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Review

The case for a typhoid vaccine probe study and overview of design elements

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ABSTRACT

Recent advances in typhoid vaccine, and consideration of support from Gavi, the Vaccine Alliance, raise the possibility that some endemic countries will introduce typhoid vaccine into public immunization programs. This decision, however, is limited by lack of definitive information on disease burden. We propose use of a vaccine probe study approach. This approach would more clearly assess the total burden of typhoid across different syndromic groups and account for lack of access to care, poor diagnostics, incomplete laboratory testing, lack of mortality and intestinal perforation surveillance, and increasing antibiotic resistance. We propose a cluster randomized trial design using a mass immunization campaign among all age groups, with monitoring over a 4-year period of a variety of outcomes. The primary outcome would be the vaccine preventable disease incidence of prolonged fever hospitalization. Sample size calculations suggest that such a study would be feasible over a reasonable set of assumptions.

1. Background

Three recent vaccines have or are soon to be introduced in the majority of low income settings, including *Haemophilus influenzae* type b (Hib) conjugate vaccine, pneumococcal conjugate vaccine (PCV), and rotavirus vaccine. For each of these vaccines, introduction was delayed in part because of the difficulty in defining disease burden. For Hib and PCV, the most common severe manifestation was non-bacteremic pneumonia, which required for diagnosis trans-tracheal aspirates or lung punctures, both of which were impractical in low-income settings. For all three diseases, other issues existed including lack of access to health care facilities, poor laboratory capacity, and lack of collection of clinical specimens by health care providers.

A solution to this issue was the development of vaccine probe studies. Probe studies employ standard clinical trial designs, ideally a blinded community or individually randomized design. However, they differ conceptually from vaccine licensing studies in that they use a previously licensed vaccine of known efficacy (or hypothesized efficacy based on established correlates of immunity) to define characteristics of disease rather than of vaccine [1]. The primary outcome of a vaccine probe study is the vaccine preventable disease incidence (also known as the vaccine attributable rate reduction), which is defined as the difference in incidence between control and intervention populations, or, mathematically equivalently, the control group incidence multiplied by vaccine efficacy. Because probe studies assess disease burden, they may provide a better assessment of a vaccine's public health value than vaccine efficacy or effectiveness. Additionally, such studies can provide a way to prioritize vaccines based on the preventable disease burden, which may be high even when vaccine efficacy is relatively low [2].

Vaccine probe studies have been successful in convincing policymakers of the importance of Hib [3], PCV [4] and rotavirus [5] vaccines and of providing anchoring data to help interpret less robust studies, such as surveillance of etiologically confirmed disease. As we describe, probe studies could provide a similar benefit for typhoid vaccine in low- and middle-income countries.

2. Justification

The expense and complexity of vaccine probe studies can be justified for numerous reasons, many of which apply to typhoid. As described above, probe studies seek to define characteristics of disease rather than vaccine. Currently, disease burden estimates are incompletely defined and inconsistent. A recent systematic

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literature review estimated that in 2010, low- and middle-income countries experienced 11.9 million typhoid cases and 129,000 deaths [6], which differs from earlier estimates [7] and the 2013 global burden of disease study [7,8]. Moreover, the latter study provides a range from 85,900 to 268,000, emphasizing the degree of uncertainty in this estimate. As with other studies, this most recent estimate has several limitations. It does not adjust for limited access to care in many of the countries with the highest typhoid burden. More problematically, the estimate of deaths relies on in-hospital case-fatality ratios, which may greatly underestimate total deaths. While outpatient antibiotic therapy may reduce mortality and morbidity even in the absence of hospital care, the degree to which this occurs remains unknown, and may be blunted in settings where counterfeit antibiotics exist or antibiotic resistance is common [9,10]. A WHO expert panel has noted the importance of estimating access to care when estimating typhoid burden [11]. A potential clue to the underestimation of burden due to limited access to care is provided by a rotavirus vaccine probe study that found that vaccine prevented six-fold more cases of severe dehydration in the community than in the clinic [5]. A 2014 review summarizes the situation in Africa as follows: "much is not known about typhoid fever in Africa; and appropriate technology to assess the actual burden of disease is not available" [12].

Laboratory diagnostics are imperfect for typhoid, particularly blood culture, which has been estimated as having a sensitivity of approximately 61% [6]. A systematic review published during 2012 estimated that adjusting for imperfect sensitivity of blood cultures increased the estimated number of cases globally from 13.5 million to 26.9 million [7]. However, other issues exist with laboratory diagnostics besides in-hospital sensitivity including that blood cultures may not be performed at all. For example, persons who present with critical illness may die or have antibiotics given before culture can be obtained, something that may occur more frequently among the youngest age groups. Laboratories in remote settings may not have diagnostic capacity. Where diagnostic capacity exists, it may be limited to certain periods (e.g., during weekdays).

Typhoid fever documentation requires a reasonable level of clinical suspicion, particularly where other common causes of fever exist such as malaria. One solution to this problem is to conduct a study in which all persons presenting with clinical fever receive diagnostic testing. This was the approach taken in an urban slum in Kenya, where community surveillance was followed by blood culture of all persons with fever or pneumonia [9]. This approach documented higher typhoid incidence than previous African studies [13], on a par with burden in Southeast Asia [14]. Nevertheless, the early case detection and small sample size prevented estimation of severe disease burden.

Similarly, a substantial contributor to typhoid burden is the complication of intestinal perforation [15]. Case fatality ratios for this complication may be high (20% in Africa and over 10% in Asia) with prolonged hospitalization. Yet few studies have attempted to estimate the incidence of typhoid-associated intestinal perforation with concurrent long-term follow-up.

In theory, robust surveillance with high levels of health care access and adjustment for false negative results could provide a more straightforward means of burden estimation. However, in typhoid endemic areas health care access is frequently low and its level for a particular disease unknown. As a characteristic of the test, blood culture and other diagnostic sensitivity may be known but positive predictive value is not and remains dependent on variable levels of pre-treatment with antibiotics, duration and severity of illness before testing, and blood volume collected. Additionally, diagnostic tests often are not performed, particularly among patients who present with critical or atypical illness, and when performed may not be processed correctly. By contrast, most of these issues could be addressed with a well-designed probe study. The remainder of this manuscript addresses some of the associated design issues.

3. Assumptions

Several assumptions are made in the proposed study design described below. We assume that a vaccine will be licensed in the target age group and that the primary indication will be for prevention of laboratory confirmed typhoid disease. We assume that the vaccine has no more than minimal side effects, on a par with those for vaccines such as a pneumococcal and Hib conjugate vaccines.

4. Goal, objectives and endpoints

4.1. Goal

To determine the burden of typhoid across various syndromic categories in suspected high burden areas.

4.2. Primary outcome

The vaccine-preventable burden of clinical typhoid presenting as hospitalization with prolonged fever of greater than 5 days.

Justification: In most settings with high typhoid burden, the main concern – other than mortality – is likely to be severe disease and high cost health care utilization. Focusing on fever with greater than 5 days duration should enrich the definition for typhoid and thus require a smaller sample size, similar to the use of a specific radiological endpoint for PCV trials [4]. Mortality is not recommended as the primary outcome due to difficulty in identifying deaths and the frequent impact the presence of a study has in decreasing mortality rates through improving care (e.g., during the RTS, S malaria vaccine trials [16]).

4.3. Secondary outcomes

- Vaccine-preventable burden of clinical typhoid presenting as hospitalization with fever of any duration.
- Vaccine-preventable burden of clinical typhoid across all-cause hospitalizations.
- Vaccine-preventable burden of clinically diagnosed intestinal perforation.
- Burden of clinical typhoid prevented through indirect protection.

Justification: The first two outcomes have greater sensitivity but less specificity than the primary outcome and thus may require unrealistic sample sizes. The third outcome assesses the primary severe complication of typhoid but requires additional diagnostic capacity.

4.4. Site-specific outcomes

- Vaccine-preventable burden of severe clinical typhoid (using systematic case definitions) in the community.
- Vaccine-preventable burden of clinical typhoid presenting to outpatient settings.
- Vaccine-preventable burden of typhoid mortality.

Justification: Researchers in some settings with poor health care access may want to include measurement of community cases. For example, a rotavirus vaccine probe study found six-fold more preventable disease in the community than in a hospital setting [5]. Conversely, in settings with better health care access and case management, the primary typhoid burden may occur in outpatient settings. Finally, mortality outcomes may be appropriate in settings