Is the timing of recommended childhood vaccines evidence based?

Yes—Kathryn M Edwards, Yvonne Maldonado, Carrie L Byington

Vaccines undergo extensive testing and review before licensing to evaluate their immunogenicity, safety, and effectiveness in preventing disease. For example, prelicensing trials of pneumococcal conjugate and rotavirus vaccines are among the largest randomised controlled trials ever conducted, enrolling tens of thousands of infants. In addition to randomised controlled trials, which produce the highest level of evidence and provide the basis for vaccine licensure, vaccine policy also benefits from the additional supportive evidence obtained from thousands of other types of vaccine studies. Such studies generate critical data regarding age specific immunogenicity, dose and dosing intervals, interaction with other vaccines, duration of immunity, and overall vaccine safety to inform schedules.

What evidence is needed to make the most appropriate schedule?

Data from clinical trials represent only a portion of the evidence considered in determining vaccination schedules. Burden of disease, immunogenicity, and efficacy studies enable countries to select vaccines and schedules appropriate for their populations, as shown by the recent infographic in *The BMJ*. Vaccine schedules are further refined by considerations such as timing and efficiency of access to the target population to optimise uptake. For childhood vaccines, integration with existing local or national well child visit schedules is a critical consideration. This concept was summarised well in the US Institute of Medicine (IoM) report on the childhood immunisation schedule: “Each new vaccine is approved on the basis of a detailed evaluation of both the vaccine itself and the immunization schedule.” The IoM further stated that randomised controlled trials in which children “would receive less than the full immunization schedule or no vaccines would not be ethical because they would be exposed to a greater risk for the development of diseases and community immunity would be compromised.”

Once vaccines are in general use local surveillance is generally conducted to evaluate their effect on disease burden. Comprehensive surveillance systems are also maintained by the Centers for Disease Control and Prevention in the United States, Eurosurveillance in Europe, and the World Health Organization expanded programme on immunisation (EPI).

Role of expert advisory bodies

In nearly every jurisdiction, decisions regarding vaccine schedules are made by formal advisory bodies consisting of experienced practitioners, public health officials, vaccinologists, and epidemiologists. Available data are reviewed, burden of disease assessed, and practical considerations for vaccine delivery evaluated to produce an appropriate schedule for each country. Thus, expert advisory bodies may develop differing recommended schedules, based on local, regional, or national considerations. For example, the second dose of MMR vaccine is routinely given in Germany at 15-23 months of age, while in the US it is administered at 4 to 6 years. Strong trial generated evidence shows that two doses separated by at least 28 days and the first dose administered on or after the first birthday will produce measles immunity in 99% or more of people. The timing of the second dose varies in each country based on the ability to provide the earliest possible second dose that will minimise the burden of measles. Ongoing surveillance of measles cases ensures that the timing of doses remains appropriate to the epidemiology of disease.

In the G8 countries, where surveillance systems are in place to monitor disease threats, public health officials are in the best position to determine timing of vaccines, taking into account evidence from trials, the epidemiology and ongoing risk of the disease, and input from providers, parents, and other stakeholders. Alternatives to these evidence based recommendations, which may be requested by parents, can create systemic obstacles that place both individual children and the general public at risk.
Consider also the primary vaccination schedule for infants. The EPI schedule recommends immunisation at 6, 10, and 14 weeks in central Africa based on the early burden of vaccine-preventable diseases and the need for efficient vaccine delivery when infants are most accessible. In contrast, the primary schedule in North America and much of Europe is 2, 4, and 6 months; in these populations, the lower risk of acquisition of many infectious diseases and better access to care permit vaccination to be incorporated into established well child visits through the first six months of life.

Monitoring optimises protection

Evidence continues to be gathered and used after implementation. The increase in Haemophilus influenzae type b (Hib) cases in the United Kingdom after implementation of a Hib conjugate vaccine schedule at 2, 3, and 4 months prompted an altered schedule that moved the 3 month dose to 12-13 months, with a resultant reduction in the burden of Hib disease.10 The value of continued surveillance was also highlighted by the introduction of maternal tetanus, diphtheria, and acellular pertussis (Tdap) vaccination to reduce pertussis among infants in the US and many European countries.11

In summary, vaccine schedules are evidence based, safe, and highly effective in reducing the global burden of infectious diseases. Evidence to develop and maintain these schedules involves a multifactorial and robust process carried out worldwide. The real world effectiveness is shown by the millions of children spared annually from the morbidity and mortality of vaccine preventable infections.

No—Tom Jefferson and Vittorio Demicheli

If taken literally, the answer to the question is a simple no. No field trials have compared the effectiveness and harms of all vaccines used according to various schedules listed in the recent BMJ infographic.6 12 The time for such studies is ethically and logistically past.

However, childhood vaccination schedules are a complex and delicate matter because they reflect a multiplicity of inputs: the threat from the target disease, the vaccines’ capacity to build immunity and offer a reasonable harms profile, duration of effect, and (last but not least) organisational factors.

The full evidence base to make such complex decisions as the timing of each vaccination, in conjunction with developmental issues and the effect each vaccine has on the response to the others, is seldom fully available when vaccination schedules are devised.

Serious childhood diseases can be prevented by immunisation programmes when children respond to a vaccination by building immunity to the target disease, when the harms profile is reasonable, and when parents or guardians find the whole idea acceptable. Giving multiple compatible vaccinations in a single session may make it more likely that children will receive the full range of recommended vaccines, and despite concerns about overloading infants’ immune systems we can find no evidence of harm. So does this mean we should vaccinate all newborn children with all available vaccines against all targetable diseases?

Knowledge about disease threat is crucial

No. The main evidence that should be used to guide the development of vaccine schedules is the threat that the targeted diseases pose in the first years of life. The threat assessment should include potential morbidity, mortality, and disability from the disease in question, as well as the risk of exposure to the disease. This type of evidence could even be more important in ascertaining the net benefit of a vaccine than detailed knowledge of efficacy.

Even if the threat of disease is remote, vaccination would still be warranted if the disease is associated with an unacceptable risk of morbidity and disability, as in the case of polio in rich countries. Assessment of the threat posed by the targeted disease should be based on public health surveillance, but surveillance has often been of low quality and there may be no reliable incidence data for a disease targeted by a new vaccine.

For most of the vaccines in The BMJ infographic,6 the evidence of efficacy is apparently good. However, because detailed reports for most clinical trials of vaccines are not available, and have not been independently reviewed, we cannot be certain of vaccines’ harms profiles.

For some vaccines, early age at first vaccination necessitates extra boosters in an attempt to maintain sufficient antibody response. In these cases, the decision when to vaccinate is tied to threat assessment: if the threat is present around birth an extra booster is well worth the lowered disease risk. This is the case for meningitis B vaccine, which requires four doses when started at 4 months of age but only three injections to obtain the same response when the vaccination is started at 6 months.13

Balancing the age at first dose with the number of doses should ideally be based on the families’ perception of threat. Even if the threat of a particular disease is of low level or unknown, the possibility of some diseases may trigger alarm and anxiety in some families. If governments decide to offer a vaccine but many families refuse it the policy may be ineffective.

Better evidence

In summary, the vaccine schedule is a function of different interventions, contexts, and values. The evidence base used in designing schedules is incomplete. So how can we improve current practice? We should start by carrying out a more accurate assessment of the magnitude of disease threats. Those vaccines not targeting impending or credible threats should then be phased out or delayed. We also need randomised trials comparing different vaccination schedules to provide good quality data on the potential harms of single or multiple vaccinations. All aspects of vaccination should be monitored and assessed by independent studies.

A recent infographic in The BMJ highlighted variation in vaccination schedules. Kathryn Edwards and colleagues argue that schedules are based on good evidence and robust processes but Tom Jefferson and Vittorio Demicheli think we need to know more about threat of disease

Competing interests: All authors have read and understood BMJ policy on declaration of interests and declare the following interests. KME has served on a data safety and monitoring committee for an influenza trial funded by Novartis and has conducted a vaccine trial of group B streptococcal vaccines funded by Novartis. Funds from these efforts were provided directly to Vanderbilt University; YM is a member of a data safety monitoring board for Pfizer; CLB has intellectual property in and receives royalties from BioFire Diagnostics. The American Academy of Pediatrics has received funding to promote child health, including immunisation programmes, from Pfizer, GlaxoSmithKline, Merck, MedImmune, Novartis, and Sanofi Pasteur. TJ and VD are both former coordinators of the Cochrane vaccines field. TJ was a recipient of a UK National Institute for Health Research grant for a Cochrane review of neuraminidase inhibitors for preventing and treating influenza.
In addition TJ receives royalties from his books. TJ is occasionally interviewed by market research companies about phase I or II pharmaceutical products. In 2011-13, TJ acted as an expert witness in a litigation case related to oseltamivir and in a labour case on influenza vaccines in healthcare workers in Canada. He has acted as a consultant for Roche (1997-99), GSK (2001-2), Sanofi-Synthelabo (2003), and IMS Health (2013) and in 2014 was retained as a scientific adviser to a legal team acting on oseltamivir. In 2014-15 TJ was a member of two advisory boards for Boerhinger and is in receipt of a Cochrane Methods Innovations Fund grant to develop guidance on the use of regulatory data in Cochrane reviews. He is a member of an independent data monitoring committee for a Sanofi Pasteur clinical trial. VD is employed by the Italian National Health Service and provides advice on vaccination policies both at regional and national level.

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