Incidence of pneumonia is not reduced by pneumococcal conjugate vaccine

Madhi et al.1 write that the pneumococcal conjugate vaccine (PCV) is an effective instrument for pneumonia prevention in children. This is not strictly true. WHO data2 suggest that there are 450 million cases of pneumonia each year and that it causes 3.9 million deaths. In the sub-Saharan region of Africa, 1,022,000 die and 702,000 die in south Asia.3 The pneumonia referred to is “clinical pneumonia” – a diagnostic syndrome within the Integrated Management of Childhood Illness – WHO and United Nations Children’s Fund (UNICEF) system for triage and clinical management in developing countries.4 The Cochrane database5 states that PCV does not reduce the incidence of clinical pneumonia, although it has been shown to reduce vaccine-serotype bacteremic pneumonia and radiological pneumonia. The benefit of reducing bacteremic pneumonia and radiological pneumonia is so minimal that it has no effect on “clinical pneumonia”. Poor nations will need to assess its cost utility carefully.

A study from the Gambia showed that mortality was 16% lower in a PCV immunized group compared to placebo recipients (25.2/1000 children years versus 30.1/1000 children years).6 Data are also provided on adverse effects and deaths within 1 week of receiving any dose of the vaccine or placebo. The mortality benefit was seen in the first week after injection, well before vaccine efficacy could have been established. There were 12 deaths in the vaccine group and 15 among controls (23.8/1000 children years versus 29.8/1000 children years). This suggests that factors other than vaccine efficacy are responsible for the difference in mortality between the groups compared.

There is also another issue that we hope to raise here. The paper states that the vaccine programme would exceed the WHO threshold in 69 eligible countries. The authors assert that these findings are conservative in the sense that they did not assume any herd protection and did not assume protection beyond the age of 2.5 years. Beutels7 has cautioned against this trend of noting the “positive” uncertainties (herd immunity, protection beyond 2.5 years) without reporting the “negative” ones (serotype replacement, increased incidence of asthma),8 which could dampen enthusiasm for the intervention.

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Pneumococcal conjugate vaccine is efficacious and effective in reducing the burden of pneumonia

While Chowdhary & Puliyel1 are correct that there has been a non-significant reduction in clinically diagnosed pneumonia in the vaccine-efficacy trials conducted to date, their assertion that pneumococcal conjugate vaccine (PCV) does not reduce severe pneumonia or reduce mortality in the Gambia is fundamentally flawed. Updated estimates indicate that there are 155.8 million clinical episodes of pneumonia globally, which contribute to approximately 1.9 million deaths, 70% of which occur in Africa and south-east Asia.3 The major drawback in evaluating the efficacy of PCV against “clinical pneumonia” is the lack of specificity of this clinical outcome measure that was designed for case management of pneumonia. The choice of clinical pneumonia as an endpoint is therefore biased in favour of high sensitivity, at the expense of specificity, in contrast to the more specific endpoints usually used in vaccines efficacy trials. Indeed, a large proportion of the cases that meet the case definitions for clinical pneumonia have a low positive predictive value and are, therefore, not pneumonia.3 In the case management strategy, one accepts a level of over-treatment because of the important mortality reduction benefits. Nevertheless, that pneumococci contribute to significant pneumonia-related mortality is evident in the success of the WHO case-management strategy of pneumonia, which is premised upon early antibiotic therapy especially targeting S. pneumoniae and

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Bull World Health Organ October 2008, 86 (10)
is associated with a 36% reduction in pneumonia-mortality.4

On the other hand, radiologically-
confirmed pneumonia is a relatively
more specific measure of bacterial pneu-
monia and so efficacy of vaccine on this
outcome measure is a better indicator
of effect on pneumonia mortality. This
outcome was indeed the primary out-
come measure for determining efficacy
of the vaccine against pneumonia,
rather than the less specific measure of
clinical pneumonia. The vaccine trials
were thus not powered to measure effi-
cacy against clinical pneumonia and it is
not surprising that the efficacy estimate
did not reach statistical significance.
Furthermore, low specificity of the
outcome measure leads to misclassifica-
tion and a substantial underestimation
of the vaccine against pneumonia,
which was 3.6 per 1000 child years
(G. Madhi, personal communi-
fication). Additionally, the higher
mortality benefit in the Gambian
study was not evident only within
1 week of vaccination, but in fact
mainly from 12 months onward when
238 (72.1%) of the 330 PCV-recipient-
s’ deaths and 289 (73.5%) of the
placebo recipients’ deaths occurred.14
The rate of mortality within 7 days of
any dose of study vaccine (n = 12;
0.15%) and placebo (n = 15; 0.18%;
P = 0.55) did not differ between the
two groups, and their reported inci-
dence calculations are incorrect. The
higher rate of reactive airway disease
observed in the South African study
was not evident upon subsequent
analysis following extended follow up
of the cohort until an average of 6.3
years of age (S Madhi, personal com-
unication). Additionally, the higher
initially reported risk (1.3 per 1000
children) needs to be weighed against
the net reduction of disease prevented,
which was 3.6 per 1000 child years
against radiologically-confirmed pneu-
monia alone.15

In conclusion, while we agree with
the assertion that the use of PCV in
developing countries needs to be weighed
in relation to its cost and benefit, we be-
lieve that the potential benefit of PCV
in developing countries is beyond ques-
tion, as indicated by the WHO recom-
mendation on PCV.16 Nevertheless, it is
essential that the introduction of PCV
be coupled with adequate surveillance
at least in representative communities of
regions in which it is introduced to fully
establish the potential to public health
of the vaccine.

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### Withdrawing from the treatment does not mean from the study

Having read the recently published paper by Williams on the ethical conflict between individual rights and public health rights when conducting research on humans, we would like to call attention to a common misconception that occurs in clinical trials: withdrawal from treatment under study necessarily implies withdrawal from the study. Failure to continue to study patients who have withdrawn from treatment can severely hinder research, as critical information is lost. While there will always be some patients who do not complete the treatment protocol, their data may and should still be used to complete the study protocol, wherever it is practical and where consent can be obtained. If the reason for stopping treatment is due to patient denial of the previously agreed consent, a conflict arises between the rights of the individual and those of the population since the latter might benefit from this lost patient information.

As Eriksson & Helgesson explain, there are various reasons why patients may choose to ask for their data to be removed from studies. These are legitimate concerns and should never be taken lightly. However, every patient who has received medical treatment has reaped the benefits of previous studies, that is to say, from individuals who have voluntarily allowed their data to be used for the benefit of humanity. It could be argued that it is the duty of every patient to repay this debt. We think that, once informed consent has been given, data belong to the protocol and may be used within the context that was previously agreed: report, publication and oral presentation. Some have argued that “once consent has been given, participants should not necessarily have unconditional or absolute rights to withdraw.”

This discrepancy hindered our own research recently when one of us tried to distinguish between withdrawing from treatment and withdrawing from the study. The Independent Review Board referred him to item 22 of the Declaration of Helsinki, which states that: “The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal.” But the World Medical Association’s International Code of Medical Ethics divides these patient’s rights into two parts. Under this code, item 2 of “Duties of physicians in general” states that: “A physician shall respect a competent patient’s right to accept or refuse treatment” and item 4 of “Duties of physicians to patients” states that: “A physician shall respect a patient’s right to confidentiality. It is ethical to disclose confidential information when the patient consents to it or when there is a real and imminent threat of harm to the patient or to others and this threat can be only removed by a breach of confidentiality.” Therefore, when volunteering to participate in a randomized clinical trial, a patient effectively agrees to two different requirements: on the one hand, to random allocation to treatment, and on the other, to measurement and use of aggregated data that is made suitably anonymous. The current wording of the Declaration of Helsinki fails to distinguish between consent to treatment and consent to data. Therefore, when the World Medical Association meets in Seoul, Republic of Korea, in October 2008, we feel that it should deliberate on how to avoid such confusion.

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