Letters

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 data[2] 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.[1] 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.[3] The Cochrane database[4] states that PCV does not reduce the incidence of clinical pneumonia, although it has been shown to reduce vaccine-serotype bacteraemic pneumonia and radiological pneumonia. The benefit of reducing bacteraemic 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).[5] 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. Beutels[6] has cautioned against this trend of noting the "positive" uncertainties (herd immunity, protection beyond 2.5 years) without reporting the "negative" ones (serotype replacement,[7] increased incidence of asthma),[8] which could dampen enthusiasm for the intervention. ■

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References

1. Madhi SA, Levine OS, Hajjeh R, Mansoor OD, Cherian T. Vaccines to prevent pneumonia and improve child survival. *Bull World Health Organ* 2008;86:365-372. PMID:18545739 doi:10.2471/BLT.07.044503
2. *Revised global burden of disease 2002 estimates*. Geneva: WHO. Available from: http://www.who.int/healthinfo/bodgbd2002revised/en/index.html [accessed 5 August 2008].
3. *Integrated Management of Childhood Illness*. Geneva: WHO; 2000.
4. Lucero MG, Dulalia VE, Parreno RN, Lim-Quianzon DM, Nohynek H, Makela H, et al. Pneumococcal conjugate vaccines for preventing vaccine-type invasive pneumococcal disease and pneumonia with consolidation on x-ray in children under two years of age. *Cochrane Database Syst Rev* 2004;CD004977. PMID:15495133
5. Cutts FT, Zaman SM, Enwere G, Jaffar S, Levine OS, Okoko JB, et al.; Gambian Pneumococcal Vaccine Trial Group. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. *Lancet* 2005; 365:1139-46. PMID:15794968 doi:10.1016/S0140-6736(05)71876-6
6. Beutels P. Potential conflicts of interest in vaccine economics research: a commentary with a case study of pneumococcal conjugate vaccination. *Vaccine* 2004;22:3312-22. PMID:15308354 doi:10.1016/j.vaccine.2004.03.001
7. Eskola J, Kilpi T, Palmu A, Jokinen J, Haapakoski J, Herva E, et al.; Finnish Otitis Media Study Group. Efficacy of a pneumococcal conjugate vaccine against acute otitis media. *N Engl J Med* 2001;344:403-9. PMID:11172176 doi:10.1056/NEJM200102083440602
8. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N; Vaccine Trialists Group. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *N Engl J Med* 2003;349:1341-8. PMID:14523142 doi:10.1056/NEJMoa035060

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

While Chowdhary & Puliyel[1] 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.[2] 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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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 pneumonia and so efficacy of vaccine on this outcome measure is a better indicator of effect on pneumonia mortality. This outcome was indeed the primary outcome 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 efficacy 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 misclassification and a substantial underestimation of vaccine efficacy.[5]

The case fatality ratio in the Gambia trial was significantly greater in children with radiologically-confirmed pneumonia (3%) compared with clinical pneumonia cases that do not fulfil the criteria of radiologically-confirmed pneumonia (0.8–1.2%) even with access to antibiotic therapy.[6] In the absence of antibiotics, this difference may have been even greater. Radiologically-confirmed pneumonia accounts for as much as 16.7–34% of cases of clinical pneumonia,[6–8] The higher case fatality rate of radiologically-confirmed pneumonia and the higher impact of vaccine on this clinical outcome suggests that the impact of vaccine is more than a "minimal" contribution. Additionally, PCV is able to reduce pneumonia with an abnormal chest X-ray, but not defined as "radiologically-confirmed", by 1.2–7% to 30–32% when the specificity of this outcome is improved for bacterial pneumonia by using a C-reactive protein of ≥ 40 mg/l as an adjunctive marker.[9,10] Thus, the impact of vaccine on true pneumonia and pneumonia mortality is substantially greater than is indicated by the efficacy against "clinical pneumonia".

Additionally, vaccine-efficacy trials may underestimate the public health benefit of vaccines, as indicated by the indirect herd-protection observed following introduction of PCV into the United States of America[11] and, more recently, the 39% reduction in the burden of clinical pneumonia hospitalization after PCV-introduction,[12] compared to a non-significant 7% reduction in northern California during the vaccine-efficacy trial.[13] It is only through the phased introduction of PCV, which has been shown to be safe and efficacious in children from diverse settings, that the true public health benefit of PCV would be realized in developing countries. This would however need to be coupled with robust surveillance systems to evaluate changes in the epidemiology of pneumonia before and after its introduction in representative populations of different regions of the world.

The 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-recipients' 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 incidence 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 communication). 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 pneumonia 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 believe that the potential benefit of PCV in developing countries is beyond question, as indicated by the WHO recommendation 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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References

1. Chowdharya S, Puliyela J. Incidence of pneumonia is not reduced by pneumococcal conjugate vaccine. *Bull World Health Organ* 2008;86:816.
2. Rudan I, Tomaskovic L, Boschi-Pinto C, Campbell H. Global estimate of the incidence of clinical pneumonia among children under five years of age. *Bull World Health Organ* 2004;82:895-903. PMID:15654403
3. Cherian T, John TJ, Simoes E, Steinhoff MC, John M. Evaluation of simple clinical signs for the diagnosis of acute lower respiratory tract infection. *Lancet* 1988;2:125-8. PMID:2899187 doi:10.1016/S0140-6736(88)90683-6
4. Sazawal S, Black RE. Effect of pneumonia case management on mortality in neonates, infants, and preschool children: a meta-analysis of community-based trials. *Lancet Infect Dis* 2003;3:547-56. PMID:12954560 doi:10.1016/S1473-3099(03)00737-0
5. Jaffar S, Leach A, Smith PG, Cutts F, Greenwood B. Effects of misclassification of causes of death on the power of a trial to assess the efficacy of a pneumococcal conjugate vaccine in The Gambia. *Int J Epidemiol* 2003;32:430-6. PMID:12777432 doi:10.1093/ije/dyg082
6. Enwere G, Cheung YB, Zaman SM, Akano A, Oluwalana C, Brown O, et al. Epidemiology and clinical features of pneumonia according to radiographic findings in Gambian children. *Trop Med Int Health* 2007;12:1377-85. PMID:18045264
7. Madhi SA, Kuwanda L, Cutland C, Klugman KP. The impact of a 9-valent pneumococcal conjugate vaccine on the public health burden of pneumonia in HIV-infected and -uninfected children. *Clin Infect Dis* 2005;40:1511-8. PMID:15844075 doi:10.1086/429828
8. Magree HC, Russell FM, Sa'aga R, Greenwood P, Tikoduadua L, Pryor J, et al. Chest X-ray-confirmed pneumonia in children in Fiji. *Bull World Health Organ* 2005;83:427-33. PMID:15976893
9. Madhi SA, Klugman KP. World Health Organisation definition of "radiologically-confirmed pneumonia" may under-estimate the true public health value of conjugate pneumococcal vaccines. *Vaccine* 2007; 25:2413-9. PMID:17005301

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10. Cheung YB, Zaman SM, Ruopuro ML, Enwere G, Adegbola RA, Greenwood B, et al. C-reactive protein and procalcitonin in the evaluation of the efficacy of a pneumococcal conjugate vaccine in Gambian children. *Trop Med Int Health* 2008;13:603-11. PMID:18331385
11. Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease — United States, 1998-2003. *MMWR Morb Mortal Wkly Rep* 2005;54:893-7. PMID:16163262
12. Grijalva CG, Nuorti JP, Arbogast PG, Martin SW, Edwards KM, Griffin MR. Decline in pneumonia admissions after routine childhood immunisation with pneumococcal conjugate vaccine in the USA: a time-series analysis. *Lancet* 2007; 369:1179-86. PMID:17416262 doi:10.1016/S0140-6736(07)60564-9
13. Black SB, Shinefield HR, Ling S, Hansen J, Fireman B, Spring D, et al. Effectiveness of heptavalent pneumococcal conjugate vaccine in children younger than five years of age for prevention of pneumonia. *Pediatr Infect Dis J* 2002;21:810-5. PMID:12352800 doi:10.1097/00006454-200209000-00005
14. Cutts FT, Zaman SM, Enwere G, Jaffar S, Levine OS, Okoko JB, et al. Efficacy of nine-valent pneumococcal conjugate vaccine against pneumonia and invasive pneumococcal disease in The Gambia: randomised, double-blind, placebo-controlled trial. *Lancet* 2005; 365:1139-46. PMID:15794968 doi:10.1016/S0140-6736(05)71876-6
15. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *N Engl J Med* 2003;349:1341-8. PMID:14523142 doi:10.1056/NEJMoa035060
16. Pneumococcal conjugate vaccine for childhood immunization – WHO position paper. *Wkly Epidemiol Rec* 2007;82:93-104. PMID:17380597

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,[1] 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.[2] 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.[3,4] 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[5] 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".[6]

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,[7] 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[8] 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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References

1. Williams JR. The Declaration of Helsinki and public health. *Bull World Health Organ* 2008;86:650-1. doi:10.2471/BLT.08.050955
2. Porta N, Bonet C, Cobo E. Discordance between reported intention-to-treat and per protocol analyses. *J Clin Epidemiol* 2007;60:663-9. PMID:17573981 doi:10.1016/j.jclinepi.2006.09.013
3. Lachin JM. Statistical considerations in the intent-to-treat principle. *Control Clin Trials* 2000;21:167-89. PMID:10822117 doi:10.1016/S0197-2456(00)00046-5
4. Cobo E. Diseño y análisis de un ensayo clínico: el aspecto más crítico. *Med Clin (Barc)* 2004;122:184-9. PMID:14998455 doi:10.1157/13057825
5. Eriksson S, Helgesson G. Potential harms, anonymization, and the right to withdraw consent to biobank research. *Eur J Hum Genet* 2005;13:1071-6. PMID:15986039 doi:10.1038/sj.ejhg.5201458
6. Edwards SJL. Research participation and the right to withdraw. *Bioethics* 2005;19:112-30. PMID:15943021 doi:10.1111/j.1467-8519.2005.00429.x
7. Declaration of Helsinki 2004. Available from: http://www.wma.net/e/policy/b3.htm [accessed on 1 September 2008].
8. World Medical Association International Code of Medical Ethics. Available from: http://www.wma.net/e/policy/c8.htm [accessed on 1 September 2008].

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