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ANALYSIS

Vaccine programmes must consider their effect on general resistance

Recent randomised trials have shown that live vaccines such as measles and BCG enhance general resistance, preventing other infections as well as the target infection. However, current vaccination strategies assume a proportionate response. **Peter Aaby**, **Hilton Whittle**, and **Christine Stabell Benn** argue that we need to rethink our approach

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Global health leaders have committed to making 2010-19 the decade of vaccines, with the aim of ensuring that lifesaving vaccines are available globally. The Bill and Melinda Gates Foundation pledged $10bn (£6.5bn; €8bn) to the new decade,[1] which was established in recognition of the astonishing technological progress in developing new vaccines and our ethical obligation to make these vaccines available to all children in the poorest countries of the world.[1 2 w1-8] The ultimate goal is to save lives, and vaccination programmes measure potential impact in terms of the lives saved.[1 2 w1]

Surprisingly, therefore, there are few observational studies and virtually no randomised clinical trials documenting the effect on child mortality of any of the existing vaccines. A notable exception is the high titre measles vaccine, which was withdrawn because an interaction with diphtheria-tetanus-pertussis (DTP) vaccine resulted in a 33% (95% confidence interval 2% to 73%) increase in mortality among children aged 4-60 months in several west African randomised trials.[3 w9] Among the newer vaccines, conjugate pneumococcal vaccine has been found to be associated with an 11% (−1% to 21%) reduction in mortality in a meta-analysis.[4]

The lack of data on mortality is not considered a problem. If a vaccine is shown to produce immunity against a specific disease, the effect on survival is estimated using the burden of disease, and the efficacy and the coverage of the specific vaccine. For example, if rotavirus causes 527 000 annual deaths, 90% occurring in low income countries, and the vaccine has efficacies of 71-93% for the different strains of rotavirus and 70% get the vaccine, it is estimated that 273 855 children will be saved by the introduction of rotavirus vaccine in the 72 countries eligible for funding for the vaccine from the GAVI Alliance.[w10]

However, this may not be a valid approach. Evidence is increasing that a vaccine's overall effect on mortality cannot always be estimated from its disease specific effects. For example, the high titre measles vaccine was as efficacious against measles infection as other measles vaccines, but administration of the vaccine at 4-5 months of age was associated with increased child mortality.[3] Furthermore, several vaccines have beneficial effects on child survival that are much larger than explained by prevention of the specific disease.[5-7 w9] The effects of many vaccines also differ for girls and boys.[3 5 8-12 w11 w12]

It is therefore essential to study the effect of vaccines on overall morbidity and mortality in real life situations to estimate the effect on survival. Such an approach will lead to stronger emphasis on general resistance to infections.

Live vaccines enhance general resistance

A focus on health as the absence of specific diseases has led to neglect of the importance of general resistance. We all know that some people get sick less frequently or get less severely sick. This variation in resistance could depend on genetic or socioeconomic differences but may also reflect previous experience with infections.[w13 w14] Animal studies document that an infection with one organism may produce heterologous immunity, which reduces or enhances the risk of dying from a subsequent infection with a completely different organism.[13 14] The same probably happens in humans, and vaccines may act in lieu of the primary infection, enhancing general resistance through cross reacting T cell responses.[w15] In animal studies examining live and inactivated vaccines containing the same antigens, live vaccines produce a T helper 1 (Th1) profile of immune responses whereas inactivated vaccines are associated with a Th2 profile. This difference is important for the response to a subsequent challenge because animals with a Th2 profile become more severely infected.[w16 w17 w18 w19 w20] Our randomised

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trials of live vaccines, including BCG and measles, found large reductions in child mortality that were unrelated to protection against tuberculosis and measles infection.[5-7] These effects persist until the next vaccine is administered.

BCG vaccine

Several observational studies have suggested that BCG has a beneficial non-specific effect on child survival.[15 w21] In six controlled trials including 45 662 children in the United States and the United Kingdom in the 1940s and 1950s, BCG reduced mortality from causes other than tuberculosis by 25% (6% to 41%).[16] More recently, in two randomised trials in Guinea-Bissau,[6 7] BCG reduced neonatal mortality in low birthweight babies by nearly 50% (table 1⇓). The main effect seems to be due to a reduction in neonatal sepsis and respiratory infections[6 7]—that is, BCG enhances resistance to infections other than tuberculosis. In animal studies BCG induces heterologous immunity to vaccinia virus in mice in just 1-2 days.[17] As several randomised trials show similar results, this is likely to be a repeatable effect.

Measles vaccine

The introduction of measles vaccine substantially improved child survival in Africa. Only three studies have examined the same population before and after the introduction of measles vaccine (table 2⇓).[18-20] The reduction in mortality was 50% or more. Since all children were not vaccinated, the real effect of measles vaccine is likely to be even stronger. In two of the three studies,[18 19] measles vaccine was the only intervention; in the last study[20] other vaccines were also introduced. Measles infection is unlikely to account for more than 10-15% of the deaths,[w22] suggesting that measles vaccine may enhance resistance to unrelated infections. We tested this in a randomised trial by giving an extra dose of measles vaccine at 4.5 months of age in addition to the standard dose of measles vaccine at 9 months. Compared with one dose of measles vaccine at 9 months, two doses of measles vaccine at 4.5 and 9 months reduced overall mortality in children aged 4.5 months to 3 years by 30% (6% to 48%),[5] with girls benefiting more than boys.

In fact, the actual benefit is probably even greater. We had previously found that neonatal vitamin A supplementation had a slightly negative effect on survival in the same population.[8] Among children who had not received vitamin A at birth, two doses of measles vaccine reduced overall mortality by 50% (22% to 68%).[5] If we exclude deaths from measles, the reduction in overall mortality was 45% (14% to 65%); hence, the reduction was not due to prevention of measles infection. Measles vaccine was particularly beneficial for children who had maternal measles antibodies at the time of vaccination.[w23] Many other studies have suggested that measles vaccine has a beneficial non-specific effect on child survival, particularly when inactivated vaccines are not administered after measles vaccine.[3 w13 w14 w24] Our results are supported by a randomised trial from Sudan that showed a similar benefit on child survival from an early two dose schedule of measles vaccine (table 3⇓).[9] Thus it seems likely that an early two dose schedule is better than the current policy of one dose at 9 months of age.

Diphtheria-tetanus-pertussis (DTP) vaccine

Unfortunately some inactivated vaccines may reduce general resistance and have negative effects on child survival.[3 10 15] When we introduced DTP in rural Guinea-Bissau in the mid-1980s, mortality was twofold higher for those who received DTP than those who did not, with girls being particularly affected.[10] No other study has measured the effect of introducing DTP, but several observational studies suggest that DTP may be deleterious in high mortality regions[3 15 w25]—for example, low birthweight girls given DTP vaccine at 2 months had sixfold higher mortality than unvaccinated girls between 2 and 6 months of age.[12] Another small randomised trial found that giving DTP and measles vaccines simultaneously was associated with increased morbidity and poorer growth compared with measles vaccine alone.[w26] In randomised trials of early measles vaccine, mortality among girls was increased when DTP was given after measles vaccine,[w27] and this was the likely cause of the increased mortality after high titre measles vaccine.[3]

Other inactivated vaccines have also been associated with increased female mortality.[w27 w28] Though the World Health Organization's Global Advisory Committee on Vaccine Safety has deemed it unethical to withhold or delay DTP,[w29] it has also indicated that conclusive evidence about the non-specific effects of vaccines, including the possible harmful effects of DTP, is unlikely to be obtained from observational studies.[w30] Hence, there is an urgent need to conduct randomised trials to test the effect of DTP on child survival. Designs to test the overall effect of DTP have been discussed by the working group on the non-specific effects of vaccines.[21]

Implications

The effect of the old vaccines (BCG, measles, oral polio, and DTP) on overall mortality was not assessed before they were introduced. It was merely assumed that an effective vaccine would reduce mortality in proportion to the burden of that disease. The global health community therefore did not realise that live vaccines like BCG and measles vaccine had far better effects than expected.[5-7] The non-specific effects of vaccines have important implication for vaccination policy.

The decade of vaccines focuses entirely on the disease specific approach and the ultimate success would be to eradicate the disease and stop vaccination.[1 2 w1-8] However, if a vaccine such as measles has general beneficial effects on resistance it may increase overall mortality to remove that vaccine or change the age of vaccination. For example, when the age of vaccination was increased from 9 months to 12 months in Latin America after measles was eliminated,[22] no study was made of the health effects of this change for children aged 9 to 11 months. Also, if BCG were to be replaced with a new TB vaccine that did not enhance general resistance or was given to an older age group, child mortality might increase even though TB control had improved. Both measles and polio are targeted for eradication.[2] Hence, the unintended harmful effects of removing a vaccine with beneficial non-specific effects may soon become important. More than 20 years after smallpox vaccinations stopped, we have found that smallpox vaccination was associated with better survival and fewer hospital admissions.[w31 w32] The eradication of smallpox and smallpox vaccination may therefore have had unintended harmful consequences.

The randomised trials of BCG and measles vaccine suggest that in terms of lives saved, enhancement of general resistance is far more important than specific disease prevention.[5-7] Thus immunisation programmes could have a much larger effect on child survival if we tailored vaccination policies according to their effect on survival. Since the most recent vaccination has the strongest effect on resistance, it would make sense to ensure that live vaccines are the most recent vaccination throughout childhood. Inactivated vaccines like DTP, which are effective against specific diseases but may reduce general resistance,[3 10 12 15 w25] should ideally be replaced with vaccines

that do not reduce general resistance. Until that is possible it may reduce mortality to give a live vaccine shortly after DTP. For example, we have shown that giving measles vaccine shortly after the third dose of DTP[5] or giving BCG after booster DTP[23] reduces overall child mortality.

A specific vaccine is currently assumed to have the same specific effect as long as the disease is a public health problem. However, the effect of an intervention may change if other factors affect the immune system—for example, new vaccines are added, the sequence of vaccinations is changed,[3] vaccines are administered simultaneously rather than in sequence,[w26] or micronutrients are introduced.[11] What was once a good intervention may cease to provide a benefit because of such interactions. For example, when the timing of measles vaccine changed and DTP was administered after high titre measles vaccine,[3] female mortality increased. Vitamin A supplementation reduced child mortality by around 23% in the original randomised trials in the 1980s and early 1990s[w33] when vaccination coverage was low. However, mortality may increase among girls who receive vitamin A and whose most recent vaccination is DTP.[w12 8 11 w34] With increasing coverage for DTP, vitamin A supplementation may no longer provide a benefit.[w34 w35] There are many more examples of interactions between vaccines or between vaccines and vitamin A.[5 23] Interactions between interventions need more study to ensure that the overall effect is still beneficial.

Another problem is that vaccines are assumed to have similar effects in boys and girls. However, they have different immune responses to some vaccines,[w15] and this may affect general resistance to infection and child mortality.[3 5 w11 w128-11] In animal studies females have a stronger Th2 profile than males,[w20] and this could be important for the response to live and inactivated vaccines.[w19] For example, the beneficial effect of measles vaccine may be stronger for girls than for boys.[5 w11] DTP after measles vaccine is associated with twofold higher mortality for girls but has little effect for boys.[3 w27] Administration of vitamin A may amplify the negative effect of DTP for girls but may benefit boys.[8] Hence, the optimal vaccination policies might have to differ for boys and girls. New vaccines should be examined for possible sex differences.

In conclusion, to benefit from the many new vaccines we need to examine their overall effects on morbidity and mortality, the sequence in which the new vaccines are given, whether they interact with other common interventions, and whether the effects are similar for girls and boys. Given that the ultimate goal of vaccination is to reduce child mortality, understanding the biological basis of both the beneficial and potential harmful non-specific effects of vaccines may further enhance their life saving benefits.

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Tables

Table 1| Neonatal mortality (0-28 days) among low birthweight children in two randomised trials of BCG vaccination at birth, Guinea-Bissau

	Mortality (%)		
Study year	BCG at birth	Controls	Mortality ratio (95%CI)*
2002[6]	4 (2/50)	11 (6/54)	0.28 (0.06 to 1.37)
2004[7]	2.3 (27/1168)	4.2 (48/1152)	0.55 (0.34 to 0.89)

* Adjusted for clustering on same-sex twin pairs. The combined estimate for the two trials was 0.52 (0.33 to 0.82).[6]

Table 2| **Community mortality rate before and after the introduction of measles vaccine**

Study site	Age group (months)	Years compared	Mortality rate (%) (No of deaths/person-years)		Mortality rate ratio (95% CI)*
			Before vaccination	After vaccination	
Kasongo, Congo[18]	7-21	1973-74 *v* 1975-77	6.1 (21/346)	2.0 (8/392)	0.34 (0.15 to 0.76)
Bissau, Guinea-Bissau[19]	6-35	1979 vs 1980	12.7 (77/605)	4.7 (29/615)	0.37 (0.24 to 0.57)
Bandafassi, Senegal[20]	9-60	1981-86 *v* 1987-88	7.4 (345/4638)	3.7 (76/2026)	0.50 (0.39 to 0.65)

*After introduction of vaccine versus before.

Table 3| Mortality rate ratio in randomised trials of early two dose measles vaccination versus vaccination at 9 months

Study	Follow-up age (months)	Mortality rate (deaths/person-years)		Mortality rate ratio (95% CI)†
		Early vaccination*	Vaccination at 9 months	
Sudan; 1989-1992[9]	5-36	8/432	13/417	0.60 (0.25 to 1.40)
Bissau, 2003-9[5]	4.5-36	25/2453	96/4703	0.50 (0.32 to 0.78)

*Participants received two doses of measles vaccine at 4-5 months and at 9 months.

†The combined estimate for the two trials was 0.52 (0.35 to 0.77).