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PREVENTION OF INVASIVE PNEUMOCOCCAL DISEASE THROUGH VACCINATION: LOOKING BEYOND CULTURE-CONFIRMED CASES

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Although vaccine efficacy is traditionally reported as a relative measure of disease incidence (e.g. 90% efficacy), the consideration of absolute estimates of disease prevented is necessary for a complete assessment of vaccination effects.^{1,2} This is particularly relevant for studies in which the endpoint definition has a low sensitivity. In these situations, a specific endpoint definition is needed to estimate relative efficacy, but additional analyses using a sensitive definition and estimates of rate differences are needed to understand the burden of disease prevented.

Culture-confirmed invasive pneumococcal disease is the current standard and most specific endpoint for randomized controlled studies that evaluate the efficacy of pneumococcal vaccines in preventing invasive disease. Importantly, cultures help identify pneumococcal serotypes and characterize patterns of antibiotic susceptibility. However, pneumococcal cultures have low sensitivity,³ and incidence estimates based on culture results alone underestimate the real disease burden. In contrast, the identification of compatible episodes of invasive disease that lack culture confirmation can be more sensitive and could better capture the burden of pneumococcal disease. Nevertheless, this approach to identify suspected invasive pneumococcal disease is less specific, includes some false cases and leads to misclassification of study endpoints.

Preference for the more or less specific endpoint in an efficacy trial has important implications for the estimate of vaccine efficacy. Notably, the misclassification introduced by these preferences is likely non-differential in the randomized trial setting. When the more specific endpoint (e.g. culture-confirmed) is used, the relative measure of vaccine efficacy is properly calculated but the absolute estimate of disease prevented is underestimated. In contrast, the use of the less specific endpoint (e.g. suspected non culture-confirmed

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Authors' contributions

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episodes) dilutes relative estimates of vaccine efficacy, favoring the null hypothesis and making real vaccine effects harder to detect. However, in the context of uncommon outcomes such as invasive pneumococcal diseases, the calculation of the difference in rates of suspected non culture-confirmed episodes between vaccinated and unvaccinated groups is less affected than the relative estimates.⁴ Thus, this approach provides a more accurate approximation of the burden of disease that could be prevented through vaccination.^{1,2}

In this issue of *The Lancet Respiratory Medicine*, Palmu et al. present findings from a well-conducted cluster randomized controlled trial of the ten-valent pneumococcal *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV10). This large study was conducted in Finland and took advantage of a comprehensive electronic record system that includes detailed healthcare encounter data for the entire country. This platform was used to identify endpoints for the ~47,000 randomized children including culture-confirmed invasive pneumococcal disease (n=16) and coded healthcare encounters that were due to suspected invasive pneumococcal disease but were not confirmed by culture (n=174). In addition, records for non culture-confirmed episodes were reviewed to identify those most likely to be invasive pneumococcal disease (n=67). The investigators previously reported a 93% efficacy of PHiD-CV10 (2+1 or 3+1 schedules combined) in preventing culture-confirmed invasive pneumococcal disease.⁵ The current study complements the previous findings by studying the effect of PHiD-CV10 on secondary endpoints: non culture-confirmed but suspected episodes of invasive pneumococcal disease.

The figure provides a schematic representation of the findings from the current study and contrasts these with the previously reported efficacy estimates of PHiD-CV10 in preventing culture-confirmed invasive pneumococcal disease. For a fixed 100,000 person-years of follow-up, the number of episodes of invasive pneumococcal disease expected in the absence of vaccination for each endpoint and regardless of serotype was estimated from incidence rates in children not randomized to PHiD-CV10 and is illustrated by the total number of green and red squares. Vaccination with PHiD-CV10 prevented invasive pneumococcal disease episodes (green squares). The figure also shows that there was residual disease (red squares) after vaccination, likely due to disease caused by non-vaccine serotypes, vaccine failure or as a consequence of limited endpoint specificity. PHiD-CV10 vaccination resulted in high relative efficacy when using the primary endpoint of culture-confirmed invasive pneumococcal disease, and approximately 61 such episodes were prevented.⁵ When the more sensitive but less specific non culture-confirmed endpoints were evaluated using verified suspected and all suspected invasive pneumococcal disease, the relative efficacy estimates declined but the estimated number of prevented episodes was 2.3 and 3.4-fold larger than the reductions in culture-confirmed episodes, respectively. Thus, a large number of invasive disease episodes prevented were missed when relying solely on culture-confirmed detection.

The demonstration of much larger absolute reductions in the burden of disease when using sensitive rather than specific endpoint definitions provides important evidence for decision making about vaccination policies. This assessment also provides a lesson both for trials as well as for continuing surveillance of vaccine effectiveness. As illustrated in the current report, results based on cultures for detection of invasive pneumococcal disease can suggest

a misleadingly low burden of disease and the number of prevented cases estimated using this strategy may appear insufficient to trigger action.^{1,6} Using the powerful framework of a randomized study design, Palmu et al demonstrate that the benefits of vaccination with pneumococcal conjugate vaccines extend far beyond traditional culture-confirmed detections.

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References

1. Feikin DR, Scott JAG, Gessner BD. Use of vaccines as probes to define disease burden. *The Lancet*. 2014
2. 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(13):2413–9. [PubMed: 17005301]
3. Vernet G, Saha S, Satzke C, et al. Laboratory-based diagnosis of pneumococcal pneumonia: state of the art and unmet needs. *Clin Microbiol Infect*. 2011; 17(Suppl 3):1–13. [PubMed: 21457174]
4. Rothman, KJ.; Greenland, S. *Modern Epidemiology*. Philadelphia: Lippincott-Raven; 1998.
5. Palmu AA, Jokinen J, Borys D, et al. Effectiveness of the ten-valent pneumococcal Haemophilus influenzae protein D conjugate vaccine (PHiD-CV10) against invasive pneumococcal disease: a cluster randomised trial. *Lancet*. 2013; 381(9862):214–22. [PubMed: 23158882]
6. Mulholland EK. Use of vaccine trials to estimate burden of disease. *J Health Popul Nutr*. 2004; 22(3):257–67. [PubMed: 15609778]

Figure.

Schematic representation of the number of episodes of invasive pneumococcal disease (without regard to serotype) according to different study endpoints: culture-confirmed invasive pneumococcal disease, non culture-confirmed file-verified suspected invasive pneumococcal disease, and non culture-confirmed suspected invasive pneumococcal disease. Footnote: Illustration is based on data for the 2+1 or 3+1 vaccination schedules combined. Some numbers represent approximations for illustration purposes and don't exactly match the reported trial results. File verified is a subset of all suspected invasive pneumococcal disease episodes; neither include culture-confirmed episodes.