

the 1980–90s are probably uncommon elsewhere. Rather, we face lower-level but often tenacious epidemics. Lastly, we gain confidence in prevention by behavioural change. Over a decade ago, a strategy was developed to contain concentrated epidemics, with success in Thailand¹³ and Cambodia.⁶ We are now also seeing apparent success in some generalised epidemics in Africa. Our understanding of what drives widespread HIV transmission, including the pivotal role of concurrent partnerships, is increasing, and our experience in promoting reduction in the number of partners and effective use of condoms continues to accumulate.¹⁴

What of the overall global epidemic? Sub-Saharan Africa and India together harbour some three-fourths of HIV-infected people.³ Kumar and colleagues' finding of declining prevalence in young women and male attendees at sexually transmitted disease clinics, and stable prevalence in older women in south India, along with fairly stable prevalence in the less-affected north, provide encouraging evidence that India's HIV incidence has also peaked. Also, recently released numbers from China present relatively modest and probably fairly stable levels of new infections.¹⁵ Thus in all likelihood, new HIV infections have peaked globally.

While celebrating this progress, we must remain ever vigilant. Incidence is still unacceptably high (especially in southern Africa) and can reverse course if gains from behavioural changes slacken. We have both gloom and hope. Too many are infected and too many will be. But the overall global decline in incidence, along with growing numbers of countries with declining HIV prevalence, confer confidence that prevention efforts can work to turn the tide against AIDS at last.

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BCG vaccination gets a boost

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It has been estimated that BCG vaccine is the most widely used immunisation in the world, with several billion doses having been given over the past decades.¹ BCG is a live-attenuated vaccine derived from a strain of *Mycobacterium bovis*, and is given to neonates and young infants throughout much of the world. Although vaccine efficacy has been a source of controversy over the years, it is now generally accepted that BCG, although it may

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not prevent infection or adult pulmonary disease, is highly effective in preventing severe childhood tuberculosis (tuberculous meningitis and miliary tuberculosis).²

In today's issue of *The Lancet*, Bernadette Bourdin Trunz and colleagues from WHO and the London School of Tropical Medicine and Hygiene, evaluate the cost-effectiveness of BCG vaccination in different regions of

the world for the prevention of severe childhood tuberculosis.³ They conclude that BCG vaccination is a highly cost-effective intervention, and should be retained in those countries with high rates of tuberculosis. They calculate that every year about 100 million doses of BCG vaccine are given to children worldwide, which results in the prevention of about 30 000 cases of tuberculous meningitis and 11 000 cases of miliary tuberculosis before these children reach their fifth birthday. This estimation translates into roughly one case of severe childhood tuberculosis prevented for every 2500 inoculations. BCG vaccination is thought to be nearly as cost effective as short-course chemotherapy for active disease, which is considered good value for money.

This result is great news for children, for paediatricians working in the front line, and for directors of BCG vaccination programmes in those regions with high rates of tuberculosis. Any paediatrician that has seen the devastating effects of tuberculous meningitis will be heartened by Bourdin Trunz and colleagues' report. Even in resource-rich countries, where there is easy access to paediatric subspecialty care, infants with tuberculous meningitis continue to have high mortality and morbidity, with deaths happening in about 15% of patients and up to 50% of infants left with serious neurological sequelae.^{4,5}

BCG vaccine has had a rather controversial existence, and has been in need of a "boost" to restore confidence. Conflicting results, from several major vaccine trials over the years, had raised questions about vaccine efficacy in the prevention of tuberculosis. Protective efficacy had been variously reported to range from 0% to 80% in different populations and regions.² In general, the main explanation put forward to account for these disparate findings has centred around differing vaccine potency, because of different strains of BCG being used in vaccine trials, as well as exposure in some patients to atypical mycobacteria infection with resultant cross-immunity, thereby nullifying the protective effects of BCG vaccination.⁶ This effect seemed to be important in those vaccine trials in tropical or subtropical regions.⁷ Meta-analyses of prospective trials have shown that BCG vaccination has an overall protective efficacy of 51%, and protective efficacy against severe forms of childhood tuberculosis of about 75%.^{8,9} However, even this protection is only relative, and might be overcome in the presence of severe malnutrition, exposure to a large

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Macrophage engulfing BCG

infecting dose of tubercle bacilli from a household contact, and also after waning immunity, many years after vaccination.^{10,11} Despite these concerns, the prevention of 40 000 cases of severe childhood tuberculosis a year worldwide is a cause for celebration.

Bourdin Trunz and colleagues make several assumptions about the epidemiology and transmission of tuberculosis and about the efficacy of BCG vaccination in different countries. They discuss the basis for their assumptions at length. Because it is unlikely that, even in resource-poor countries, infants with severe forms of childhood tuberculosis would have a mortality rate of 100%—ie, the same as in the prechemotherapy era—the overall cost-effectiveness of BCG vaccination may have been overestimated.

However, as Bourdin Trunz and colleagues point out, on many other issues, their calculations may have led to underestimates of cases prevented and ultimately the cost-effectiveness of the vaccine. Regionally, the highest numbers of cases prevented were in southeast Asia (46%), followed by sub-Saharan Africa (27%), and the western Pacific (15%). These are areas where tuberculosis infection rates and BCG coverage are highest. Cost-effectiveness of the vaccine decreases in those richer countries where the risk of tuberculosis infection is low.

The authors pose the question whether BCG should be withdrawn from routine use in these countries, and reserved for high-risk individuals. This is currently the situation in the UK, where routine BCG vaccination of schoolchildren has now been stopped, and the emphasis is on targeting high-risk infants and children.¹²

Bourdin Trunz and colleagues should be congratulated for their excellent study. **This important report should provide the theoretical basis for underpinning health policies about BCG vaccination worldwide.**

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New look at the oxyhaemoglobin dissociation curve

If you ask a final-year medical student what he or she knows about the oxyhaemoglobin dissociation curve and its clinical relevance, you are likely to receive the answer that you have to be aware of the “slippery slope” of rapidly falling haemoglobin saturation with progressive arterial hypoxia, with the associated risk of inadequate delivery of oxygen to the tissues (figure, left). The thoughtful student may even go on to comment that it is intriguing to think that evolution would have led to such an apparently flawed physiological relationship.

In reality, the curve has evolved to achieve a highly beneficial physiological relation with two particular features that serve to protect the individual from tissue hypoxia.¹ The first characteristic is that the initial flat portion of the curve means that almost maximum haemoglobin saturation is achieved despite marked reductions in arterial oxygen tension associated with cardiovascular or respiratory disease. In other words, the blood is almost fully oxygenated despite low oxygen-tension. The second characteristic is that the steep portion of the curve means that, despite rapidly falling oxyhaemoglobin saturation, the oxygen tension remains relatively preserved, with the partial pressure of arterial

oxygen (PaO₂) decreasing by about 1 mm Hg for every 2% drop in saturation. This property facilitates the continued delivery of oxygen to the tissues despite progressively lower levels of saturation. In this respect the partial pressure of oxygen is the determinant of the force driving oxygen across cellular membranes.

It could be argued that the oxyhaemoglobin dissociation curve would be better presented if the haemoglobin saturation was shown on the x-axis and the oxygen tension on the y-axis (figure, right). This realignment would not only overcome the dominant appearance of the “slippery slope”, but also allow emphasis of the two key features of the curve, namely that it facilitates both the pick-up of oxygen and its delivery to the tissues.

A better appreciation of these beneficial physiological characteristics of the oxyhaemoglobin dissociation curve might change the current clinical practice of oxygen therapy. For decades, doctors, nurses, and paramedics have been driven by the fear of allowing their patients to get close to the “slippery slope”, leading to a standard response of routinely administering supplementary high-flow oxygen. This practice has led to both the administration of oxygen to patients who are not