The non-specific effects of vaccines in low income countries

In their commentary on my article about the non-specific effects of vaccines, Paul Fine and David Elliman state that we are dealing with 'unproven non-specific effects' and imply that these effects may not be of widespread importance because 'much of the evidence' comes from Guinea-Bissau.[1] First, proof is never possible in medicine. Second, Fine and Elliman completely ignore the extensive laboratory evidence of the importance of non-specific (heterologous) immunity.[2] Third, attenuated *Mycobacterium bovis* (BCG vaccine) has unequivocal effects on *M tuberculosis*, *M leprae* and bladder cancer. Fourth, I presented evidence from 11 randomised trials suggesting that BCG and measles vaccines reduce mortality from diseases other than tuberculosis and measles—and only two of the 11 trials were performed in Guinea-Bissau.[2] The evidence for non-specific effects is therefore very strong indeed, and most of it comes from outside Guinea-Bissau. Importantly, no randomised trials of adequate power support the assumption that the Expanded Program on Immunization (EPI) vaccines affect only their target disease.

Fine and Elliman state that diphtheria–tetanus–pertussis (DTP) vaccine might 'appear' to increase total mortality under the 'unusual' circumstance of high background infectious disease risks but low pertussis risk. However, even in unimmunised communities, the risk of death from pertussis is low compared to the risk of death from pneumonia, sepsis and diarrhoea—so a relatively low risk of death from pertussis is the norm in high-mortality areas, and is not at all 'unusual'.[3] DTP will therefore increase total mortality if it causes even a small increase in mortality from pneumonia and sepsis, even though it reduces mortality from DTP. Compared to BCG and measles vaccines, there is less evidence that DTP has non-specific effects—but, by the same token, there are no randomised trials of the effect of DTP on total mortality, so we do not have adequate evidence that DTP is safe in high-mortality areas. When DTP was first introduced into Guinea-Bissau (a community with 'high' pertussis risk), mortality was 11.3 per 100 person-years among children given DTP, and 5.1 per 100 person-years among children who did not receive DTP (risk ratio 2.03, 95% CI 1.17 to 3.52).[4] I know of no other study of the introduction of DTP in a high-mortality area that has sufficient power to test the effect on total mortality.

The current EPI vaccines target tuberculosis, diphtheria, tetanus, pertussis, polio and measles, which are not the main causes of death in children. The main reason that the EPI programme has been beneficial may not be because it protects against these diseases, but rather because the non-specific effects of BCG and measles vaccines reduce the very large number of deaths from pneumonia and sepsis.

It is time to accept the clear evidence from immunology and randomised trials that vaccines and infections have non-specific effects, and investigate how we might save several million more lives each year just by making better use of the current EPI vaccines. This exciting prospect should be welcomed enthusiastically, rather than characterised as an unproven hypothesis with little application outside Guinea-Bissau.

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REFERENCES

1. **Fine P,** Elliman D. Non-specific effects of vaccines: in context. *Arch Dis Child* 2010;**95**:661.
2. **Shann F.** The non-specific effects of vaccines. *Arch Dis Child* 2010;**95**:662–7.
3. **Preston SH.** *Mortality patterns in national Populations*. New York: Academic Press 1976.
4. **Aaby P,** Jensen H, Gomes J, *et al.* The introduction of diphtheria-tetanus-pertussis vaccine and child mortality in rural Guinea-Bissau: an observational study. *Int J Epidemiol* 2004;**33**:374–80.