realistic. For these secondary rates, both regimens had outcomes similar to those recorded in other studies.[9] Another difficulty with the 12-week endpoint is the very low 33% response of patients with *C glabrata* to either regimen. Is this worse than infection with other species of *Candida*? I do not know.

To end at the beginning: is voriconazole effective and safe in treatment of candidaemia in a general hospital population? Yes. But will it be extensively used? With generic fluconazole for the less seriously ill, and with almost non-toxic echinocandins for the more seriously ill, I see relatively little use for voriconazole in the general hospital setting. In patients with cancer and in some with solid-organ transplants, the major population where voriconazole is likely to be used for its coverage of mycoses caused by filamentous fungi, Kullberg and colleagues' study gives some comfort for added coverage against fluconazole-susceptible *Candida* spp. But this same group of patients may have been heavily pre-exposed to fluconazole, and some patients may have refractory *C glabrata* or even *C albicans*. For these patients I fear that any triazole might have limited value. Pending additional data, I would consider voriconazole a modest addition to our alternatives for treatment of candidaemia.

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I have received research funding from Merck, Pfizer, Schering, Indevus, Astellas, and Vicuron. I have been part of speaker's bureaux for Merck and Schering, and advisory boards for Merck, Schering, and Vicuron.

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BCG: the story continues

Published online October 13, 2005
DOI:10.1016/S0140-6736(05)67535-6
See Articles page 1443

More people worldwide have been vaccinated with bacillus Calmette-Guerin (BCG) than with any other vaccine, but its mechanisms of protection against tuberculosis remain largely unknown. In today's *Lancet*, Ahmet Soysal and colleagues[1] add a new element to the debate, reporting that, in a population of children who were in close contact with infectious cases of tuberculosis in Istanbul, BCG protects against infection with *Mycobacterium tuberculosis*. Using a newly developed ELISpot assay measuring the interferon-γ response to specific *M tuberculosis* antigens as a marker of infection, these authors report that infection with *M tuberculosis* was more likely to be detected in children without a BCG scar than in those with such a scar. This ambitious study addresses a question that has been central to tuberculosis control for decades: namely, how effective is BCG, and to what extent does it protect against infection or disease?

BCG, the oldest vaccine still in use in the world today, was derived between 1906 and 1919 by in-vitro attenuation of an isolate of *M bovis*, and was first used as an antituberculosis vaccine in humans in 1921. The question of its protective efficacy against tuberculosis has been raised for several decades,[2] and evidence from several randomised controlled trials and observational studies showed that, in adults, efficacy varied greatly in different populations, from 0 to 80%.[3] The commonest explanation for the variability in BCG vaccine's protective efficacy is the difference between populations in terms of exposure to cross-reacting environmental mycobacteria, which can either mask or inhibit the protection induced by BCG.[4] In children, however, the protection from BCG appears to be better, especially against the most severe disseminated forms of the disease (miliary tuberculosis and meningitis).[5] This finding has justified the recommendation by WHO that infants should be vaccinated as soon after birth as possible with a single intradermal dose of BCG in countries with a high risk of tuberculosis infection.[6] The standard test for tuberculosis in the absence of

significant disease was, until recently, the tuberculin skin test, which measures the reaction to intradermal injection of purified protein derivative (PPD). However, because this test lacks specificity due to the presence of antigens shared among most mycobacteria (including BCG),[7] it has never been clear whether BCG vaccination prevents *M tuberculosis* infection as distinct from clinical disease.[8]

The immunodiagnostic test used by Soysal and colleagues is based on two antigens of *M tuberculosis*, ESAT-6 and CFP10, which are deleted in all strains of BCG presumably due to the attenuation process.[9] This test is therefore not confounded by BCG vaccination and there is substantial evidence to suggest that immune response to these antigens is a sign of *M tuberculosis* infection.[10–12] The authors found that many children who would have been scored as positive in the tuberculin skin test are negative in the ELISpot test. Given that the ELISpot test has repeatedly been shown to be at least as positive as the tuberculin skin test, and considerably more specific, this finding suggests that the discordant results are due to false positive results to the tuberculin skin test. More interestingly, these discordant results (tuberculin skin test positive, ELISpot negative) are strongly associated with BCG vaccination. This finding is consistent with previous studies, which showed that the tuberculin skin test can be confounded by recent BCG vaccination.[7] More importantly, however, the authors point out that the presence of a BCG scar is associated with a significantly lower risk of positivity in the ELISpot test, which can be assumed to be a better marker for *M tuberculosis* infection. Does this result suggest that BCG vaccination can prevent infection?

On the basis of autopsy studies in Finland in 1979, Sutherland and Lindgren[13] stated that there was no evidence to support the suggestion that, in human beings, BCG vaccine could prevent the establishment of *M tuberculosis* infection in an exposed person. According to Sutherland and Lindgren, BCG acted by limiting the multiplication and dissemination of the bacilli and the development of lesions after infection. More recently, studies in neonates in The Gambia showed that BCG vaccination induced potent Th1-type immune responses, associated with "adult-like" production of interferon-γ by CD4+ lymphocytes.[14] The use of an interferon-γ assay in BCG-vaccinated infants could then be a marker of vaccine-induced immunity and not of tuberculosis infection. The absence of a response would thus reflect a lack of immunity rather than an absence of infection.

Science Photo Library

BCG vaccination scar

The question is of importance and is more than just an academic debate. If BCG does protect against the development of disease given infection (which has been shown to be of variable efficacy), public-health strategies should focus on finding and treating latent infection as early as possible. However, if instead BCG gives some protection against *M tuberculosis* infection, the implication is that effort can most usefully be expended on preventing new infections in early adulthood.

In view of the points above, the study by Soysal and colleagues does not provide a definitive answer. Their work highlights the difficulties inherent in the study of tuberculosis, where distinguishing between latent asymptomatic infection and exposure to infection has proved extremely difficult. One of the reasons for this difficulty might be that the degree of positivity to ESAT-6 (and presumably CFP10 or other antigens) is affected by the degree of exposure and hence the degree of infection.[15] Vaccination studies in animals indicate that successful vaccination can greatly reduce the level of ESAT-6 responsiveness, without necessarily preventing infection.[16] So we are left with the same quandary: it appears from Soysal's report that BCG vaccination might reduce the intensity of infection, but can it indeed prevent infection? Only large-scale longitudinal studies will provide more definitive answers.

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We declare that we have no conflict of interest.

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Reorienting health-research communication

Much commentary and exhortation focuses on getting research evidence into health policy and practice. Bowen and Zwi[1] advocated that strategies to promote evidence-informed policy and practice should be built on theory and empirical evidence, and take into account the interactive and changing relations between science and society. Unfortunately, these considerations are often disregarded when health research is communicated.

Using evidence to guide action is a central tenet of health researchers, but apparently not when they communicate their findings. Eccles et al[2] reviewed 235 evaluations of guideline dissemination and implementation strategies over 25 years and found that: "few authors gave any rationale for their choice of interventions and presumably used their common sense to choose the interventions." The absence of a strong empirical and theoretical base for health-research communication risks duplication of efforts and ineffective strategies, hinders evaluation and learning, and provides little guidance for further research, policy, and practice.[2,3] Yet, communication and policy studies, and the philosophy and sociology of science, have long focused on the complex relations and multidirectional influences between science, state, and wider society.[4–7] Health-research communication would benefit greatly from drawing more consistently on this multidisciplinary base.

Like their religious forebears, the "high priests" of medical research and other health sciences typically issue "messages" as if these should unquestioningly be accepted and society transformed as a result. Lord Winston, an eminent UK scientist, called for a re-evaluation of the role of scientists in society in a recent interview.[8] He cited the drop in infant immunisation rates after the measles-mumps-rubella vaccine controversy as one example of research communication failures and of declining social trust in science.

The broader context for these observations is that, around the world, cost-effective health interventions are underused or misused, resulting in significant human and financial costs.[9] Responses to contemporary health problems increasingly depend on the involvement of those who need to adhere to treatment regimens and change behaviours and lifestyles. At the same time, people are less deferential and more demanding of health research, policies, and services.[3,7,9] There is also scepticism about authoritative claims and the "truthfulness" of scientific messages, in part, simply because orthodoxies are periodically overturned.[5] For example, a contemporary randomised trial indicated that the widely accepted use of corticosteroids to treat head injuries could be harmful.[10] Additionally, experts can and do interpret evidence differently and, indeed, use evidence to lobby for different policies and interests.[4,5,7] Ultimately, what is at stake in failures of health-research communication is not only the