HUMAN VACCINES & IMMUNOTHERAPEUTICS
2018, VOL. 14, NO. 12, 2900–2903
https://doi.org/10.1080/21645515.2018.1496771

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COMMENTARY

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Implementation and assessment of vaccination programmes: the importance of vaccination sequence for overall health outcomes

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ABSTRACT

In addition to their effect on the target infections, accumulating evidence indicates that vaccines have non-specific effects. Live measles vaccine (MV) has beneficial NSEs reducing mortality by more than can be explained by preventing measles infection. In contrast, non-live diphtheria-tetanus-pertussis vaccine (DTP) has negative NSEs; in spite of protecting against diphtheria, tetanus and pertussis, it is associated with increased mortality. The most recent vaccine has the strongest effect on child health, and therefore sequence of vaccines is important.

There is consistent evidence that DTP with or after MV is associated with increased mortality compared with having MV as the most recent vaccine, but the sequence of vaccines is not considered in the current evaluation and implementation of vaccination programmes.

To maximise the impact of current vaccination programmes on child health, increased emphasis should be placed on receiving MV after DTP. Increasing time with live MV as the most recent vaccine through better adherence to the schedule, and modified recommendations for catch-up vaccinations for children who do not follow the recommended schedule are likely to result in improvements in child health.

ARTICLE HISTORY
Received 5 June 2018
Accepted 22 June 2018

KEYWORDS
Non-specific effects of vaccines; heterologous immunity; expanded programme on immunizations; child mortality

Benefits of vaccination are extended to children worldwide through the Expanded Programme on Immunizations (EPI). The EPI schedule seeks to optimise the protection against target diseases though a number of vaccines during infancy. Timeliness of the scheduled vaccines is considered important because delays render children susceptible to the targeted diseases for a longer period. Once a vaccine has been given, from the perspective of preventing the targeted infections, the order of vaccines is not considered important. This translates to simple recommendations for administration of vaccine doses, which were missed earlier in life, at any later contact.[1] However, increasing evidence indicates that vaccines have non-specific effects (NSEs),[2] affecting the overall health of the child beyond preventing target infections. These effects are strongest as long as a given vaccine is the most recent vaccine[2]. Hence, the sequence and combination of vaccines may be more important than so far appreciated.

In 2013, WHO commissioned a review of the NSEs of the live Bacillus Calmette Guérin (BCG) vaccine, the live measles vaccine (MV) and the non-live diphtheria-tetanus-pertussis (DTP) vaccine.[3] The evidence indicated that the live BCG and MV reduced mortality by more than could be explained by the prevention of tuberculosis and measles infection, respectively. By contrast, the majority of the studies indicated that receiving DTP was associated with increased mortality[4]. Thus, there were marked contrasts between the overall health effects of live BCG and MV on one hand, and the non-live DTP vaccine on the other hand.

The NSEs are most pronounced for the most recent vaccination.[5] Therefore, alterations to the sequence of vaccinations may be important: in addition to affecting susceptibility to the target infection during a delay it may reduce or increase the susceptibility to other infections dependent on the sequence of vaccines. In the WHO review, the importance of sequence of MV and DTP was also studied: Receiving DTP together with MV compared with receiving MV after DTP was associated with 2.29 (1.55–3.37) times higher mortality while DTP after MV compared with receiving MV after DTP was associated with 2.66 (1.04–6.81) times higher mortality.[4] The reviewers concluded that the evidence on NSEs of BCG, DTP and MV and effects of out-of-sequence vaccinations caused sufficient concern to strongly recommend further studies as randomised trials. The paper describing the results of the review ends: "Until the results of such trials are available, detrimental non-specific effects of DTP, if any, can probably be minimised by ensuring that infants receive their routine immunisations according to the currently recommended WHO schedule".[4]

Currently, it is not ensured that children receive their vaccinations according to the recommended WHO schedule. Though DTP is scheduled to be given long before MV in most low-income countries, with 3 doses of DTP-containing

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vaccine scheduled at 6, 10 and 14 weeks of age and MV scheduled at 9 months of age,[6] the recommended sequence is not always followed. Based on 102 datasets from Demographic Health Surveys, analysed in 2014, 6% received a DTP-containing vaccine with or after MV.[7] Hence, the proportion receiving DTP after MV may still be substantial in some populations.

In addition to the data included in the WHO review, further data on out-of-sequence vaccinations also indicate that the sequence of vaccines is important. In northern Ghana, the proportion of children receiving DTP-containing vaccines with or after MV has decreased from 86% in 1989 to less than 1% in 2012.[8] Throughout the period, the mortality of children, who had received DTP or DTP-containing vaccines with or after MV was around 30% higher than for the children, who had received the vaccines in the recommended sequence.[8]

In addition to effects on mortality, receiving DTP after MV may also increase the risk of hospital admissions. In Guinea-Bissau, vaccination status was assessed when children presented for outpatient consultations at the paediatric ward at the national hospital in 2003–04.[9] Among children aged 9–17 months, children who had received DTP after MV had a 1.60 (1.15–2.24) times higher risk of being admitted while children with MV = DTP had 1.51 (1.16–1.97) times higher risk of being admitted compared with children vaccinated in sequence.[9]

Similar patterns have also been observed in high-income countries. In a register based study from Denmark, receiving measles-mumps-rubella vaccine (MMR) after the third dose of DTP-containing vaccine (as a pentavalent vaccine; DTP-inactivated polio-*Haemophilus influenzae* type b) was associated with 14% (12–16%) lower risk of admission for infectious diseases.[10] In contrast, among children who had received MMR after the second dose of DTP, receiving the third DTP after MMR was associated with 1.62 (1.28–2.05) times higher risk of admission for infectious diseases.[10] A recent study from the US also assessed the risk of admission by whether the most recent vaccine was live or non-live. It was observed that having a non-live vaccine as the most recent vaccine was associated with a higher risk of admissions than having a live vaccine as the most recent vaccine, adjusted Hazard Ratio 2.00 (1.75–2.33).[11]

Finally, the effect of providing DTP+ MV+ OPV vs MV + OPV was assessed in a small randomised trial in Guinea-Bissau. The trial found that providing DTP with MV was associated with poorer growth in girls and a tendency towards higher rates of admissions and consultations in the year after randomisation.[12]

Taken together, the available data worryingly indicates that providing an inactivated DTP-containing vaccine (and possibly other inactivated vaccines) with or after the live MV has negative effects on child health.

If these findings are correct, we could improve child health through simple measures. We recommend the following action be taken:

1. Revision of vaccine programme indicators

Currently, the sequence of vaccinations is not reflected in the evaluation of the vaccination programmes. The performance indicators focus on coverage rather than sequence, and there is no incentive to provide the vaccines in the recommended order. Presumably, we could improve the effect of the vaccination programme on child health by ensuring that no inactivated DTP-vaccine is given with or after MV. To underline that this is important, we think a better indicator for the performance of the EPI would be the proportion of children vaccinated timely with MV, after the final dose of DTP-containing vaccine. I.e., rather than reporting only the number of doses of DTP and MV given to children by 12 months, the number of MV doses given should be complemented by the number of doses of MV given to already DTP3 vaccinated children by 12 months.

2. Trials of vaccine schedules to optimise the schedules impact on overall child health

Using MV-after-DTP3 as the main indicator of the vaccination programme may optimise the present programme's effect on child health. However, modifications to the programme, which consider NSEs may have stronger effects. Following the review, WHO's "Strategic Advisory Group of Experts on Immunisation" in 2014 tasked the "Immunization and Vaccines related Implementation Research Advisory Committee" (IVIR-AC) with providing advice on priority research questions and adequate studies to assess the NSE.[13]

In 2017, the WHO IVIR-AC presented protocols for two trials to assess NSEs.[14] In neither of the trials, the existing evidence on the importance of sequence of vaccinations was taken into account in the proposed designs. Follow-up periods include different/co-administered vaccines, and thus, the sketched trials will measure a mix of vaccine effects.[14] One of the outlined trials seeks to define a post-polio eradication MV and DTP vaccination programme.[15] In this trial, the current schedule is planned to be compared with three alternative schedules. In the first alternative schedule, an extra dose of MV is provided with DTP3. In the two other arms, DTP3 is moved to be given with MV at 9–12 months either with or without providing an extra dose of MV with DTP2 (Table 1). All the alternative schedules thus include co-administering MV and DTP for part of the follow-up period. Bearing in mind the existing evidence, this is not likely to be the optimal schedule.

Based on current evidence, a better vaccination programme would require an extra infant vaccination contact to provide MV shortly after DTP (Table 1). We have previously tested alternative "Bandim A" below in Guinea-Bissau and

Table 1. Trial designs for evaluating a potentially better vaccination programme.

	Birth	6w	10w	14w	18w	8mo	9mo
Current EPI schedule:	BCG	DTP	DTP	DTP			
IVIR-AC schedules to be tested							
IVIR-AC arm 1:	BCG	DTP	DTP	DTP+ MV			MV
IVIR-AC arm 2:	BCG	DTP		DTP+ MV			DTP+ MV
IVIR-AC arm 3:	BCG	DTP		DTP			DTP+ MV
Our proposed alternative schedules to be tested							
Bandim A	BCG	DTP	DTP	DTP	MV		MV
Bandim B	BCG	DTP	DTP	MV		DTP	MV

found that in the per-protocol analysis, an extra dose of early MV 4 weeks after DTP3 reduced mortality by 30% (6–48%) compared with the recommended dose of MV at 9 months only.[16] However, OPV campaigns appeared to neutralise the effect of early MV[17] and when we repeated the trial in a context with numerous OPV campaigns in 2012–15, we found no effect on mortality.[18] As a post-polio eradication strategy, we think this would be a better policy than the ones suggested by IVIR-AC. Furthermore, we would also assume that schedule B would be even better, and since children of vaccinated mothers have very low levels of antibodies, this might also be better for controlling measles infection.[18]

3. Reviewing and revising vaccination recommendations for children who do not follow the schedule.

Defining a better vaccination programme, which optimises the overall impact on child health, is high priority, but the policies should also account for the children who do not follow the schedule. With many new antigens being added to the schedule, this also creates more room for departures from the vaccination schedule in the future. When these departures occur, a simple catch-up programme as the one currently used with no consideration of sequence, is unlikely to be optimal.

As described above, we hope that trials of potential better alternative vaccination programmes will be initiated soon. Within such trials, we urge that the infrastructure is also utilised to study how the catch-up programme for children who depart from the recommended schedule is optimised. Dependent on how restrictive the enrolment criteria are defined, there are likely to be a smaller or bigger group of children, who do not fulfil enrolment criteria because their vaccinations have been delayed. Rather than excluding and not studying these children at all, it could be assessed whether a better health outcome for these children could be obtained, for example by not giving a missing third dose of DTP with or after MV.

Conclusion

The accumulating evidence of negative effects of providing the non-live DTP vaccine with or after MV should be utilised in translating evidence to better health for children. If the effects described above are close to reflecting the real life effects of vaccination sequence, the implications are enormous, and the recommendation for the vaccination programme should reflect this. RCTs are called for to test NSEs and potentially improve the vaccination programme; we urge the trial designs to take into account all the evidence. Meanwhile, we may improve the implementation of the current vaccination programme by using MV after DTP3 as the main programme indicator.

Disclosure of potential conflicts of interest

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the Danmarks Grundforskningsfond [DNRF104].

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