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Review

Methodological challenges in measuring vaccine effectiveness using population cohorts in low resource settings

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ABSTRACT

Post-licensure real world evaluation of vaccine implementation is important for establishing evidence of vaccine effectiveness (VE) and programme impact, including indirect effects. Large cohort studies offer an important epidemiological approach for evaluating VE, but have inherent methodological challenges.

Since March 2012, we have conducted an open prospective cohort study in two sites in rural Malawi to evaluate the post-introduction effectiveness of 13-valent pneumococcal conjugate vaccine (PCV13) against all-cause post-neonatal infant mortality and monovalent rotavirus vaccine (RV1) against diarrhoea-related post-neonatal infant mortality. Our study sites cover a population of 500,000, with a baseline post-neonatal infant mortality of 25 per 1000 live births.

We conducted a methodological review of cohort studies for vaccine effectiveness in a developing country setting, applied to our study context. Based on published literature, we outline key considerations when defining the denominator (study population), exposure (vaccination status) and outcome ascertainment (mortality and cause of death) of such studies. We assess various definitions in these three domains, in terms of their impact on power, effect size and potential biases and their direction, using our cohort study for illustration. Based on this iterative process, we discuss the pros and cons of our final per-protocol analysis plan. Since no single set of definitions or analytical approach accounts for all possible biases, we propose sensitivity analyses to interrogate our assumptions and methodological decisions.

In the poorest regions of the world where routine vital birth and death surveillance are frequently unavailable and the burden of disease and death is greatest We conclude that provided the balance between definitions and their overall assumed impact on estimated VE are acknowledged, such large scale real-world cohort studies can provide crucial information to policymakers by providing robust and compelling evidence of total benefits of newly introduced vaccines on reducing child mortality.

1. Background

The 13-valent pneumococcal conjugate vaccine (PCV13) and monovalent rotavirus vaccine (RV1) were introduced to the routine infant vaccine schedule in Malawi in November 2011 and October 2012, respectively. Evidence of their effectiveness and population impact on mortality in sub-Saharan Africa is needed, particularly where HIV, malaria and malnutrition are prevalent. To date several modelling studies have projected their impact in this setting, but observational data on their empirically observed mortality impact, which exist elsewhere, are lacking for sub-Saharan Africa [1–7].

Pre-licensure vaccine efficacy is determined through placebo-controlled double-blind randomized trials [8]. Post-licensure studies are needed to determine vaccine effectiveness (VE) and

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population impact, including indirect effects (herd immunity and changes in transmission dynamics at the population level) in the 'real world' setting. Effectiveness is often assumed to be lower than efficacy, since cold chain implementation and stock administration are frequently suboptimal compared with strict trial conditions [9]. Measures of effectiveness are by nature observational and therefore vulnerable to confounding and bias, namely being unable to fully account for the individual decision to seek vaccination [10]. However, they may provide a more generalizable result, and because of size and exclusions, it is difficult for licensure trials to include an assessment of herd protection (unless randomized by cluster), a key benefit of many infant vaccines. Therefore, post-licensure effectiveness evaluations are crucial for policy makers to assess vaccine roll-out, highlight issues in programme implementation and determine total impact of direct and indirect effects at population level [8,11].

Several observational methods exist for evaluating VE: serological (using correlates of protection), ecological (population-level surveillance, including analysis of electronic medical records), cohort and case-control studies [8,12–17]. Each method has biases, advantages and disadvantages in practice, and variable utility in assessing potential non-specific vaccine benefits or risks. Each method also addresses slightly different questions about vaccine effectiveness and the preferred design may be context dependent; for example, a case-control design where the disease is extremely rare; or a cohort when investigating multiple outcomes for one exposure. Using a carefully selected and complementary combination of observational methods affords a more comprehensive understanding of vaccine impact, effectiveness and changing epidemiology of the target disease.

Cohort studies are resource intensive, requiring large sample sizes if events (such as death) are uncommon or if absolute effect sizes are small. As under-5 mortality rates are declining globally [18], cohorts with mortality end-points will become increasingly challenging. However, they avoid biases arising from selecting appropriate controls and censoring by survivorship to which other observational methods for estimating VE are more susceptible [19]. Three definitions are key to the design of a cohort study: the denominator (defining the study population), exposure ascertainment (with respect to vaccination status) and outcome ascertainment (mortality and cause of death) [20]. With these key parameters, the standard approach to analysis would be a comparison of the hazard of death or survival by vaccination status adjusted for key confounders.

In this paper, we aim to discuss key methodological challenges inherent to cohort designs focusing specifically on these three domains and apply them to our study setting to clearly illustrate practical considerations in establishing an *a priori* 'per-protocol' and sensitivity analysis plan. These analyses aim to give VE estimates, acknowledging that in complex field environments with unmeasured confounding (such as bias in the decision to receive vaccines or not), causality is difficult to assign.

2. Methods

We conducted a methodological review of cohort study design for evaluating vaccine effectiveness in a developing country setting. We searched Web of Science and PubMed using the following terms: method* AND/OR cohort, AND vaccine effectiveness AND/OR survival analysis, and included secondary references and highly-cited papers in the field. Our subsequent discussion focuses on the key challenges and considerations highlighted in the literature and use our field setting to illustrate key considerations. Based on this iterative process, we develop and present our primary and sensitivity analysis plan.

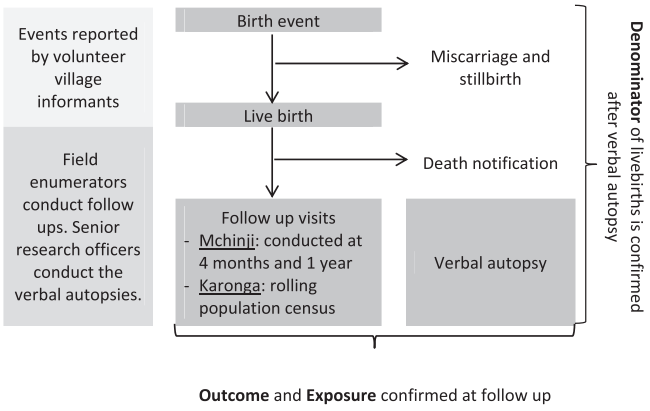

Fig. 1. Schematic of study recruitment, follow up and definitions.

3. Cohort recruitment

3.1. Setting

A prospective cohort study is ongoing at two sites in Malawi: Mchinji district in the central region, and the Karonga demographic surveillance site (DSS) in northern Malawi [21,22]. Since 1 March 2012, we have conducted an open prospective cohort study in Mchinji district, which has a population of 465,000. The DSS site in Karonga has been running since 2002, covering a population of 35,000. Both sites are rural and the main occupation is subsistence farming [23]. Around 20% of the population is aged under 5 years and crude birth rate is approximately 40/1000 person years. Under-5 mortality has declined by 18 deaths/1000 live births over a 5 year period to a rate of 71/1000 in 2013 [24], with much of this effect seen in post-neonatal infants. The primary research questions for this cohort study are:

- What is the effectiveness of three doses of PCV13 against all-cause mortality in infants?
- What is the effectiveness of two doses of RV1 against diarrhoea-specific mortality in infants?

This study is being conducted alongside case-control studies with a range of morbidity and laboratory confirmed endpoints, to provide comprehensive data on vaccine effectiveness and impact in different population settings in Malawi [21].

3.2. Data collection

The DSS methods for Karonga have been published in detail previously [22]. The Mchinji surveillance site uses similar, but less resource-intensive methods, to the Karonga site [21]. Briefly, both systems are based on networks of volunteer village-level key informants who report monthly on births and deaths (Fig. 1). Selecting appropriate key informants was done with extensive community engagement to ensure they were acceptable to the community since without this support accurate reporting of events would be unlikely. In Mchinji infants are followed up by field enumerators with a home visit at 4 months and 1 year of age to capture vaccine status and confirm survival. At these visits, a one-page questionnaire is administered, collecting information on infant and mother survival, vaccine status (from documented health record or parental recall when documentation is unavailable), maternal education, household composition and assets. The large population size and human resource constraints limited the length of the questionnaire in the Mchinji setting. In the Karonga DSS, a rolling population demographic census visits all households in the entire population

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