Optimization of vaccination schedules in low and middle income countries

SUMMARY

The current vaccine schedule in use in many countries was established more than 25 years ago as part of the Expanded Programme on Immunization (EPI). However, despite a global increase in vaccine uptake compared to the early years when EPI was first introduced, vaccine-preventable diseases still remain important causes of childhood morbidity and mortality. Since the establishment of the initial global vaccination schedule (i.e. 6, 10 and 14 weeks for DTP-OPV and 9 months for measles vaccine), the epidemiology of these infections has greatly changed, new vaccines have been designed and introduced, health services have changed and expanded, and other interventions have been linked to EPI activities (such as micronutrient supplementation and preventive treatments for malaria). In addition, much has been learnt about the mechanism of action and impact of all vaccines. Given all these developments, there is growing recognition that new or alternative schedules may be desirable to optimise impact and reduce child mortality. The varying country specific burden of diseases as well as varying health infrastructures and resources suggest that it is unlikely that a single, uniform immunisation schedule would now suit all countries.

This project's overall goal is to ensure long term and sustainable reduction of vaccine-attributable disease and overall child mortality. Several epidemiological and modelling studies have explored the effect of specific vaccines on child morbidity and mortality, but there has been little work on a comprehensive evaluation of vaccination schedules at global or country level. This project aims to determine how best to design vaccination schedules in order to reduce vaccine preventable diseases burden in a cost effective manner. We intend to begin with a review of 7 antigens; pneumococcal conjugates, rotavirus, Diptheria-wPertussis-Tetanus, Hepatitis B and Hib vaccines, drawing data from existing or ongoing reviews. As appropriate we will systematically review the existing data on vaccination schedules for these initial seven vaccines in terms of epidemiology, immunology, safety and logistic and programmatic issues. This process may identify critical evidence gaps that hinder full evaluation and encourage a research agenda to answer key issues. The data collated will be used to inform an evidence-based decision making approach that will enable key stakeholders to design optimal vaccination schedules for these vaccines on the basis of local context and data. Endorsement by SAGE and demonstration studies of impact and feasibility of new optimised schedules in selected countries will be critical milestones for the success of this project.

The project will be executed by a global multi-disciplinary network of experts, covering epidemiological and immunological methods, clinical trials, mathematical modelling and, vaccine-preventable-disease specific experts, under the leadership of the Initiative for Vaccine Research (IVR). A core group of institutions will coordinate the activities under this project. Their interactions will be coordinated by a Steering Group that will provide scientific advice to the Initiative for Vaccine Research (IVR). The members of the Steering Group will also act at the leaders of independent multidisciplinary clusters, each one with a designated "Cluster Coordinator". Each cluster will be in charge of addressing the issues specific to given antigen, disease parameters or epidemiological methods. Core members include the London School of Hygiene and Tropical Medicine, UK, the University of Bern, Switzerland, the Agence de Medicine Preventive, France, the Institute of Child Health, UK, Bocconi University, Italy and, the World Health Organization. Annual updates will be presented during the Strategic Advisory Groups of Experts (SAGE) meetings, to ensure that the outcomes of this project remain both appropriate and relevant to global immunization priorities and realities.

BACKGROUND

The Strategic Advisory Group of Experts (SAGE) was established in 1999 by the Director-General of WHO to provide guidance on the work of the Department of Immunization, Vaccines and Biologicals (IVB). SAGE recognises that the introduction of new vaccines and the scaling up routine vaccination activities are essential if the Millennium Development Goals for child survival are to be met. In November 2005, SAGE highlighted the importance and timeliness of reviewing the scientific and operational basis for the choice of the optimal schedule for childhood

immunization: *"More than 20 years have passed since the "EPI schedule" of 6, 10 and 14 weeks for DTP-OPV and 9 months for measles vaccine was introduced, and more information has accrued, together with the development of improved techniques for assessing immune responses. There was recognition that vaccination schedules in use today vary greatly around the world, and it is unlikely that a single, uniform vaccination schedule would suit all countries. WHO should aim to provide countries with advice on the parameters to be considered when they select a schedule. There was unanimous support for a new review of the evidence base, and agreement that changes in schedule are not appropriate without strong evidence to demonstrate benefit. It has also been stressed that is difficult to design ONE schedule for ALL countries as there are differences in epidemiology, health infrastructure and resources. In developed countries these discussions take place at national level based on local data however, low resource countries often rely on decisions made by others"*[1]

Encouraged by SAGE, the Initiative for Vaccine Research (IVR) is leading efforts to review evidence supporting current recommended schedules for vaccines in use and also proposed schedules for new vaccines, in order to inform decisions on the optimization of vaccine recommendations. Current discussions surrounding pneumococcal vaccines illustrate the complexity of the issues at stake. Several countries in Sub-Saharan Africa are planning to introduce pneumococcal conjugate vaccines in the next 2-5 years. There is growing evidence that PCVs are immunogenic/effective, but appropriate evaluation is needed. Several studies have indicated that a reduced number of doses of PVC appear to provide similar direct protection to three doses during infancy followed up by a booster at 12 months of age. A case-control study from in the United States reported that nearly all schedules provided some protection compared to no vaccine, with the exception of one dose before 7 months of age [21]. An immunogenicity study from the UK demonstrated that the proportion of children achieving titres >0.35 µg/mL following two PCV9 doses at 2, 4 months of age with a booster was comparable to the response following three doses at 2, 3, 4 months with a booster [22]. In developing countries, phase III trials of the 9-valent vaccine in South Africa and The Gambia showed that a 3-dose primary series conferred substantial protection against disease in the absence of a later fourth dose [20, 23]. Ideally, future vaccination schedules for PCV need to be designed to correspond to the epidemiology of pneumococcal disease in particular regions. Data on Pneumococcal infection, carriage and disease in the developing world, particularly Africa are limited, but are needed for modelling of impact of vaccine schedules. And any decisions on PCV vaccine schedules must be coordinated with those on other vaccines and on broader logistic issues surrounding EPI programmes. Given the very considerable potential for mortality reduction by new vaccines, combined with the relatively high cost per dose of these products, there is great need to revisit vaccination schedules with a goal of optimizing public health impact and minimizing cost. Moreover, there is a need to adapt the vaccine delivery strategies to ensure wide access. Current experience at country level supports the critical role that alternative delivery strategies (i.e. besides fixed vaccination sites) can achieve both in terms of equitable vaccine access and disease control goals, especially in areas with weak health systems. Reaching a large proportion of the population in a brief time period can enhance the indirect vaccine effects (population herd immunity) of several vaccines. Experience with measles, polio and conjugate vaccines demonstrate that the successful use of mass immunization campaigns requires a deep understanding of the disease epidemiology and transmission (e.g. epidemiology of carriage, age groups most critical for disease transmission). In addition, an evaluation is required of the need for periodic follow-up campaigns and the role of routine immunizations. The interplay between routine and campaign delivery strategies should be studied in various settings. It is well recognised that there are still important barriers to ensuring equitable access to high quality vaccines to all children in the world. This project addresses the issue of how best to select a vaccination schedule at country level based on costs, implementation and delivery, disease burden and vaccine responses by age and number of doses. Though the intention is to consider all vaccines the plan is to focus on the development of a strategy and its application to a selected group of vaccines where the impact on child mortality and morbidity is thought to be greatest. The structure of this strategy will be shaped and developed throughout the project and will depend largely on the quality and quantity of data obtained as well as ease of use, who will use it and what are the identified critical policy questions regarding vaccination schedules. Although we promote that any decision should be based on evidence, some consequences of changing a schedule may not be foreseeable or predictable. We intend to collaborate with projects aiming at the development of national immunization technical advisory groups, in particular those aiming to

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[1] Weekly Epidemiological Record June 2006, 6/1/06

help national health authorities in low resource countries to set up vaccination policy and programs adapted to their needs and to introduce new vaccines[2].

Project Goal

To propose an appropriate adjustment of vaccination schedules by (in particular less developed) countries for new and current vaccines

- Development of an APPROPRIATE PROCESS (step-wise, algorithmic and/or consultative, web-based) for determining optimal vaccination schedules according to local / national circumstances.

- An up to date REVISION of the vaccination schedules for an initial group of vaccines is completed. This initial group includes pneumococcal conjugate, rotavirus and D wP T-HepB- Hib vaccines.

OBJECTIVES

Objective 1: METHODS - To develop a strategy to guide decisions on optimising immunisation schedules.

Consensus on:

- APPROACH to make evidence based decisions on vaccination schedules
- KEY PARAMETERS for each individual vaccine: epidemiological, immunological, vaccine-technical, safety, operational, other relevant factors

- METHODS that should be considered during the design of optimal vaccination schedules: epidemiological, systematic reviews, mathematical models, cost-effectiveness analysis, other methods

Objective 2: EXISTING EVIDENCE -To review the relevant evidence (relevant to schedules) of current and new vaccines

- A list of PRIORITY RESEARCH questions for all vaccines

- Appropriate REVIEWS completed on vaccines, vaccine preventable diseases and relevant operational issues.

Objective 3: NEW EVIDENCE – To identify and encourage a research agenda to generate critical missing evidence

- A RESEARCH AGENDA appropriate to address the gaps in evidence will be generated.A call for proposals leading to the initiation of appropriate research to fill the gaps will be implemented[3].
- New evidence is generated/collated for initial group of antigens.

Objective 4: TRANSLATION- To apply the strategy to an initial group of vaccines and scenarios (pilot studies). This initial group includes pneumococcal conjugate, rotavirus and D wP T- HepB-Hib vaccines.

- A STRATEGY is used to propose a number of vaccination schedules for various scenarios.

- A draft STRATEGY is available for pilot study application in various national programme scenarios.

Activities:

Objective 1- DEVELOP METHODS: Activities under this objective aim to develop an evidence-based decision-making process for use at country level, which is particularly needed in view of the complexity of the immunization programs and cost of new vaccines. We will use existing evidence and expert consultations to define a list of key parameters and their relevance to each

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[2] For example: The 'SIVAC Initiative': Supporting Independent Immunization Vaccine Advisory Committees) http://www.aamp.org/index.php?page=detailfiche&fiche=6&type=CAPcooperation and Vaccine European New Integrated Collaboration Effort (VENICE).

[3] Some of these studies will be encouraged but not all funded by this project.

individual antigen. Moreover, we will critically review decision-making approaches in use by immunization programmes as well as, other decision making approaches in use by the health sector. Through expert consultations we will select and adapt the most appropriate approach for the analysis of evidence related to vaccination schedules and its translation into policy. At a mid point in the project, we will apply the selected approach to at least one country scenario (with inputs from country level decision makers[4]) and assess its robustness and suitability for use at country level. To ensure that the data generate by this project is obtained using agreed standards, we will also review current generic guidelines (e.g. systematic reviews, meta-analyses, modelling, cost effectiveness evaluations, clinical trials, observational studies) and propose -if appropriate- methodological adaptations relevant to vaccination schedules. Concise, structured user-friendly checklists and data collection forms will be made available to country level collaborators. The relevance and usefulness of these summary formats will be assessed through structured feedback collected from collaborators at each country.

Objective 2 - EXISTING EVIDENCE: Activities under this objective aim to ensure that available data pertinent to vaccination schedules is synthesized as part of a research process to support policy decisions on vaccination schedules. We aim to draw conclusions on the quality of existing evidence and the strength of current schedules recommendations for the initial group of seven antigens. An initial step includes rapid reviews of available data through expert consultations to outline major data gaps. Whenever possible, syntheses will build on existing systematic reviews. This will be followed by in depth systematic reviews addressing questions previously agreed. In parallel to the global review of the evidence, detailed review and analysis of data from selected countries will take place[5]. As part of the sustainability activities, a web based interface will be built as a repository for the data being identified or generated. Initially it will allow access to data for the project collaborators and later on will serve as a source of schedules evidence for decision makers at various levels. Early efforts will also include expanding capacity for the conduct of systematic reviews using methods adapted to vaccine schedules among project collaborators at country level.

Objective 3 - NEW EVIDENCE: Activities under this objective aim to generate data to address any critical evidence gaps uncovered under Objective 2. This is conceived as a dynamic process along the project's duration. An initial step will involve an analysis of the outcomes of the rapid reviews and expert inputs in order to develop and publish a research agenda to guide the project decisions on studies to support or promote. Available funds will be allocated to support studies to address critical gaps in evidence. In addition, there will be concerted advocacy and fundraising efforts by the collaborators to encourage additional financial support for remaining research questions which are identified along the way.

Objective 4 - TRANSLATION: The activities under this objective will have three main aims. First, to synthesize and analyse the country data generated by Objectives 2 and 3 from the selected countries using the proposed approach. This will be conducted as a concerted effort with the national immunization committee members and institutions supporting the development of such committees in those countries. Included in this step is a consideration of the logistic and other factors affecting EPI schedules in the particular regions, including of other child health services whose activities have been or may logically be related to EPI Second, to develop a set of recommended schedules for the initial seven antigens under various epidemiological and health infrastructure scenarios with inputs from selected antigen and disease experts. This will be accomplished by using the proposed approach to analyse and translate the global data generated Objectives 2 and 3 and, by exploring additional scenarios using dynamic age-structured mathematical models. Third, we will propose for the SAGE's consideration and endorsement both the agreed approach for the design of the vaccination schedules and the preliminary vaccination schedule recommendations for the selected initial seven antigens at global level and for the selected countries. We will summarize the approach elements and lessons learnt in a tool that promotes the use of the best available evidence as a basis for vaccination schedules decisions for use by decision makers at various levels.

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[4] This will involve collaborating with national immunization advisory committees and the use of the approach by its members to make decisions on the schedule at country level. It also implies collaboration with other projects aiming to develop/strengthen similar capacity at country level (e.g. SIVAC, EpivNet).

[5] Countries selected for geographical representativeness, availability of data and willingness to collaborate.