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Commentary

The Yin and Yang of the Non-Specific Effects of Vaccines

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The Non-Specific Effects (NSE) of vaccines refers to any other effect of a given vaccine, other than the intended effect of reducing disease from the specific vaccination. This area of public health has received a large amount of attention in recent years, with arguments on both sides suggesting that vaccines have either beneficial or detrimental NSE. So, where did it all start, what does it all mean and how does the present study contribute to our understanding of this complex and emotive issue?

Some of the first evidence of the NSE of vaccines came from a group in Guinea-Bissau studying the introduction of a high titer measles virus into the WHO's Expanded Programme on Immunization (EPI) vaccine schedule (Aaby et al., 1993a; Aaby et al., 1993c). The authors conducted a randomised controlled trial to determine if high titer measles virus (MV), given at 4–6 months, was as effective as the standard MV dose that was being routinely given at 9 months of age. It was, but subsequent studies noted that there was a twofold higher mortality rate in infants given the high titer MV vaccine, and that this effect was seen only in girls, and not boys (Aaby et al., 1993b). It is important to note that both of the MV vaccines are live, attenuated vaccines. Subsequent analysis (Aaby et al., 2003) suggested that the sex-specific mortality associated with high titer MV was due, not to the MV vaccine itself, but the later administration of non-live vaccines, such as the combination vaccine Diphtheria/Pertussis/Tetanus (DPT). Recently, the same group has reanalysed survival data from a more recently developed non-live vaccine, the anti-malarial vaccine, RTS,S (Klein et al., 2016). The data presented in this analysis would also suggest that if the last vaccine you are given is a non-live vaccine (DPT or RTS,S for example), then there is a higher mortality rate in females receiving these vaccines than if you were given a live vaccine as the last vaccine. There appears to be no deleterious NSE for any vaccine in males.

But things are not as bad as they seem. The same group from Guinea-Bissau has shown that if another live vaccine, BCG, is given at the time of birth to underweight babies, there is a significant decrease in all-cause mortality in the first four weeks of life (Aaby et al., 2011). Others have shown that BCG confers a non-specific benefit in adults given influenza vaccination (Leentjens et al., 2015), likely in a process known as "trained innate immunity" (Saeed et al., 2014). It is not currently clear how the deleterious effects of non-live vaccines interrupt the beneficial effects of live vaccines, but more clearly needs to be done to understand these phenomena.

So, where do we go from here? There is no question that vaccines save lives, and millions of them every year where they are administered. One could make the argument that if mortality rates due to the NSE of vaccines are low enough (but nevertheless twofold higher in females), then there is still a population benefit in giving vaccines. In other words, if the vaccine saves more lives by preventing death from disease than it does by causing a death, then there is a population benefit in giving vaccines. But this does not help the parent whose otherwise healthy child has just died from having been administered a vaccine known to induce higher rates of mortality. One might reasonably ask then, given the above evidence, whether we shouldn't be giving non-live vaccines in a sequence where the last vaccine to be given is a live vaccine. Or co-administration of non-live and live vaccines. This is where the present study in this issue of EBioMedicine comes in (Aaby et al., 2017).

In the current study, the authors reanalysed historic data from 37,984 children born in Bangladesh between 1986 and 1999. Although the WHO recommendation is BCG at birth, followed by other EPI vaccines (such as DPT) at later time points, in many areas of the world BCG is co-administered with other vaccines. The authors found that where BCG was given along with DPT, all-cause mortality was reduced even further than when BCG alone was given. This is a striking finding, and suggests that co-administration of a live vaccine (such as BCG) with a non-live vaccine (such as DPT) might reverse the deleterious effects of the non-live vaccine.

As stated above, vaccines save lives. However, this study highlights just how much we don't know about the NSE of vaccines, how they interact when live and non-live vaccines are given together, and indeed whether the current EPI schedule is the best schedule for our global infant population. The WHO itself states that more studies need to be done to understand these effects (WHO, 2014), and this study serves to throw these issues back into the spotlight again.

Disclosure

The author declares no conflicts of interest.

References

Aaby, P., Andersen, M., Sodemann, M., Jakobsen, M., Gomes, J., Fernandes, M., 1993a. Reduced childhood mortality after standard measles vaccination at 4–8 months compared with 9–11 months of age. BMJ 307 (6915), 1308–1311.

Aaby, P., Knudsen, K., Whittle, H., Lisse, I.M., Thaarup, J., Poulsen, A., Sodemann, M., Jakobsen, M., Brink, L., Gansted, U., et al., 1993b. Long-term survival after Edmonston-Zagreb measles vaccination in Guinea-Bissau: increased female mortality rate. J. Pediatr. 122 (6), 904–908.

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Aaby, P., Samb, B., Simondon, F., Knudsen, K., Seck, A.M., Bennett, J., Whittle, H., 1993c. Divergent mortality for male and female recipients of low-titer and high-titer measles vaccines in rural Senegal. Am. J. Epidemiol. 138 (9), 746–755.

Aaby, P., Jensen, H., Samb, B., Cisse, B., Sodemann, M., Jakobsen, M., Poulsen, A., Rodrigues, A., Lisse, I.M., Simondon, F., Whittle, H., 2003. Differences in female-male mortality after high-titre measles vaccine and association with subsequent vaccination with diphtheria-tetanus-pertussis and inactivated poliovirus: reanalysis of West African studies. Lancet 361 (9376), 2183–2188.

Aaby, P., Roth, A., Ravn, H., Napirna, B.M., Rodrigues, A., Lisse, I.M., Stensballe, L., Diness, B.R., Lausch, K.R., Lund, N., Biering-Sorensen, S., Whittle, H., Benn, C.S., 2011. Randomized trial of BCG vaccination at birth to low-birth-weight children: beneficial nonspecific effects in the neonatal period? J. Infect. Dis. 204 (2), 245–252.

Aaby, P., Andersen, A., Ravn, H., Zaman, K., 2017. Co-administration of BCG and diphtheria-tetanus-pertussis (DTP) vaccinations may reduce infant mortality more than the WHO-schedule of BCG first and then DTP. A re-analysis of demographic surveillance data from rural Bangladesh. EBioMed. http://dx.doi.org/10.1016/j.ebiom.2017.07.012.

Klein, S.L., Shann, F., Moss, W.J., Benn, C.S., Aaby, P., 2016. RTS,S malaria vaccine and increased mortality in girls. MBio 7 (2), e00514–00516.

Leentjens, J., Kox, M., Stokman, R., Gerretsen, J., Diavatopoulos, D.A., van Crevel, R., Rimmelzwaan, G.F., Pickkers, P., Netea, M.G., 2015. BCG vaccination enhances the immunogenicity of subsequent influenza vaccination in healthy volunteers: a randomized, placebo-controlled pilot study. J. Infect. Dis. 212 (12), 1930–1938.

Saeed, S., Quintin, J., Kerstens, H.H., Rao, N.A., Aghajanirefah, A., Matarese, F., Cheng, S.C., Ratter, J., Berentsen, K., van der Ent, M.A., Sharifi, N., Janssen-Megens, E.M., Ter Huurne, M., Mandoli, A., van Schaik, T., Ng, A., Burden, F., Downes, K., Frontini, M., Kumar, V., Giamarellos-Bourboulis, E.J., Ouwehand, W.H., van der Meer, J.W., Joosten, L.A., Wijmenga, C., Martens, J.H., Xavier, R.J., Logie, C., Netea, M.G., Stunnenberg, H.G., 2014. Epigenetic programming of monocyte-to-macrophage differentiation and trained innate immunity. Science 345 (6204), 1251086.

WHO, 2014. Meeting of the Strategic Advisory Group of Experts on immunization, April 2014—conclusions and recommendations. Wkly Epidemiol. Rec. 89 (21), 221–236.