Reviewer's report

Title: A randomised controlled trial of 10-valent pneumococcal-Haemophilus influenzae protein D conjugate vaccine in preventing respiratory exacerbations in children with recurrent protracted bacterial bronchitis, chronic suppurative lung disease and bronchiectasis: rationale and protocol

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Reviewer: elisabeth A.M. sanders

Reviewer's report:

Introduction:

Though this is an ambitious study and very well set-up and applied methodology is OK, and many interesting data will become available, the authors need to discuss more past reports on efficacy on ntHI by the 10-valent pneumococcal-PD vaccine. There are good reasons to at least discuss the impact of the vaccine on NTHi acquisition in particular in more chronic/recurrent disorders of the airways in older children.

I think in the introduction or discussion section, one also needs to discuss the paper of Veenhoven et al, Lancet published in the Lancet. 2003 Jun 28;361(9376):2189-95 in 400 children with recurrent AOM aged 1-7 years. This study may reveal some points of interest to discuss in view of prevention.

In the randomised, controlled study by Veenhoven et al, the 7-valent pneumococcal conjugate vaccine reduced vaccine serotype nasopharyngeal carriage, but replacement by non-vaccine serotypes was complete. Importantly, PCV-7 vaccinated children even experienced more AOM episodes (significant in the per protocol analysis) also due to more involvement of non-pneumococcal bacteria like S. aureus. Though the current study focuses completely on NTHi, the Veenhoven study as compared to other studies like FinOM or POET made 2 things clear. First: primary prevention at early (infant) age may be required and secondary prevention at older age for NTHi colonization/acquisition may be too much to ask for. Second: replacement by other bacteria than pneumo and NTHi, like S.aureus and M. catarrhalis and possibly pseudomonas also needs to be explored, in particular in patients with bronchiectasies.

The authors state that acquiring new H. influenzae strains can lead to exacerbations in COPD. Recently, a paper by van den Bergh et al, Clin Infect Dis. 2013 February 1; 56(3): e30–e39. was published that showed that the 10-valent vaccine had no effect on NTHi acquisition, presence or density as established by conventional culture or molecular methods. The NTHi bacterial load in the nasopharynx of infants vaccinated with either 10-valent pneumococcal-PD vaccine compared with children vaccinated with PCV-7 was similar. This was confirmed by PCR, also distinguishing NTHi from H. haemolyticus. If no effect at all is observed in the nasopharynx, why do the
authors expect still benefit in prevention of chronic bronchitis, possibly induced by acquisition of new NTHi strains? No studies have shown (consistent) impact of 10-valent pneumococcal-PD vaccine (which is not the same as not PCV-11-PD as used in the POET study) on bacterial ntHI acquisition.

Indeed, adult studies provide ‘proof of concept’ that a H. influenzae vaccine may be beneficial. I agree with this, but I think 10 valent PCV-PD with only one ntHI protein antigen is actually very different from the oral whole-cell vaccine and this needs to be mentioned.

Also, the authors refer to the fact that vaccine-induced anti-PD antibodies are associated with protective efficacy against H. influenzae infection in middle ear and pulmonary clearance in rat disease models. [30] Though the PD-vaccine does prevent disease in animals, results may be completely different in the human situation, as is often shown to be the case. Meanwhile, a RCT of an 11-valent prototype for PHiD-CV (POET study) where child participants underwent tympanocentesis during with their first episode of acute otitis media found that the vaccine reduced the overall incidence of otitis media by 34%, including a 35% reduction in cases caused by H. Influenzae. [31] It needs to be recognized however that primary prevention in infants is completely different from vaccination later in life (see also earlier comments). Also, in the present study children are primed with PCV-7. This may change the impact on ntHI since these pneumococcal and ntHI pathogens interact. Lastly, the amount of PD has changed in the 10-valent compared with the 11-valent-vaccine. So far, except for the POET with the previous 11-valent PCV-PD vaccine, no benefit in prevention of NTHi disease with 10-valent PD vaccine has been published yet in humans.

Methods and statistics are OK. For the discussion, see introduction section. The authors may choose where to discuss more in detail additional relevant reports.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

No