

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] and outbreaks of mumps. An indirect effect of this scare was reduced uptake of the vaccine protecting against *Haemophilus influenzae* 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.

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.

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:

- 1) to identify a published model of the impact of differing levels of effective coverage of vaccination on disease burden, or in the absence of a suitable model to develop one, or if infeasible to develop one to identify historic data linking effective coverage of vaccination to disease burden;
- 2) to convert the burden of disease obtained from the process at step (1) into an annual loss of quality adjusted life years (QALYs).
- 3) to combine (1) and (2) to estimate the residual QALY loss associated with that disease at different levels of effective coverage of vaccination.

The approach taken in step (1) for the 12 VPDs currently included in the UK routine childhood vaccination campaign is set out in detail in Appendix A. To summarise, for those diseases where a mathematical model was available (summarised in Table S3 of Appendix A), we varied the vaccine coverage for a fixed vaccine efficacy and projected the disease burden as the number of annual cases of the disease in all ages at different levels of effective coverage among children under 5 years of age (vaccine coverage among children under 5 years of age times vaccine efficacy). Using the constraints provided by the known disease burden before vaccination started and by assuming that at 100% effective coverage no disease burden is expected (except in the cases of Men B, rotavirus and Pneumococcal – see sections A13 and A14 in Appendix A for reasoning) we then determined a relationship between disease burden and effective coverage of the associated vaccine.

Where no mathematical models could be feasibly applied¹, historic publicly available data on disease burden and vaccination for England was used. Across different diseases the unit of disease burden was either the number of notified or laboratory confirmed cases of the disease (stratification per disease is outlined in Table S3 in Appendix A). In this case, the historically available data on vaccine uptake, efficacy and burden were combined to determine a relationship between disease burden and effective coverage among children under 5 years of age of the associated vaccine.

We identified and were able to use or adapt published models relating to Hib, Rotavirus, Pneumococcal and Men B. For measles and the remainder of the diseases (polio, diphtheria, tetanus, pertussis, Men C, mumps and rubella) we had to resort to use of historical data on effective coverage and disease burden.

At step (2) we calculated the QALY loss per disease case using the method described by Sassi in [21] with details given in Appendix B. This uses published disability weights, duration of disease (as days per year) and discounting (currently at 3.5%). For some diseases, such loss of QALYs per episode of the disease values were available from the literature and we checked their comparability with the multiplier determined by our chosen method from Sassi [21].

At step (3), we simply scaled the disease burden for each disease obtained at step (1) by the respective QALY multiplier obtained at step (2) to give the relationships between effective coverage among the children under 5 years of age and the estimated residual QALY loss associated with that disease.

¹ Because vaccination has been successful and disease burden is low, utilising transmission models is either not needed (e.g. polio, diphtheria, tetanus), or the application of the model is longer than our timescale (e.g. Men C, mumps, rubella and pertussis).

Once these steps were completed for all vaccine preventable diseases considered, the total residual burden of disease associated with a given schedule was obtained by assuming that the residual burdens associated with different diseases are independent and additive and then summing across diseases.

Application to schedules relevant to the routine childhood immunisation programme in the UK

To illustrate the feasibility and utility of our approach, we applied it to the set of diseases that are currently (December 2016) included within the routine childhood vaccination programme in the UK. The childhood vaccination programme in the UK includes five scheduled GP visits timed at 2,3,4,12-13 months and 40-60 months and comprises immunisation against twelve infectious diseases (Table 1): Polio, Diphtheria, Pertussis, Tetanus, Neisseria Meningitides Group C (Men C), Haemophilus influenzae B (Hib), Measles, Mumps, Rubella, Pneumococcal disease (Pneumo), Rotavirus and Neisseria Meningitides Group B (Men B).

Full details of the models used, adapted and developed are given in Appendix A. All of the disease transmission models we used have been calibrated to historic data on disease burden from Public Health England (PHE) for England or England and Wales. Within the calibrated models, projections were made for disease burden, in terms of number of disease cases in all ages, at different levels of effective vaccine coverage.

The QALY multipliers calculated at step (2) for the 12 diseases are given in Appendix B, based on which, along with the output of step (1), we quantified the relationship between effective coverage and QALY loss for each of the 12 diseases.

To illustrate the feasibility of our approach and how it might bring useful insights on the impact of childhood vaccination in the UK that are currently not available, we applied our techniques to four different vaccination schedules relevant to the childhood vaccine programme in the UK (schedules A-D outlined in Tables 1-4). These reflect A) the vaccine schedule that applied in July 2016, B) a plausible alternative to this schedule with different products and timings, C) the schedule that applied in August 2015 with no vaccination against Men B and D) the current (December 2016) schedule. The differences between vaccine schedules A-D are illustrated in Table 5.

For each of these schedules, we applied the simulation model from [20] (details in Appendix C) to estimate the effective coverage against each of the 12 diseases over the first 60 months of life. The simulation accounts for observed relationships between age at vaccination offer, the number of opportunities for a previous adverse experience of vaccination and uptake. We then calculated a vector of effective coverage for each disease by taking an average of the projected effective coverage over 0-60 months (using the method from section A3.4 in Appendix A). For each of these four vectors of effective coverage, we used the projections of disease burden at different levels of effective vaccine coverage from our new framework, to estimate the associated four vectors of disease burden associated with each schedule.

Results

The relationships between the annual loss of QALYs and effective coverage among the children under 5 years of age obtained from combining our analysis of the models (for four diseases) and data (for eight diseases) (Appendix A) and the calculated QALY multiplier for each disease (Appendix B) are shown in Figure 1.

For each of the 4 schedules A-D, the vectors of effective coverage among the children under 5 years of age against each disease, as estimated using the simulation model [20], and the

corresponding estimates of residual burden of disease are shown in Table 6, which also shows the total residual burden of disease associated with each schedule.

Mindful that our intent is to demonstrate the feasibility and utility of this approach rather than provide a definitive analysis of schedules, we focus on those results that illustrate the potential of this approach. First, the results in Table 6 and Figure 2 suggest that the 4 schedules explored differ by at most 19% (reduction in schedule C compared to schedule B) in terms of the residual burden of disease expressed in QALYs loss. The estimated burden for each disease within each schedule suggests that the largest residual burden of disease is associated with infections of measles (around half of all residual burden in different schedules) and pneumococcal disease (around a quarter of all residual burden in different schedules). The residual burden of measles infections is large due to the low time-averaged effective vaccine coverage, whereas the large burden due to pneumococcal infections is associated with strains not covered by the vaccine used currently. The differences between the estimates of residual burden of disease associated with schedules A and B (9%) illustrate the potential benefits of scheduling vaccination to be completed at younger ages, with benefits driven by two effects within the model - younger vaccination being associated with slightly higher uptake [20] and younger vaccination giving higher time-averaged protection among the cohort of children under 5.

The value of having an approach that incorporates indirect effects is illustrated by comparing schedules A and C or schedules A and D. Here, our analysis suggests that vaccinating against Men B (in schedule A and not in schedule C) reduces the overall burden. However, the benefits of vaccinating against Men B are tempered slightly by the additional injections at 2,4 and 12 months having the indirect effect of slightly reducing uptake of later vaccinations

against other diseases and hence inducing a slight increase in the residual QALY loss in the other diseases in the schedule.

Removing one dose of the Men C vaccine (in schedule D compared to schedule A) reduces the averaged effective coverage in children under 5 years of age against Men C, hence directly increasing the burden associated with this disease. However, within the model, having one less injection indirectly increases the averaged vaccine effective coverage of the vaccines later in the schedule inducing a reduction in the residual QALY loss in these diseases and a reduced overall disease burden.

Discussion

The novel approach set out in this paper allows disease-specific models of the impact of immunisation to be combined with schedule designs and a quantified model of vaccine uptake to give high-level assessments of vaccine schedules. We consider that this approach has the potential to augment the other analyses and knowledge available to decision makers faced with choosing between candidate schedules as new products become available, others are withdrawn and as new threats from vaccine preventable disease emerge. In addition to putting the benefits of each component of a schedule in the context of the total residual burden of disease associated with the set of vaccine preventable diseases considered, the approach we have developed allows account to be taken of indirect or spill-over effects, whereby one change to one component of the schedule may enhance or undermine uptake of other components of the programme. Our work could thus be useful in highlighting the trade-offs between different candidate vaccine schedules in a way that is not currently done.

While we have demonstrated the feasibility of this approach using the example of the UK childhood immunisation schedule, the modular structure of our approach means that incorporating immunisation against different diseases (for instance Respiratory Syncytial Virus) is relatively straightforward, so long as a quantified relationship between effective coverage and estimated residual burden of that disease is available. Similarly, as improved or updated disease specific models become available, these can simply be used instead of the disease specific models we have implemented (given in Appendix A).

This flexibility hinges on the key limiting assumptions of our work that the health benefits conferred by immunisation against distinct diseases can be considered independent and additive. This is one of the three possible approaches in quantifying the burden of diseases with different co-morbidities [22]-[23]. Specifically, we assume that the effectiveness of immunisation against one disease is independent of whether an individual is immunised against another disease. We also assume that known significant short-term vaccine interactions are avoided in the design of candidate schedules. The separate assumption of additive benefits is that the disease prevented by different immunisations would have been spread across a sufficient pool of people that competing cause-effects can be ignored. The impact of these assumptions on the estimated results may be tempered by the fact that the component disease models used have been developed with or calibrated against data obtained in the context of a multi-disease immunisation programme.

Inevitably, a framework that builds on disease-specific models of immunisation impact and a quantified behavioural model of uptake carries forward the limitations associated with those component models. The limitations of SEIR models are widely recognised [24], there are known uncertainties around employment of regression models to make predictions for infectious disease spread and vaccination [25] and we stress that the QALY loss calculation study in Appendix B was intended to give a consistent approach fit for the purpose of this

feasibility work and not to provide definitive QALY loss estimates. For the inputs to the simulation model in [20], partial-uptake of a primary course of vaccination is not considered and we assume that missed vaccines will not be given at the next or additional visit. These assumptions potentially underestimate effective vaccine coverage and overestimate disease burden as even initial doses of most vaccines have some efficacy against VPDs. We note that these assumptions were made to give plausible estimates consistent with observed uptake data and they could be relaxed should more granular data become available.

We also made specific assumptions as to what a vaccine schedules comprise, and specifically considered plausible schedules to be those that are designed to avoid major vaccine interactions. There is a scope in future, when extending our model, to relax these assumptions.

We should also note that the estimated indirect effects we report stem from effects included in the simulation model developed by our team previously to project the schedule specific time varying vector of effective coverage against a set of vaccine preventable diseases. The development of that simulation model was informed by the qualitative literature on vaccine uptake and calibrated to be consistent with historic uptake data, but its predictive accuracy has not been formally assessed. Indeed, for the potential of the approach we outline in this paper to be fully realised, collaborative research effort is required between experts in vaccine uptake and vaccine hesitancy, and quantitative modellers to construct quantified behavioural models of vaccine uptake in the context of multi-disease childhood immunisation programmes. This is potentially an area of work that would benefit from the emerging discipline of behavioural operational research [26].

Conclusions

We have successfully developed and demonstrated the feasibility of a novel analytical framework to compare the impact of different candidate vaccination schedules against a set of vaccine preventable diseases, illustrating the approach with results based on the UK routine childhood immunisation programme. Intended to augment and build upon disease-specific epidemiological and health economic modelling, this work presents an important step towards providing decision-makers means for exploring the direct and indirect trade-offs between different candidate schedules and informing a strategic approach to adapting vaccination schedules to reduce further the burden of vaccine preventable disease.

Competing interests

The authors declare that they have no competing interests.

Author contributions

PG approached SC, CP and MU with the idea for the study. JPG and MU developed the work described in this paper with contributions from PG, CP and SC. JPG did the data analysis, extended and applied the transmission model for Hib, modified and applied the transmission model for rotavirus, developed and applied the transmission model for measles, implemented the overall framework and generated the paper results. TS applied an existing transmission model for Pneumococcus.

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