

52. Garly ML, Jensen H, Martins CL *et al.* Hepatitis B vaccination associated with higher female than male mortality in Guinea-Bissau: an observational study. *Pediatr Infect Dis J* 2004;23:1086–92.
53. Aaby P, Garly ML, Nielsen J *et al.* Increased female-male mortality ratio associated with inactivated polio and diphtheria-tetanus-pertussis vaccines: Observations from vaccination trials in Guinea-Bissau. *Pediatr Infect Dis J* 2007;26:247.
54. Benn CB, Lund S, Fisker A, Jørgensen MJ, Aaby P. Should infant girls receive micronutrient supplements? *Int J Epidemiol* 2009;38:58–90.
55. Benn CS, Netea MG, Selin LK, Aaby P. A small jab – a big effect: non-specific immunomodulation by vaccines. *Trends Immunol* 2013;34:431–39.
56. Welsh RM, Selin LH. No one is naïve: The significance of heterologous T-cell immunity. *Nature Rev* 2002;2:417–26.
57. Kleinnijenhuis J, Quintin J, Preijers F *et al.* BCG induces NOD2-dependent non-specific protection to reinfection via epigenetic reprogramming of monocytes. *Proc Natl Acad Sci U S A* 2012;109:17537–42.

Commentary: Potential implications of non-specific effects of childhood vaccines

Harshpal Singh Sachdev

Department of Pediatrics and Clinical Epidemiology, Sitaram Bhartia Institute of Science and Research, B-16 Qutab Institutional Area, New Delhi 110016, India. E-mail: hpssachdev@gmail.com

International Journal of Epidemiology, 2014, 653–654
doi: 10.1093/ije/dyu109



The World Health Organization states that: ‘A vaccine is a biological preparation that improves immunity to a particular disease. A vaccine typically contains an agent that resembles a disease-causing microorganism, and is often made from weakened or killed forms of the microbe, its toxins or one of its surface proteins. The agent stimulates the body’s immune system to recognize the agent as foreign, destroy it, and ‘remember’ it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters’.¹ This statement is in conformity with the usual scientific and lay perceptions that vaccines have only specific disease-protective effects. However, historically it has been suspected that *Vaccinia*² and BCG vaccination³ confer protection against non-targeted infectious diseases. Emerging evidence suggests that vaccines can positively or negatively affect the resistance to other infectious diseases—the so-called non-specific effects of vaccines or non-specific immunomodulation by vaccines. The bulk of this evidence has been generated from Guinea-Bissau by researchers led by Peter Aaby. The current status of global evidence has been summarized by them in this issue of *IJE*⁴ and elsewhere.⁵ On this basis, they also suggest a new definition of vaccines: ‘A vaccine is a biological preparation that improves immunity to a particular disease and at the same time, may alter the general level of resistance towards unrelated pathogens in the recipient’.⁵

If this perception is indeed true, it may have important public health implications especially in relation to child survival in high-mortality settings. The relevant findings are: (i) BCG and measles vaccinations reduce mortality from non-targeted infectious diseases till the child receives an inactivated vaccine; (ii) whole cell DTP vaccine increases mortality from infections other than diphtheria, tetanus and pertussis until a live vaccine is given; the effect is stronger in females than in males; and (iii) live and killed vaccines may interact to produce good or bad non-specific effects when given simultan-

ously or when the sequence is changed, and the effect may be modified by Vitamin A.⁶ There may well be potential implications for high-income countries, if the following observations are confirmed: (i) in Danish children, rates of hospital admission for any infection were lower in children most recently vaccinated with live MMR vs those most recently receiving inactivated DTaP-IPV-Hib;⁷ and (ii) BCG vaccination had a small protective effect against development of asthma.⁸

This accumulated evidence has not influenced global immunization policy, because of epidemiological and biological plausibility concerns. A major criticism is that a substantial proportion of the evidence emanates from poor West African populations, with high child mortality risks reflecting their infectious disease burden, which evidence cannot be generalized to other settings with a different profile of target diseases. However, recently corroborative evidence has also emerged from other African and South Asian high-mortality settings; investigators from the Guinea-Bissau team were co-authors in some of these publications.⁴ Second, the bulk of the evidence is observational in nature (case-control and cohort studies), which is prone to residual confounding and other biases including selection, survival, attrition and missing data. Simultaneous administration of live oral polio vaccine (OPV) would have almost completely confounded the observations related to whole-cell DTP vaccine. The GRADE rating⁹ of this evidence is unlikely to be above low quality. The few supporting randomized and quasi-randomized trials (none in relation to DTP) are undoubtedly of better quality but are restricted to some regions only. Finally, incomplete understanding of biological mechanisms is a valid but not an indispensable concern. Exciting work has begun to unravel the possible biological mechanisms^{5,10,11} which could be related to cross-reactivity of the adaptive immune system with unrelated pathogens, and to training of the innate immune system through genetic reprogramming.

Given the current state of uncertain evidence, is any modification desirable in the Expanded Programme on Immunisation (EPI) schedule in high-mortality settings? If BCG and measles vaccinations result in additional non-targeted mortality reduction, this should provide impetus for maximizing coverage for BCG inoculation around birth and for two doses of measles vaccination at the recommended ages. Stopping DTP vaccination is not an option because of the risk of resurgence of these serious diseases. However, modifications in the sequencing and timing of the EPI schedule are worth exploring.¹² Currently, DTP is the most recent vaccine for 50 of the first 60 months of life—the vulnerable period, according to the non-specific effect observations. This period can be reduced to 4 months by two additional doses of measles vaccine (at 18 weeks and 19 months) or to 3 months by advancing the measles immunization to 14 weeks and 13 months.¹² It has been extrapolated that these minor modifications in the immunization schedule could reduce child mortality by at least 30%.¹² However, there is insufficient justification to lower the age of first measles vaccination below 9 months until concerns about vaccine failure are addressed in different settings, particularly those with low measles transmission.

There is an immediate need to generate robust evidence to settle this continuing debate. Multi-centric randomized controlled trials in high-mortality settings should examine the benefits and safety of modifications in the sequence and timing of the EPI immunization schedule on a priority. Similar trials are relevant for high-income settings in relation to hospitalizations and non-targeted morbidities. Ethical considerations will preclude randomized experiments for established vaccines. However, imaginatively designed studies can evaluate the sequential introduction of a new vaccine. The sequencing and co-administration of separate immune modulators deserve systematic exploration, especially for other vaccines, drugs or micronutrients (mega-dose Vitamin A supplementation, zinc, Vitamin D).⁵ Basic research to unravel the immunological mechanisms also assumes importance.

In March 2013, WHO's Strategic Advisory Group of Experts (SAGE) constituted a Working Group to revisit the issue of non-specific effects of vaccines included in the routine immunization schedule. Their specific mandate was to determine if the current evidence is sufficient to lead to adjustments in policy recommendations or to warrant further scientific investigation, and if so, to define the path towards obtaining unequivocal evidence on these issues that would support future robust, evidence-based adjustments in immunization policies, if warranted.¹³ These recommendations are awaited with keen interest to guide policy and practice, especially because of the exponential accumulation of supportive evidence over the past 15 years. It is hoped that their counsel will finally pave the path to settle the continuing debate on potential implications of non-specific effects of vaccines.

Conflict of interest: None declared.

References

- World Health Organization. Vaccines. <http://www.who.int/topics/vaccines/en/> (8 April 2014, date last accessed).
- Mayr A. Taking advantage of the positive side-effects of smallpox vaccination. *J Vet Med B Infect Dis Vet Public Health* 2004;51:199–201.
- Naeslund C. Resultats des experience de vaccination par le BCG poursuivies dans le Norrbotten (Suede) Septembre 1927–Decembre 1931. In: *Vaccination Preventative de la Tuberculose de l Homme et des Animaux par le BCG: Rapports et Documents Provenant des Divers Pays (la France exceptee)*. 1932.
- Sankoh O, Welaga P, Debuur C *et al*. The non-specific effects of vaccines and other childhood interventions: The contribution of INDEPTH Health and Demographic Surveillance Systems. *Int J Epidemiol* 2014;43:645–53.
- Benn CS, Netea MG, Selin LK, Aaby P. A small jab – a big effect: non-specific immunomodulation by vaccines. *Trends Immunol* 2013;34:431–39.
- Nolan T. Why are we reviewing the evidence on non-specific effects (NSE) of vaccines on mortality in children <5 years of age? http://www.who.int/immunization/sage/meetings/2013/april/1_NSEforSAGE_Apr_2013_T_Nolan.pdf (10 April 2014, date last accessed).
- Sørup S, Benn CS, Poulsen A, Krause TG, Aaby P, Ravn H. Live vaccine against measles, mumps, and rubella and the risk of hospital admissions for non-targeted infections. *JAMA* 2014;311:826–35.
- Linehan MF, Nurmatov U, Frank TL, Niven RM, Baxter DN, Sheikh A. Does BCG vaccination protect against childhood asthma? Final results from the Manchester Community Asthma Study retrospective cohort study and updated systematic review and meta-analysis. *J Allergy Clin Immunol* 2014;133:688–95.
- Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004;328:1490–94.
- Kleinnijenhuis J, Quintin J, Preijers F *et al*. Bacille Calmette-Guerin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes. *Proc Natl Acad Sci U S A* 2012;109:17537–42.
- Kleinnijenhuis J, Quintin J, Preijers F *et al*. Long-lasting effects of BCG vaccination on both heterologous Th1/Th17 responses and innate trained immunity. *J Innate Immunol* 2014;6:152–58.
- Shann F. Nonspecific effects of vaccines and the reduction of mortality in children. *Clin Ther* 2013;35:109–14.
- SAGE Working Group on non-specific effects of vaccines (established March 2013): Terms of Reference. http://www.who.int/immunization/sage/sage_wg_non_specific_effects_vaccines_march2013/en/ (11 April 2014, date last accessed).