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Expanding vaccine efficacy estimation with dynamic models fitted to cross-sectional prevalence data post-licensure

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ABSTRACT

The efficacy of vaccines is typically estimated prior to implementation, on the basis of randomized controlled trials. This does not preclude, however, subsequent assessment post-licensure, while mass-immunization and nonlinear transmission feedbacks are in place. In this paper we show how cross-sectional prevalence data post-vaccination can be interpreted in terms of pathogen transmission processes and vaccine parameters, using a dynamic epidemiological model. We advocate the use of such frameworks for model-based vaccine evaluation in the field, fitting trajectories of cross-sectional prevalence of pathogen strains before and after intervention. Using SI and SIS models, we illustrate how prevalence ratios in vaccinated and non-vaccinated hosts depend on true vaccine efficacy, the absolute and relative strength of competition between target and non-target strains, the time post follow-up, and transmission intensity. We argue that a mechanistic approach should be added to vaccine efficacy estimation against multi-type pathogens, because it naturally accounts for inter-strain competition and indirect effects, leading to a robust measure of individual protection per contact. Our study calls for systematic attention to epidemiological feedbacks when interpreting population level impact. At a broader level, our parameter estimation procedure provides a promising proof of principle for a generalizable framework to infer vaccine efficacy post-licensure.

1. Introduction

Mathematical epidemiological models for the dynamics of microparasite infections have a long history of development and use in the design and optimization of intervention programmes (Anderson et al., 1992). Yet, many challenges remain in applying such models retrospectively to interpret and quantify intervention effects in host–pathogen systems (Keeling, 2005; O'Hagan et al., 2014; Wikramaratna et al., 2014; Goeyvaerts et al., 2015). It is of public interest to quantify the relative effectiveness of different control strategies, assess the ongoing changes in transmission dynamics following such interventions, and optimize their design through a cost–benefit analysis for the future. In this paper, our focus is on vaccination as a transmission-reducing intervention, and more specifically, in the context of endemic pathogens. Although the amount of data available from epidemiological trials, cross-sectional and longitudinal surveys is vast and rapidly increasing, our understanding and interpretation of such data on the basis of transmission mechanisms and epidemiological feedbacks is limited. This is apparent for many pathogen systems, including *Streptococcus pneumoniae* bacteria, human papillomaviruses, dengue, malaria, influenza and rotaviruses. Currently several vaccines are being used or contemplated to control these pathogens around the world (Comanducci et al., 2002; Insinga et al., 2007; del Angel and Reyes-del Valle, 2013; Sabchareon et al., 2012; Agnandji et al., 2011; Black et al., 2000), and assessing their efficacy is crucial.

Conceptual models can play a key role in this assessment, first by clearly defining the measures of interest, secondly, by distinguishing individual from population indicators, and thirdly, by enabling us to anticipate future outcomes of vaccination programmes. An important vaccine parameter is efficacy against pathogen acquisition, defined as reduction in the probability of infection per contact of each vaccinated individual (Haber et al., 1991). Before a vaccine is introduced, vaccine efficacy estimation is typically performed through randomized controlled trials, involving a subset of a given

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population (Halloran et al., 2010). Such vaccine evaluation studies use 1 − RR (1 minus risk ratio), as a measure of efficacy, where RR is some estimate of relative risk in vaccinated vs. non-vaccinated individuals. This tends to ignore indirect effects (Halloran et al., 1991), such as the changes in transmission mediated by the intervention, which while in the time and coverage of trials are indeed expected to be negligible, are not quite negligible when mass-immunization is in place (Shim and Galvani, 2012).

The assessment of vaccines post-licensure is also of interest, and here is where dynamic mathematical models can be useful, alongside statistical approaches (Biondi and Weiss, 2015; Crowe et al., 2014; Andrews et al., 2014). There are several reasons for why such a-posteriori assessment is important. First, only a dynamic model can properly link pre-licensure vaccine expectations and observed outcomes in a population undergoing immunization, thereby providing a validity test for the numerical estimates of *vaccine efficacy* obtained from trials, and a validity test for the public-health projections made a priori regarding *effectiveness*, or population level impact. Second, only a dynamic model can take into account in a mechanistic manner the time since the onset of the vaccination programme, regardless of equilibrium requirements (Rinta-Kokko et al., 2009), and consider the actual vaccine coverage in a given setting. Third, in the context of multi-strain pathogens, where multivalent vaccines target a subset of pathogen types, only a dynamic model can properly implement the nonlinear interactions between pathogen types (Lipsitch, 1997; Martcheva et al., 2008), arising through direct competition, cross-immunity or asymmetric vaccine protection.

Although there has been recognition of the importance of dynamic transmission models for vaccine assessment (Shim and Galvani, 2012), few studies so far have attempted to infer vaccine efficacy fitting dynamic models to temporal prevalence trajectories post-vaccination (Choi et al., 2011; Gjini et al., 2016). Other approaches have suggested that prevalence odds ratios may be more suitable than prevalence ratios to determine vaccine efficacy, and that special attention must be given to the time of sampling post-vaccination (Scott et al., 2014). Another study by Omori et al. (2012) has used dynamic models (SIS and SIR) to illustrate the bias in odds-ratio estimators of vaccine efficacy for two competing pathogen types, but their estimation was based on prevalences at endemic steady state only, posing a strong restriction on the method. A recent study by van Boven et al. (2013) deals with vaccine efficacy estimation in an epidemic scenario, and applies a dynamic modelling framework to mumps outbreak data in the Netherlands.

Here, we advocate a similar dynamic spirit in the context of endemic diseases. We propose a novel approach to vaccine efficacy estimation using cross-sectional prevalence data integrated within dynamic mathematical models. This enables a deeper understanding of vaccine performance in the field, as mediated by transmission intensity, competition between pathogen subtypes and host factors. When vaccine coverage is high, the transmission cycle encompasses vaccinated and non-vaccinated individuals interacting through contact, thus affecting and being subject to a dynamic force of infection. With a gradually diminishing exposure to vaccine types, in polymorphic systems, subtype relative frequencies can change in the population from the combined effects of vaccination and interactions between target and non-target pathogen types. If a vaccine induces a replacement phenomenon, as it has been argued for pneumococcus (Weinberger et al., 2011) and HPV (Biondi and Weiss, 2015), vaccine efficacy against targeted pathogen strains, can be estimated while these strains are still in circulation, namely while type replacement is not yet complete, and sufficient information can be extracted. It is precisely in this intermediate dynamic phase that most vaccine observational studies are conducted, and where epidemiological feedbacks, including changes in exposure and interaction between multiple strains, are most likely to play a role.

To correctly capture all these processes, more refined mathematical frameworks are needed. This requires going beyond direct statistical comparisons, based on static data, e.g. snapshot prevalence odds ratios from observational studies (Thompson et al., 1998), or the indirect cohort method for case–control data (Andrews et al., 2011), which neglects pathogen subtype interference altogether. Even more importantly, the cohort method fails to acknowledge that the probability of infection of an individual depends on the infection prevalence in the population, i.e. on the infection status of others.

With a dynamic modelling approach, instead, the problem of constant hazard ratios (Hernán, 2010) can be circumvented, as can limitations of the indirect cohort method (Moberley and Andrews, 2014) for purposes of vaccine efficacy estimation. Furthermore, data can be interpreted relaxing the stationarity requirement and accounting for pathogen type replacement. Other statistical estimation methods such as incidence density sampling (Richardson, 2004), might also not require the assumption of stationarity, but they do not deal with competition in multi-strain pathogen systems.

The definition of vaccine efficacy that we consider in this paper has a clear biological meaning: reduction of the probability of pathogen acquisition per contact, which enables extrapolation beyond a single study population. This contrasts classical estimates of vaccine efficacy that are based on comparing attack rates in vaccinated and unvaccinated individuals (the cohort method), or those that use the vaccination status of the infected individuals relative to the population vaccination coverage (the screening method). Such vaccine efficacy indicators lack a clear biological meaning, which makes interpretation problematic, and prevents anticipation of the critical vaccination coverages needed to reach certain desired outcomes.

In this study, we argue that temporal effects of vaccination programmes can be addressed through dynamic mathematical models, where parameters of efficacy are explicitly defined in terms of underlying transmission mechanisms, and where epidemiological feedbacks among immunized and non-immunized individuals, and between pathogen strains are correctly accounted for. In the interest of simplicity and clarity, we only consider minimal epidemiological models to illustrate vaccine effects on single and multiple infection with different pathogen types, but the uncovered trends should apply in similar vein to more complex vaccination scenarios (Halloran et al., 1991, 2010). We delineate a proof-of-concept inference procedure, based on ODE model fitting, to cross-sectional data collected over different time points after vaccine implementation.

2. Materials and methods

To build intuition in our reader, initially we present susceptible-infected (SI) model frameworks accounting for one and two pathogen types, while the susceptible-infected-recovered (SIR) analogues are elaborated in the Supplementary Text S2. Then we proceed to susceptible-infected-susceptible (SIS) models with many-type pathogens, grouped according to whether they are targeted by a polyvalent vaccine or not. We always assume that the vaccine is effective against type 1 pathogen (SI/SIR models), or against pathogen subtypes in group 1 (SIS setting). The mode of action of the vaccine we consider is leaky (Halloran et al., 1991), and the vaccine efficacy is defined as the reduction in probability of infection/pathogen acquisition per contact. Notice that in this paper, we will use the terms ‘infection’ and ‘carriage’ interchangeably. As the source of prevalence data, we consider active