity, nor do they factor in the increasing use of vaccines against common bacterial respiratory pathogens – hence the need to reconsider.

THE IMPACT

Dr Jehan's double blind trial is projected to have academic, social and economic impact. First and foremost, the results will help to rationalise the use of antibiotics, and thus decrease the out-of-pocket expenses for healthcare centres and caregivers. Rationalising antibiotic use will reduce the monetary burden on healthcare systems and provide resources to improve preventive interventions such as immunisation and child nutrition. Children will also be spared from the undesirable side effects of antibiotics, including the long-term damaging effects on native gut micro-biota, which could lead to impaired growth, malnutrition and a weak immune system.

Results may help to rationalise the use of antibiotics, and thus decrease the out-of-pocket expenses for healthcare centres and caregivers

Q&A

Is one trial enough? How much evidence will it take to convince those in charge that change is necessary?

While science is tempted by positive results, one trial is never enough. Evidence from several well-designed, high-quality (ethically and robustly conducted) trials needs to be replicated in different settings. A meta-analysis of randomised controlled trials is done. A similar trial is going on in an African setting in Malawi and one more trial in several OPDs of tertiary care hospitals in Pakistan was conducted by Tabish Hazir. Results of these can be used in meta-analysis.

What is the official procedure for revising the WHO guidelines?

A WHO guideline is any document containing recommendations about health interventions, whether these are clinical, public health or policy recommendations. A recommendation provides information about what policy-makers, health-care providers or patients should do. Recommendations are based on a comprehensive and objective assessment of the available evidence.

In case of pneumonia, pneumonia classification and management guidelines had been developed based on evidence generated in the 1970s and early 1980s, and were incorporated into the original version of Integrated Management of Childhood Illness (IMCI). In the intervening time, new evidence is emerging, which is prompting the development of revised guidelines. Research results provided solid scientific evidence to guide and support the revision of the pneumonia guidelines in 2013 and 2014. During two related consultations, a panel of experts assessed the new evidence according to the GRADE methodology ("Grading of Recommendations, Assessment, Development and Evaluation"). The revisions include changing the recommendation for the first-line antibiotic and re-defining the classification of pneumonia severity.

Realistically speaking, what is the time frame – how long for approval, how long for implementation?

It takes a minimum of about 9–12 months to develop/revise a guideline. It really depends on the disease in question and the reason for guideline change. In the case of fast breathing pneumonia, the momentum is on for re-evaluating its definition and treatment. Implementation is a long overhauling process; one researcher concluded that it takes an average of 17 years for health research to be translated into practice. (http://journals.sagepub.com/doi/full/10.1258/jrsm.2011.110180)

Are there any foreseen obstacles that might prevent this change initiative from progressing and materialising?

We need to complete the trial ensuring participant safety to answer fully about the favourability of withholding antibiotics. The safety of this approach will also need to be evaluated in varying settings across multiple countries.

What will happen if the trial results are ineffective?

Even if the trial fails to show positive results, a lot can be gained from the knowledge generated with regards to efficacy of antibiotic use in the era of vaccines as well as with different respiratory rate cut-offs.

Overall, the results of this study could potentially increase the effectiveness of healthcare systems in developing countries, allowing health care physicians and caregivers to methodically address the most important cause of death and illness in these communities. There will be significant academic implications as well. The use of nasopharyngeal samples to detect viral carriage in fast breathing pneumonia and determining their relation to treatment outcomes within a trial will provide insight into the role of organisms, especially common viruses. Dr Jehan's work has the potential to reduce the financial burden caused by unnecessary prescription of antibiotics while taking steps to prevent increased microbial antibiotic resistance.

Detail

RESEARCH OBJECTIVES

Dr Jehan's research provides evidence-based solutions that aim to reduce the burden of childhood pneumonia in Pakistan and other developing countries.

FUNDING

- MRC Wellcome DFID Joint Global Health Trials
- Bill and Melinda Gates Foundation (BMGF)

CO-INVESTIGATORS

- Dr Muhammad Imran Nisar, Aga Khan University
- Dr Nick J Brown, Salisbury NHS Foundation Trust

BIO

An Infectious Disease Specialist in Aga Khan University Hospital, Dr Fyezah Jehan received a Bachelor of Medicine & Bachelor of Surgery in 2001, specialising in Paediatrics in 2008 and Paediatric Infectious Diseases in 2011. Dr Jehan also obtained an MSc in Epidemiology and Biostatistics in 2011. She is currently Assistant Professor at Aga Khan University Hospital. Dr Jehan's research focus is pneumonia and optimisation of its management and diagnosis in resource limited settings.

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