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A method for evaluating and comparing immunisation schedules that cover multiple diseases: Illustrative application to the UK routine childhood vaccine schedule

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ABSTRACT

Background: In the UK, the childhood immunisation programme is given in the first 5 years of life and protects against 12 vaccine-preventable diseases. Recently, this programme has undergone changes with addition of vaccination against Meningitis B from September 2015 and the removal of the primary dose of protection against Meningitis C from July 2016. These hanges have direct impact on the associated diseases but in addition may induce indirect effects on the vaccines that are given simultaneously or later in the programme. In this work, we developed a novel formal method to evaluate the impact of vaccination changes to one aspect of the programme across an entire vaccine programme.
Methods: Firstly, we combined transmission modelling (for four diseases) and historic data synthesis (for eight diseases) to project, for each disease, the disease burden at different levels of effective coverage against the associated disease. Secondly, we used a simulation model to determine the vector of effective coverage against each disease under three variations of the current childhood schedule. Combining these, we calculated the vector of disease burden across the programme under different scenarios, and assessed the direct and indirect effects of the schedule changes.
Results: Through illustrative application of our novel framework to three scenarios of the current childhood immunisation programme in the UK, we demonstrated the feasibility of this unifying approach. For each disease in the programme, we successfully quantified the residual disease burden due to the change. For some diseases, the change was indirectly beneficial and reduced the burden, whereas for others the effect was adverse and the change increased the disease burden.
Conclusions: Our results demonstrate the potential benefit of considering the programme-wide impact of changes to an immunisation schedule, and our framework is an important step in the development of a means for systematically doing so.

1. Introduction

Routine immunisation against infectious diseases of childhood prevents 2–3 million annual deaths worldwide [1]. At the end of 2016, the UK's routine childhood vaccine programme protects against twelve vaccine-preventable diseases (VPDs) and is administered within the first five years of life (Table 1). Potential changes to this schedule such as adding a new vaccine or changing the age at which a vaccine is administered are evaluated on a case-by-case basis, often informed by cost-effectiveness analysis [2–6] focussed on the disease directly affected. However, alterations to one component of a vaccine schedule may have additional, indirect effects on the burden of other diseases covered by vaccines administered at the same time or later in the schedule.

For example, it is well documented that the measles-mumps-rubella (MMR) vaccine scare in the late 1990s, based on now discredited [7] research from 1998 [8], induced a dramatic reduction in the uptake of the MMR vaccine (from 92% in 1995 [9] to 79% in 2003 [10] at 2 years old), resulting in resurgence of measles [11]

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Table 1
Schedule A = July 2016 schedule for childhood vaccination programme in the UK, including protection against Men B.

	2 months	3 months	4 months	10/11 months	12 months	18 months	3years 4 months-5years
Men B	Bexsero		Bexsero		Bexsero		
Diptheria	Pediacel	Pediacel	Pediacel				Repevax or Infanrix IPV
Tetanus							
Polio							
Pertussis							
Hib					Menitorix		
Men C		NeisVac-C OR Menjugate Kit					
Pneumococcal	Prevenar13		Prevenar13		Prevenar13		
Rotavirus	Rotarix	Rotarix					
Measles					MMR-VAXPRO or Priorix		MMR-VAXPRO or Priorix
Mumps							
Rubella							

and outbreaks of mumps. An indirect effect of this scare was reduced uptake of the vaccine protecting against Haemophilus influenza type b (Hib) delivered at the same point in the schedule as the MMR vaccine: Hib uptake at 2 years declined to 93% in 2003 [10] from a record high 96% in 1996 [12] resulting in 4-fold increase in invasive Hib cases: from 51 in 1996 to 241 cases in 2003 [13].

Assessing the potential size of indirect effects associated with changes to a vaccination programme is particularly relevant in the context of national routine childhood vaccination programmes which often change as vaccine preventable diseases emerge as significant threats to population health and as new vaccine products become available. For example, in the UK, recent changes to the routine childhood immunisation programme include the addition of the Hib/MenC vaccine booster dose in 2006, the introduction of vaccination against Pneumococcus from October 2006, the introduction of the Rotavirus vaccine in 2013 [14], the addition of the vaccine against Meningitis B from September 2015 [15] and the removal of the primary dose vaccine against Meningitis C from July 2016 [16].

The direct benefit of vaccinating against an individual VPD is based on formulation and application of mathematical models used to simulate disease outcomes under different vaccine scenarios. These can be mathematical and statistical models that consider the historic trends in disease burden and effective vaccine coverage and employ statistical techniques to make future predictions [17]. Alternatively, dynamic disease transmission models that estimate the temporal evolution of (age or risk-stratified) cohorts of Susceptible, Exposed, Infected and Recovered populations (SEIR modelling framework – reviewed in Appendix A with more details in [18]) may be utilised. Dynamic transmission models are based on disease epidemiology, parametrised to setting-specific data (e.g. the POLYMOD contact patterns data obtained across UK are relevant to those infections transmitted by the respiratory or close-contact routes [19]) and calibrated to reproduce historic disease burden (e.g. disease notifications, hospitalisations or laboratory confirmed incidence or prevalence data). The calibrated models project how disease burden is likely to change under different vaccination strategies and, combined with health economic analysis, can be used to identify optimal schedules for vaccination against individual VPDs. (e.g. [2–6]).

However, there is currently no accepted method to assess the indirect impact of changes to a schedule on the residual disease burden of a set of VPDs, or to compare the residual per-disease and overall burden of different vaccination schedules. In our previous work [20] we developed a modelling framework to estimate, for a given vaccine schedule, the age-dependent effective vaccine coverage (uptake times vaccine efficacy) for each disease within a set of diseases comprising a vaccine schedule. This enabled us to project the vector of effective vaccine coverage, at different time points over the first five years of life, for a set of VPDs. However, the modelling framework in [20] was limited because it did not extend to disease burden. Therefore, in this work, which was at the request of and commissioned by the Department of Health - Health Protection Analytical Team (DH HPAT), we developed a modelling framework to quantify the disease burden, expressed in quality adjusted life years (QALY) lost per year, at different levels of effective vaccine coverage against a set of VPDs.

By combining this framework with the model from [20], we aim to derive estimates of the vectors of the effective vaccine coverage (time-averaged over the first five years of life) and residual disease burden for a set of VPDs associated with a given vaccine schedule.

This gives a method to assess the benefit of candidate vaccination schedules across a set of VPDs, allowing direct schedule level comparison of benefits that accounts for any indirect effects.

To demonstrate the feasibility and utility of this work, and on advice of our colleagues within the DH HPAT, we populated the framework with the VPDs included in the current routine childhood immunisation schedule for the UK. We applied our methodology to the schedule at the end of 2016 and 3 recent or plausible variations of this schedule.

2. Materials and methods

We first describe how we obtained, for each of a set of VPDs a quantified relationship between the effective coverage against that disease and the residual burden of disease. We then describe how we used these relationships to quantify the residual burden of disease associated with 4 distinct vaccine schedules relevant to the UK routine childhood vaccination programme.

3. Modular framework for projecting disease burden at different levels of effective coverage of vaccination

We developed a modular framework for estimating the burden of remaining disease associated with a vaccination schedule, with each module concerning a single vaccine preventable disease. For each VPD considered, the steps involved in estimating the burden of disease were: