Efficacy of gene therapy for SCID is being confirmed

In this issue of *The Lancet*, Bobby Gaspar and colleagues report successful immunological correction in four patients with the X-linked form of severe combined immunodeficiency (SCID-X1), a disease characterised by a block in the differentiation of T and natural-killer cells as a consequence of defective expression or function of γc-cytokine receptor-subunit, or both.[1]

Gaspar and colleagues' report is welcome because they confirm data from a previous report that described a correction of immunodeficiency in nine of ten patients with SCID-X1.[2,3] Meanwhile, Aiuti et al[4] had previously reported the successful correction of the immunodeficiency caused by adenosine deaminase (ADA) deficiency in two (and now four) patients. Thus the four cases described in Gaspar and colleagues' report from London bring to 18 (ie, 14 with SCID-X1 and four with ADA deficiency) the total number of SCID patients treated by an optimised ex-vivo retroviral-mediated gene-transfer protocol into CD34+ haemopoietic precursor cells. Remarkably, 17 of these 18 patients had their immunodeficiencies corrected with clear and sustained clinical benefits. The data show that the results of this gene-therapy strategy are reproducible.

However, the therapy relies on the growth advantage provided to transduced lymphocyte precursors in the SCID environment. The kinetics of T-cell development and sustained benefit appear to be independent from the conventional variables that influence the outcome of allogeneic haemopoietic stem-cell transplantation, such as age, clinical status (especially pulmonary infection), and degree of HLA disparity between donor and recipient.[5] In SCID-X1, a conditioning regimen is dispensable, which thus prevents the early lethal toxicity observed in many severely infected patients who receive haploidentical haemopoietic stem-cell transplants. The absence of graft-versus-host disease in this situation also contributes to a potentially more favourable outcome. Therefore, because haploidentical haemopoietic stem-cell transplantation carries a good prognosis (survival ⩾95%)[6,7] in SCID patients aged less than 3 months old, and accounting for the potential adverse effect of gene therapy (see below) in that age group, it is reasonable to restrict gene therapy to SCID patients older than 3 months of age. Despite the low number (14) of SCID-X1 patients treated so far, we can see a correlation between the number of transduced precursor CD34+ cells injected and the quality of immunodeficiency correction. For future applications of this gene-therapy strategy, a lower threshold of about 3 million CD34+γc+ cells per kg of bodyweight can be defined.[2,3] The London protocol is different from the Paris protocol[2] because in Gaspar's protocol there is no fetal calf serum in the culture medium and the gibbon-leukaemia-virus envelope is used. Both factors could have a role in the apparently higher transduced rate achieved in B and myeloid cells compared with that seen with the Paris protocol. A longer follow-up will tell whether the higher transduced rate is relevant for long-term persistence of effective immunity, as suggested by the transduction of immature progenitor cells.

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Clonal T-cell lymphoproliferations occurred in two patients with SCID-XI who were successfully treated in Paris by gene therapy.[2,8] The lymphoproliferations have obviously raised concerns about the safety of this strategy. So far, none of the patients treated in London have developed any severe adverse effects, nor have any of the patients manifested biological evidence of lymphoproliferation. Although the data are still preliminary, they support an association between the risk of severe adverse events and the patient's age (⩽3 months) at the time of gene therapy.[8] Age as a safety consideration, balanced with the efficiency of gene therapy, which looks more efficient than conventional haploidentical haemopoietic stem-cell transplantation, has led researchers to resume the French trial with a lower age restriction (ie, the patient needs to be older than 3 months). Trials in the UK and USA are ongoing. The age restriction does not eliminate the need to improve the safety of vectors designed for future trials. A specific concern is avoiding the enhancer activity of the retroviral vectors' long-terminal repeat.[3] Overall, the available reports of gene therapy's efficacy in SCID-X1 and ADA deficiency[2,4] should encourage researchers to extend the treatment to target other life-threatening immunodeficiencies and, possibly, other genetic diseases of the haemopoietic system. In extending gene therapy to treat other conditions, we must carefully monitor patients, not only to detect potential toxic effects, but also to guide the setup of safer and more efficient gene-transfer strategies.

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We declare we have no conflict of interest.

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Vaccination and child mortality

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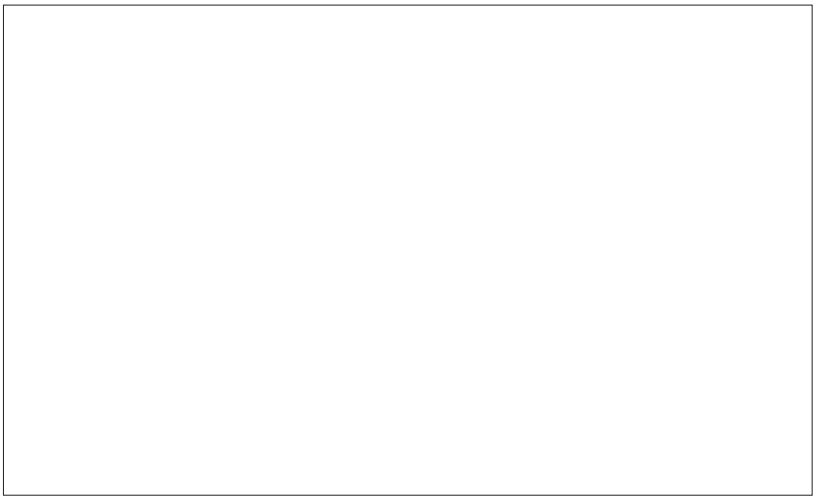
A report in 2000 from Guinea Bissau suggested a worrisome association between diphtheria, pertussis, and tetanus (DPT) vaccination and mortality.[1] In this issue of *The Lancet*, Robert Breiman and colleagues respond to concerns about DPT with a highly detailed and reassuring study of vaccination and mortality in Bangladesh.

At an epidemiology conference in Helsinki in 1989, Peter Aaby and I spent a few days discussing a problem: vaccines are usually introduced into developing countries with no assessment of their potential effect on overall mortality.[2] The key issue is that if trials of vaccines are to show a beneficial effect, or at least that they cause no harm, the trials need to be so large that they are difficult to fund. Another problem is that once a vaccine has been shown to reduce the frequency of the target disease, it becomes ethically questionable to have an unvaccinated group. Aaby tried to address this issue by using observational data from demographic surveillance in Guinea Bissau. He has published papers[3–6] suggesting unexpected associations between vaccine use and later patterns of mortality. His findings on DPT vaccine prompted WHO to look closely at his data (including a site visit by independent experts), to commission studies around the world where the association could be studied, and then to hold a meeting of experts to review and report all data in WHO's *Weekly Epidemiological Record*.[7]



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Breiman and colleagues' study was one that WHO commissioned and reviewed. It was one of the strongest pieces of evidence presented, because it was based on prospectively collected vaccination data and careful investigations of child deaths in the population. In addition, a careful statistical analysis was done (it is refreshing to see the details fully reported), which addressed the specific issues Aaby raised. The quality of the data and the care of the analysis are critical. Vaccinations are highly associated with another vaccination: people who get one are likely to get another. Breiman was unable to separate the effects of DPT and oral poliovaccine because they were so often given together. Also, those who get vaccinated are different from those who do not; thus the finding in Bangladesh that maternal education increases the likelihood of her child being vaccinated. For researchers to separate the effects of different vaccinations, including the timing and sequence of these vaccinations, requires great care. To attempt such a separation, a very large and detailed dataset is necessary. In particular, the process requires an accurate record of a large number of deaths. For example, the WHO expert committee found that in the original Aaby study[1] a change in the vaccine status of just two of the people who died made the result non-significant. Confidence intervals do not reflect the fragility of the analysis. The WHO committee concluded that the only evidence for an association between DPT and increased mortality was from Guinea-Bissau; such evidence was found in no other countries. This finding could be because of a country-specific issue or a peculiarity of the data.

Although Breiman and colleagues' study contradicts the Guinea Bissau findings on DPT, they do find a benefit from both measles vaccine and from Bacillus Calmette-Guerin vaccine in early life that goes beyond what one would