Letters

Non-specific effects of vaccination

Vaccines have non-specific (heterologous) effects

EDITOR—I support Fine's plea that we review the optimal immunisation schedule in developing countries using evidence from controlled trials rather than observational data.[1] There are almost no controlled trials of the effect on mortality from all causes for any of the vaccines in the World Health Organization's schedule.

Fine says, incorrectly, that literature does not support non-specific effects of vaccines.

Firstly, BCG protects against leprosy and is the treatment of choice for some types of bladder cancer.[2]

Secondly, an individual's history of previous infection or immunisation can clearly influence the response to subsequent infections—immunologists call this heterologous immunity, rather than non-specific immunity.[3 4]

Thirdly, evidence that vaccines have heterologous effects comes from controlled trials, and not just observational studies.[5]

It is important to be clear about what is meant by the hypothesis that vaccines have heterologous (non-specific) effects. The hypothesis says that in high mortality areas, vaccines may affect mortality from diseases other than the target disease (for example, measles vaccine may reduce mortality from infectious diseases other than measles); these effects are much stronger in girls than boys; they are strongest in the first three to six months after immunisation; and they are largely determined by the most recent vaccine received.

The immunological basis of heterologous immunity is now well established,[3 4] and this knowledge should be used to help design controlled trials to determine the optimal immunisation schedule for children in developing countries. Millions of lives could be saved.

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Competing interests: None declared.

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Author's reply to Shann

EDITOR—Shann rightly questions the subtitle to my editorial, "Literature does not support either beneficial or detrimental effects." I did not write it and failed to note its insertion by the editor at the last moment before the article went to press—for which I apologise.

Of course, there are many well documented non-specific effects of vaccines, two of which I mentioned explicitly: "Some vaccines have effects on non-target diseases—for example, BCG protects against leprosy. Some vaccines have rare adverse reactions—for example, myopericarditis after smallpox vaccine."

The existence of some non-specific effects is not an issue—and they extend far beyond the limits of the hypothesis proposed in Shann's letter. My scepticism was, and remains, aimed at the spate of studies on the supposed "non-specific effects" (both beneficial and detrimental) of vaccines on mortality, typified by the paper by Vaugelade et al and several by Aaby et al.[1 2 3]

These studies faced very difficult methodological challenges and have been unable convincingly to get round the obvious huge confounding associated with the selective distribution of vaccines. Given that confounding, the only way rigorously to study such outcomes is by trials, and these may be justified not only to study these proposed non-specific effects (some will believe there is insufficient a priori evidence of such effects to justify the cost of trials) but to compare different vaccine regimens and timetables, and with specific disease incidence as well as non-specific morbidity and mortality among the measured outcomes.

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Competing interests: PF has attended several conferences on vaccines, which were subsidised by manufacturers of vaccines.

1 Vaugelade J, Pinchinat S, Guiella G, Elguero E, Simondon F. Non-specific effects of vaccination on child survival: prospective cohort study in Burkina Faso. *BMJ* 2004;329:1309-11. (4 December.)
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Survival bias may explain findings

EDITOR—Vaugelade et al found the BCG and diphtheria-tetanus and pertussis vaccines (DTP) to be associated with reductions in mortality greater than expected from disease prevention.[1] However, as they admit, dead vaccinated children may have been misclassified because their vaccination cards were destroyed.

In a survival analysis using vaccination dates as time dependent covariates, surviving children change status at date of vaccination even though vaccinations were only known later, whereas dead vaccinated children and their follow up time remain in the unvaccinated group.[2 3] As a result, risk free survival time will be allocated to the vaccinated group, creating survival bias.[2] Consequently, mortality is too high in unvaccinated children; 45% of children were vaccinated before age 6 months, but only 12 vaccinated children died compared with 435 unvaccinated children. This corresponds to an unlikely mortality that is 10-15 times as high among unvaccinated children younger than 6 months. In contrast, mortality in Guinea-Bissau was only twice as high.[4]

To control for misclassification, Vaugelade et al claim to replicate our analysis, using time fixed vaccination status. However, these analyses had several methodological differences.[4] Most importantly, we registered non-vaccination and excluded 35% for missing information,[5] whereas they did not exclude any child.[1] Hence, their "unvaccinated" group included unvaccinated and children without information. This may have inflated mortality, the rate being 129% (76-198%) higher in unvaccinated than vaccinated children, compared with only 35% (−3-89%) in Guinea-Bissau.[5] The reference group may hence be irrelevant and the corresponding estimates of DTP and BCG being associated with 50% reduction in mortality may be misleading.[1]

Vaugelade et al recognised potential misclassification but probably underestimated the effect and therefore maintained the conclusion that BCG and DTP had beneficial effects. However, introducing survival bias in an analysis can turn a negative estimate into a positive one and can therefore not document non-specific effects or provide assurance that DTP has no increased mortality.

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Authors' reply to Aaby et al

Editor—Aaby et al raise issues of general rather than specific interest, as their references indicate. The study of the effects of vaccines, which pioneered the randomised controlled trials method more than 50 years ago, is still topical and of general interest.[1] The limitations discussed by Aaby et al are intrinsic to all observational datasets and, in this respect, the assets of our study are to rely on both independent and shared pre-planned analyses[2] of observational datasets, issued from a country other than Guinea-Bissau. The simulations we performed (which are available on request) on the effects of a possible survival bias logically influenced our estimates towards 1 but did not yield different conclusions.

In addition to the misclassification aspect, causal inference is also an issue at stake. In this respect, we agree with Fine that the conclusion of our study is no evidence for a positive association between any vaccine and increased mortality in infants.[3] Although the title of our paper mimicked that of Aaby et al's work on non-specific effects of vaccines, our conclusion concerned the statistical association, not the effects. Such methodological aspects—misclassification and bias—raised by studies on the effects of vaccines, highlight the need for improved surveillance and implementation of phase VI or pharmacoepidemiological studies in areas with high mortality.

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Competing interests: SP has been a consultant statistician for Aventis Pasteur and Aventis Pasteur MSD on pertussis, rotavirus, and herpes zoster. EE has been funded by Aventis to attend a meeting.

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DTP in low income countries: improved child survival or survival bias?

Editor—We proposed that BCG and measles vaccine have non-specific beneficial effects, whereas diphtheria-tetanus-pertussis (DTP) vaccination might have no beneficial effect.[1] In response, the World Health Organization commissioned several studies.[2–4] A WHO expert task force found substantial evidence against a deleterious effect of DTP; all studies showed DTP to be associated with reduced mortality. A negative DTP effect was found only in Guinea-Bissau, and this was presumed to be due to a country specific issue or a peculiarity of the data.[5]

In our survival analysis, vaccination status was a time fixed variable, held constant from the initial visit to the next; without perfect information for all children, vaccinations during follow-up could not be accounted for, which means a potential source of bias.[1] In the WHO sponsored analyses, vaccination status was a time varying variable changing status at the date of vaccination, based on information achieved at a subsequent visit.[2–5] We used this approach to re-analyse our data (table).

The distribution of deaths was similar. When we used time varying variables, person years decreased for the unvaccinated and BCG groups, and mortality went up. Person years increased for the DTP groups and mortality decreased. Hence, DTP was associated with reductions in mortality (table), similar to results from WHO sponsored studies.[2–4]

Why this difference? Information on vaccinations is typically collected through periodic home visits. When a child dies, the vaccination card is usually thrown away; and information on vaccination is therefore collected conditionally on survival to the subsequent visit. If an unvaccinated child was vaccinated and died before the next visit the death would be classified as unvaccinated, in an analysis using time varying variables. If a vaccinated child survived then the follow up time as vaccinated would be moved to the new vaccination. This survival time is risk free—that is, we only know that the child was vaccinated because it survived. Such survival bias may turn a negative estimate into a positive one: our original 84% increase in mortality for one dose of DTP became a 32% reduction (table).

Survival bias can be avoided only if all vaccinations are provided by the researchers, or perfect vaccination information is obtained from all children. Nothing indicates that these conditions were met in the WHO commissioned studies.[2–4] In contrast

Deaths and person years according to vaccination group, using vaccination status as time fixed or time varying variable, Guinea-Bissau, 1990-6

	Vaccination status as time fixed variable			Vaccination dates as time varying variables		
	Deaths	Person years at risk	Mortality per 1000 person years	Deaths	Person years at risk	Mortality per 1000 person years
Vaccination status						
No BCG+DTP one dose	2	9.0	222	2	16.3	123
No BCG+DTP two doses	0	4.5	0	0	3.5	0
No BCG+DTP three doses	0	1.4	0	0	4.2	0
BCG+no DTP	33	537.6	61	33	334.4	99
BCG+DTP one dose	59	595.5	99	60	679.5	88
BCG+DTP two doses	21	266.6	79	20	443.4	45
BCG+DTP three doses	12	119.6	100	15	425.0	35
Vaccinated	127	1534.2	83	130	1906.3	68
Unvaccinated	95	875.1	109	92	503.0	183
All	222	2409.3	92	222	2409.3	92
Mortality ratio (95% CI)						
Unvaccinated *v* vaccinated		1.35 (0.97 to 1.89)			2.96 (2.15 to 4.08)	
BCG *v* BCG unvaccinated		0.55 (0.36 to 0.85)			0.62 (0.41 to 0.92)	
One dose DTP *v* DTP unvaccinated		1.84 (1.10 to 3.10)			0.68 (0.44 to 1.04)	
Two doses DTP *v* DTP unvaccinated		1.38 (0.73 to 2.61)*			0.26 (0.15 to 0.47)	
Three doses DTP *v* DTP unvaccinated					0.16 (0.08 to 0.32)	

*Two and three doses of DTP were combined in original study.[1]

to our study, none of the WHO studies documented which children were unvaccinated; they do not distinguish between "unvaccinated" and "no information." The contradiction between our study and the WHO sponsored studies might be due to methodological differences and not peculiarity of the data.

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1 Kristensen I, Aaby P, Jensen H. Routine vaccinations and child survival: follow up study in Guinea-Bissau, West Africa. *BMJ* 2000;321:1435-8.
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Phenobarbital for epilepsy: much is still to be learnt

Editor—Kale and Perucca contrast the widespread use of phenobarbital for epilepsy in the developing world with its disfavour in the developed world.[1]

In the developing world up to two thirds or more of people with epilepsy receive no treatment at all.[2] With limited resources and infrastructure health authorities' promotion of a cheap but effective drug, phenobarbital, is understandable and desirable. In developed countries the problem is often overtreatment. In the United Kingdom three other standard anti-epileptic drugs (phenytoin, carbamazepine, valproate) have been joined by eight new anti-epileptic drugs in the past 15 years. Polytherapy is increasing. Many doctors are bewildered by the potential choice of drug or drug combinations.

My colleagues and I conducted one of the few randomised efficacy and toxicity studies comparing phenobarbital with other standard anti-epileptic drugs.[3 4] In adults and children with newly diagnosed generalised or partial seizures long term efficacy was similar for phenobarbital, phenytoin, carbamazepine, and valproate. Neurotoxicity of phenobarbital was only slightly greater in adults but much greater in children. Phenobarbital remains useful in adults but should be used with caution in children if it is the only available drug. When a single drug fails doctors still do not know whether combining two drugs is better than another single drug, or which combination of two drugs is best.[5]

After more than 80 years much is still to be learnt about phenobarbital, the most widely used anti-epileptic drug in the world. The same is true of the standard and newer drugs, and of any combination. To expect the World Health Organization or the International League Against Epilepsy (ILAE) to undertake the necessary clinical trials and basic research is unrealistic. WHO is a public health organisation which promotes best practice within limited existing knowledge and resources, as in the global campaign against epilepsy.[2] Indeed, scientific institutions in the developing world should undertake such studies, either alone or in collaboration with similar institutions in the developed world, especially designated WHO collaborating centres.

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Competing interests: EHR was president of the International League Against Epilepsy 1993-7 and first chairman of the International League Against Epilepsy/International Bureau for Epilepsy (IBE)/WHO Global Campaign against Epilepsy 1997-2001.

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Use of chaperones in general practice

GPs try to balance doctors' and patients' needs

Editor—In two separate papers Rosenthal et al and Conway and Harvey studied the use of chaperones in general practice settings.[1 2] Conway and Harvey say that chaperones are used for the protection of the doctor rather than the patient. We have found that practitioners who perform vaginal examinations feel that they are juggling competing interests when deciding on the offering and use of a chaperone.

We interviewed primary care practitioners about their approach to the management of menstrual disorders.[3] The role of the chaperone was understood as both protecting the doctor and reducing the patient's perception of vulnerability. Practitioners were aware of the guidelines produced by professional bodies and the potential medicolegal consequences of not using a chaperone. A chaperone could, however, adversely affect patient and consultation.

In keeping with general social perceptions, female patients being examined by male doctors were considered most vulnerable and hence in most need of a chaperone. Protecting the patient from vulnerability and embarrassment required that the chaperone be of the same sex as the patient. The use of a male chaperone for the examination of a female patient or of a female chaperone when a male patient was being examined was judged inappropriate by interviewees of both sexes.

For many practitioners, blanket guidelines were a source of stress. In primary care, where patients may choose the doctor they see, practitioners judged that many patients had already made a decision about which doctor they felt comfortable consulting. Suggesting that a chaperone might be required was perceived as introducing into a previously good relationship between doctor and patient the idea that the doctor was not trustworthy. More experienced practitioners argued that the key to reducing difficulties for practitioners and patients lay in better communication training.

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1 Rosenthal J, Rymer J, Jones RH, Haldane S, Cohen S, Bartholomew J. Chaperones for intimate examinations: cross sectional survey of attitudes and practices of general practitioners. *BMJ* 2005;330:234-5. (29 January.)
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Chaperones protect both parties

Editor—The two papers on the use of chaperones in general practice are relevant to genitourinary medicine (GUM) clinics, where intimate examinations are routine.[1 2] In response to recent guidance we published and repeated a survey on patients' preferences for chaperones (table).[3–5]

Doctors completed proformas before intimate examinations of patients, over consecutive sessions from June to December 2003. Patients declined chaperones because they trusted the doctor, thought it unnecessary, wanted privacy, were embarrassed, or were not bothered. Ninety two per cent of patients (232/252) were offered a chaperone; 22% (52) accepted, 12% (27) expressed no preference, and 66% (153) declined.

Significantly fewer male patients accepted chaperones than female patients (3.0%, 95% confidence interval 0.6% to 8.4%, and 37.4%, 29.1% to 45.7%, respectively). Significantly more female patients accepted chaperones from male doctors (85.4%) than from female doctors (9.6%; $P \leq 0.001$, χ^2 test).

Most patients declined chaperones, except when the doctor was male and the patient female. We continue offering chaperones to all patients requiring intimate examinations, which has not affected workload. However, Conway and Harvey found

Results of chaperoning survey. Values are numbers of patients unless otherwise indicated

Type of consultation	Patients seen by doctor	Chaperone not offered	Chaperone offered	Chaperone accepted (%)
Female patient:				
Female doctor	93	10*	83	8 (9.6)
Male doctor	56	8†	48	41 (85.4)
Male patient:				
Female doctor	44	2‡	42	1 (2.4)
Male doctor	59	0	59	2 (3.4)

*No reason given (6), doctor forgot (1), language difficulties (1), mother present (1), sexual assault (1).
†Considered necessary because of male doctor.
‡ Doctor forgot (1), examined by male doctor instead (1).

that nearly half of male general practitioners never and rarely used chaperones when intimately examining women. Some used receptionists as chaperones, which is unsuitable in genitourinary medicine.[1] Rosenthal et al found that only 37% of general practitioners had a chaperoning policy, but lack of staffing and resources are unacceptable excuses.[2]

Doctors who continue performing intimate examinations unchaperoned risk allegations of misconduct.[5] Chaperones are there for the protection of both parties. Perhaps further guidance will arise for other healthcare professionals, who until now may see patients unaccompanied.

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Ethics and research governance in a multicentre study: add 150 days to your study protocol

Editor—Concern is growing that health service research will be impeded by "research governance" procedures, in addition to the difficulties of gaining ethical approval.[1-3] We describe the problems experienced by an evaluation study team (funded by the Service Delivery and Organisation Research Programme) that wanted to assess the impact of modernising endoscopy services in 20 NHS Trusts in England. Ethical approval was given by a multicentre research ethics committee in 47 working days. Achieving research governance approval was more difficult.

The study used postal surveys of patients to assess the impact of endoscopy service innovations on waiting times and other outcomes, using validated quality of life, patient satisfaction instruments, and health economic data. A qualitative component used interviews with clinicians, change agents, and patients. No experimental intervention was undertaken.

The range of familiarity with research governance "approval" procedures in NHS trusts was wide, from full awareness to total ignorance, illustrated by two trusts providing immediate verbal approval. Substantial variation occurred in the application procedures. Many trusts required more information than the ethics committee, such as confirmation of sponsor and copies of peer review reports (often not made available to researchers). Documentation was "lost" in two trusts.

Some trusts gave approval authority to one person while others relied on research and development committees, which typically sat monthly. These committees often had long lead times and full agendas, resulting in delays. One such trust committee imposed its own "research" conditions, altering the protocol and leading to the site being abandoned, to the dismay of the trust clinician who wanted to participate.

In summary, the research governance framework has been interpreted in many different ways.[4 5]

The figure shows the number of working days from application to final approval. The median time to approval was 61 days (95% confidence interval 51 to 81 days); the most time taken was 103 days (equivalent to 5 months). Applications took place from November 2003 to March 2004, and to exclude the possibility of improvements taking place over time we estimated a possible correlation (Spearman's r) between the order of the application and the time taken. We found a non-significant ($P = 0.22$) negative correlation ($r = -0.28$), indicating that order had no effect.

Obtaining research governance approval for all 20 NHS trusts required 103 days. This is a rate limiting step, as a simultaneous start was needed across all 20 sites. With the addition of the 47 days taken to obtain ethical approval, this resulted in a total delay of 150 days.

Research studies requiring multiple NHS sites should build in substantial lag times before research processes can be initiated. We anticipate that failure to address this new obstacle to health service research will block evaluation work and accelerate the migration of clinical studies to other parts of the world.

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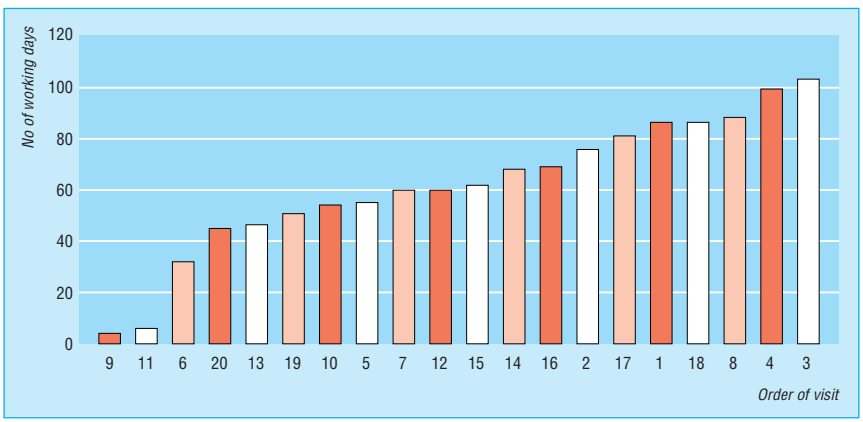

Time taken to gain approval for research and development from trusts