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## Dengue and chikungunya in India

Sanjit Bagchi recently highlighted the surge in cases of dengue in India.<sup>1</sup> It is worth noting that chikungunya, another disease borne by the *Aedes aegypti* mosquito, also poses a major health threat to large populations.<sup>2</sup> The 2 diseases have similar symptoms, although hemorrhagic manifestations are relatively rare with chikungunya. Therefore, care should be taken when caring for patients suffering from either of these diseases as the diagnosis could be incorrect. Although cases of dengue are mostly seen in the northern parts of India, chikungunya is more prevalent in India's southern states.

The control of mosquito-borne diseases in India usually involves a strategy based on that used to control the spread of malaria by *Anopheles* mosquitoes. However, unlike *Anopheles* mosquitoes, the *Aedes* mosquitoes that spread dengue and chikungunya can breed in clean as well as in dirty water, and they usually bite during the daytime.

These mosquito-borne diseases have a socio-economic impact as well. A few foreign tourists have reported symptoms of chikungunya upon their return home from tropical areas.<sup>3</sup> Assuming that the number of tourists visiting tropical countries from non-endemic countries would decline owing to epidemics of these diseases, Mavalankar and colleagues reported that the loss of tourism revenue would be comparable to the estimated annual cost of preventing or treating chikungunya and dengue in these countries.<sup>4</sup> Such a decline in tourism revenue would be a major setback for a country

like India, which is a hotspot for tourism and where almost 80% of patients with chikungunya live below the poverty line.<sup>5</sup>

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## Efficacy of pneumococcal polysaccharide vaccine

In their commentary about our meta-analysis of the efficacy of pneumococcal polysaccharide vaccine,<sup>1</sup> Ross Andrews and Sarah Moberley stated that our conclusions go beyond the evidence presented and that a need exists for new trials to contribute more data, rather than repeated analyses of existing data.<sup>2</sup>

Unlike the recent Cochrane review by Moberley and colleagues,<sup>3</sup> our study thoroughly examined sources of heterogeneity in trial results.<sup>1</sup> We found little evidence of vaccine protection in trials of higher methodologic quality for presumptive pneumonia, all-cause pneumonia and all-cause mortality. Given that the combined relative risks (RR) for these analyses are all either on the side of no protective effect or very close to 1, we do not believe that our conclusion can be described as an overstatement. The area of debate and uncertainty relates to vaccine efficacy against invasive pneumococcal disease. We found no strong evidence of efficacy (RR 0.90, 95%

confidence interval [CI] 0.46–1.77) whereas the Cochrane review showed a statistically significant protective effect (RR 0.26, 95% CI 0.15–0.47). The results for invasive pneumococcal disease are greatly dependent on which studies are selected for inclusion. For example, if trials of lower quality that were not double blind (a process that Andrews and Moberley agree is worthwhile<sup>2</sup>) are excluded from the Cochrane review, the effect is no longer statistically significant (RR 0.47, 95% CI 0.13–1.72). The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group considers that inconsistencies in results reduce the quality of evidence.<sup>4</sup>

Andrews and Moberley said that the recommendations made by the World Health Organization in its latest position paper on the use of the vaccine remained unchanged.<sup>5</sup> This is not entirely correct, as in 2003 the organization recommended pneumococcal vaccination for individuals at increased risk of invasive pneumococcal disease,<sup>6</sup> and in 2008 this recommendation was removed.<sup>5</sup> The organization's current position paper does not support the introduction of pneumococcal polysaccharide vaccine in resource-limited settings and suggests that priority should be given to the introduction and maintenance of pneumococcal conjugate vaccination for infants.<sup>5</sup> Instead of a recommendation there is now a statement that results are consistent with a protective effect for selected outcomes in restricted groups of individuals.

Pneumococcal infections cause a large burden of disease worldwide, and control of this disease with an efficacious vaccine would be highly desirable. However, we do not think that the pneumococcal polysaccharide vaccine is the answer. After over 60 years of research on the pneumococcal polysaccharide vaccine, we might expect there to be convincing evidence of efficacy if the vaccine offered worthwhile protection. We do not recommend conducting further studies on this vaccine, as Andrews and Moberley suggest, but rather suggest exploring alternative possibilities to pneumococcal polysaccharide vaccine. Currently, the conjugate vaccine seems

to be the most promising candidate, but it needs to be thoroughly evaluated.

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## The commentators respond:

Our commentary<sup>1</sup> was intended as a critical review of the evidence base provided by Anke Huss and colleagues' meta-analysis.<sup>2</sup> We challenged what we perceived as an implied recommendation for countries to cease vaccination programs with polysaccharide pneumococcal vaccine for adults if they had an existing program for children.

We agree that the major area of debate and uncertainty concerning meta-analyses of clinical trials relates to efficacy against invasive pneumococcal disease and that the results of such analyses are greatly dependent on the selection of trials for inclusion. On this

point, we queried the basis reported by Huss and colleagues for excluding 2 studies<sup>3,4</sup> from their meta-analysis and including another.<sup>5</sup> It is unfortunate that these concerns were not addressed in their letter. For the reasons given in our commentary, we suspect the inclusion or exclusion of these 3 studies to be methodologic errors in the meta-analysis undertaken by Huss and colleagues.

Prevention of invasive pneumococcal disease is the primary purpose of vaccination programs with polysaccharide pneumococcal vaccine in adults. We contended that the World Health Organization had considered the findings of the meta-analysis by Huss and colleagues in its recent position paper on the use of pneumococcal vaccine in adults but that its recommendations had remained "virtually unchanged."<sup>6</sup> We accept the points of clarification by Huss and colleagues on the subtle wording changes they identified, but by our reading the World Health Organization falls well short of calling for cessation of existing polysaccharide pneumococcal vaccine programs for adults in its recent position paper. In their letter, Huss and colleagues appear to have moved away from this suggestion, which we think is appropriate given the evidence provided in their review.

Rather than demonstrating a lack of convincing evidence of efficacy after 60 years of research on the polysaccharide pneumococcal vaccine, we think the study by Huss and colleagues further highlights the limitations of the available clinical trial data when assessing the vaccine's impact against rare events like invasive pneumococcal disease. The most recent and best quality clinical trials, as determined by Huss and colleagues, were conducted largely among populations with chronic illness or severe immunosuppression or both. In these trials there were very few cases of invasive pneumococcal disease: 7 cases of definitive pneumococcal pneumonia from 2 studies and 44 cases of bacteremia from 6 studies (most of which were among HIV-infected adults in Uganda).

As we stated in our commentary, the World Health Organization's position

is that the data from randomized trials, meta-analyses of randomized trials and most observational studies are consistent with a protective effect against invasive pneumococcal disease among healthy adults and, to a lesser extent, among adults aged 65 years and older.<sup>6</sup> We welcome calls to investigate new approaches with new vaccines, but on the basis of the evidence provided by Huss and colleagues, we see no compelling rationale for excluding polysaccharide pneumococcal vaccine from these considerations.

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## Correction

In the April 28 editorial,<sup>1</sup> we stated that the Canada Health Act is 24 years old. In fact, it received Royal Assent and came into effect on April 1, 1984, 25 years ago.

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