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Safer prescribing for children

Will be boosted by European and US laws and the new British national formulary for children

Paediatric prescribing can be precise, beneficial, and safe. It can also be confusing, based on little or no evidence of effectiveness, and can put children at risk. The nature of marketing authorisations (formerly product licences) for drugs merely enhances the paradox. They were designed as a means of obtaining approval for use by an appropriate regulatory body, usually a government agency; so the decision to apply for authorisation is influenced more by commercial than clinical considerations.[1] One result is that unlicensed and "off label" prescribing is common. Paediatricians, general practitioners, and others are torn between providing treatment which their experience and reason have deemed suitable and denying it because of the lack of research data underpinning indications, dosages, or formulations.

A study in five European hospitals showed that 39% of drugs prescribed for children were off label and a further 7% were unlicensed.[2] Similar studies in general practice of prescriptions for children found that 11% were off label or unlicensed in the United Kingdom, 33% in France, and 29% in the Netherlands.[3–5] Furthermore, neonatologists have little choice but to use drugs in unauthorised ways because their patients are rarely entered into trials of new preparations: 80% of infants in an Australian neonatal intensive care unit received an off label or unlicensed preparation.[6] Such prescribing is a problem not just for doctors: patients in a paediatric isolation ward in Germany who were treated with unlicensed or off label drugs had a significantly increased risk of adverse drug reactions.[7]

Complacency about the lack of evidence based information on medicines for children is unacceptable. But several initiatives—three which should encourage high quality research and one which should provide authoritative information on prescribing—should go a long way to solving this problem.

The NHS health technology assessment programme is to commission a portfolio of research projects on medicines for children. Proposals should reach www.ncchta.org by 1 pm on 19 October 2005.

The European Commission has responded to professional and public concerns by proposing a directive on medicinal products for paediatric use.[8] It includes establishing an expert committee to assess and approve all protocols for paediatric drug trials. This committee would consider whether studies are likely to show therapeutic benefit and would be expected to turn down those it thought would unnecessarily duplicate other work, while not delaying authorisation of medicines for other ages. In addition the European Medicines Agency has issued a draft guideline on pharmacovigilance among children.[9]

The proposed European directive on medicinal products for children has much in common with the Pediatric Research Equity Act passed by the US Senate in July 2003. This empowers the Food and Drug Administration (FDA) to require manufacturers to test medicines for safety and effectiveness in children and to establish protocols for paediatric dosing and administration. The FDA can waive such requirements when a drug is unlikely to be used in children and can defer decisions on paediatric prescribing when a drug needs urgent authorisation for adult use.[10]

This week sees the publication of the *BNF for Children*, which aims to offer sound up to date information on paediatric prescribing, much of which goes beyond marketing authorisations.[11] Its provenance is the *British National Formulary* (BNF), which has provided authoritative and regularly updated prescribing advice for the past 50 years, and *Medicines for Children*, a popular and much used publication of the Royal College of Paediatrics and Child Health.

The *BNF for Children* has been validated against emerging evidence, guidelines on best practice, and advice from a network of clinical experts. The UK Departments of Health will distribute it to all prescribers in England, Wales, and Scotland and to a limited number in Northern Ireland. An online version for England is almost ready.

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Competing interests: HM is an employee of the BMJ Publishing Group and an external relations adviser to the Royal College of Paediatrics and Child Health, which are among the publishers of the *BNF for Children*, but he has received no remuneration related to BNFC.

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Stopping routine vaccination for tuberculosis in schools

Brings the UK into line with much of the rest of the world

From autumn 2005 the long running routine programme to vaccinate schoolchildren against tuberculosis with BCG vaccine will stop. This follows a decision by the chief medical, nursing, and pharmaceutical officers in July that there should be selective vaccination of high risk infants and other groups rather than routine vaccination of adolescents negative on tuberculin testing.[1] This decision comes after several years of discussion within the Joint Committee on Vaccination and Immunisation, and it closes an important chapter in the complex history of BCG vaccination. It comes as notifications of tuberculosis in England and Wales are at their highest level since 1983. The decision is well justified.

This BCG programme has been unique from its start in the mid-1950s, when a Danish vaccine (later produced by Glaxo) was introduced on the basis of efficacy shown in a trial carried out by the UK Medical Research Council.[2] The trial had been carried out in approximately 30 000 adolescents for pragmatic reasons—in order to recruit participants who were still tuberculin negative, but who were about to enter a period of high risk of disease. That trial remains the most rigorous trial of BCG vaccination carried out anywhere and is an important monument in the history of research in tuberculosis.

At the same time trials were carried out by the US Public Health Service (USPHS) in Georgia, Alabama, and Puerto Rico which found that the Tice BCG vaccines used there had little or no effect.[3] Faced with these results, each nation did the locally responsible thing—the USPHS decided not to introduce BCG vaccination because they had no evidence that it worked among their populations, whereas the UK authorities did introduce it, as they had good evidence of its value.

This touched off a controversy over the magnitude and determinants of the efficacy of BCG, which still continues. Many explanations have been proposed. Perhaps the most popular is that different populations are exposed to different environmental mycobacteria, which can provide as much immunity as BCG or otherwise interfere with it, and that the US trials happen to have been conducted in areas where such environmental exposure is highly prevalent.[4] Whatever the explanation for those initial trial results, they determined the policy of vaccinating adolescents in the United Kingdom, and the efficacy of the vaccines so given has since been confirmed repeatedly in observational studies.[4 5]

The epidemiology of tuberculosis in the United Kingdom has changed greatly over the years since the BCG programme began. The annual risk of infection has declined from about 2% a year in 1950 to less than 1 per 1000 today, and the disease has become increasingly restricted to identifiable segments of the population, in particular immigrant communities: two thirds of cases in 2003 were in people born outside the United Kingdom.[6] Recent increases in the incidence of tuberculosis in the UK thus reflect patterns and trends in the movements of populations and in the epidemiology of tuberculosis worldwide.

That non-indigenous groups were at higher risk was first recognised in the 1960s and led to a national policy encouraging health authorities to consider supplementary BCG programmes for neonates or for people in contact with tuberculosis in these communities. The Joint Committee on Vaccination and Immunisation repeatedly examined the cost effectiveness of the routine programme in schools as an increasing proportion of the population at high risk received the vaccine in infancy and as the risk of disease in the general population fell. The number of cases in people born in the United Kingdom reached an all time low in 2003.[6]

Although the criteria set by the International Union against Tuberculosis and Lung Disease for moving away from routine BCG vaccination were achieved in the 1990s,[7] policy makers were reluctant to stop the programme in schools because of lingering concerns that increases in the prevalence of HIV and in tuberculosis internationally might increase the risk of tuberculosis in the UK general population. This has not occurred, and it is clear that the risk of tuberculosis among immigrant communities declines over time once they have settled in the United Kingdom and that the imported disease has not led to increases in the risk of disease for the indigenous population.

BMJ 2005;331:647–8