The second threat to emerge in the last 20 years is drug resistance, which came to prominence in the early 1990s with multiple outbreaks of multi-drug resistant (MDR) TB throughout the world. MDR-TB is defined as resistance to the two major drugs used in first-line treatment, isoniazid and rifampicin. The majority of these early cases were associated with HIV and with very poor prognosis. Global surveys, coordinated by WHO, observed significant increases in MDR-TB, particularly in the former Soviet Union, but also in China and India.[3] However, it was in a district hospital in KwaZulu Natal, South Africa, that the largest outbreak to date of extensively-drug resistant (XDR) TB (defined as MDR-TB plus resistance to any of the fluorquinolones, and resistance to any one of the injectable second-line agents, amikacin, capreomycin, or kanamycin) was reported. This too was strongly associated with HIV and had a 98% case fatality rate.[4] The underlying causes include failure to supervise patients' treatment (resulting in several different strains becoming extensively resistant) and a lack of infection control measures in the hospital. Globally, in 2006 there were an estimated 489,000 cases of MDR-TB.[5]

TB (and leprosy) is extraordinary among infectious diseases in that the chief diagnostic tool, microscopy, using the Ziehl–Neelsen stain, has remained virtually unchanged since 1886. Culture and isolation have changed little, although liquid culture systems have accelerated the time to diagnosis compared to solid media. However, it is in diagnostics that the first big revolution in the management of TB since the advent of chemotherapy is about to happen. DNA-based line probe assays, using polymerase chain reaction methods, have enabled development of tests that can diagnose MDR-TB from a sputum positive sample within a day. At the time of writing, WHO is about to recommend their deployment at country level.

First-line treatment has not changed a great deal in the last 30 years. Fluoroquinolones have anti-TB activity, but their use has been mostly restricted, at least in the public sector, to treatment of drug-resistant cases. Oxazolidinones are also active against TB, but their cost has confined their use to difficult cases in high-resource settings.

Globally, however, it is not to technical fixes that the advances of the last 30 years, and the flattening of the TB epidemic, are owed. Rather it is to a simple public health methodology that has been introduced in almost all developing countries – the DOTS strategy – based on the pioneering work of Karel Styblo, first in Czechoslovakia, and later in Tanzania, Benin, Malawi and Mozambique.[6] The elements of DOTS are: political commitment, without which little can happen in most places; bacteriological diagnosis, usually sputum smear microscopy, but culture and isolation if it is affordable; directly observed treatment with standardised regimens; a secure supply of quality assured drugs; and a recording and reporting system that evaluates the outcome of every single patient at the end of treatment.

In 2006, WHO expanded its control strategy to keep up to date with new knowledge and persuade countries to address not only drug-susceptible TB, but also drug-resistant cases, and those with HIV.[7] All healthcare providers should be involved in TB control, which in turn, should add to health system strengthening efforts. Communities and individuals affected by TB are encouraged to get involved and research and development is actively promoted. Serious progress towards TB elimination, defined as an incidence of less than one case per million, will demand better tools than we have at present, particularly a more effective vaccine than BCG.

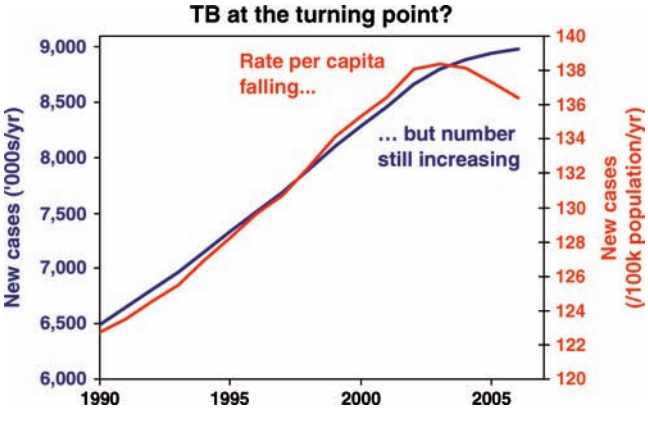

Fig 1. Comparison of global incidence rates (red) and total case numbers (blue). Derived from Reference 1.

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Immunisation in the UK: protected for the future

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Introduction

In the Peckham Report of 1989, immunisation coverage in the UK was among the lowest in Europe.[1] Recently, coverage of seasonal influenza vaccine was among the highest in Europe[2,3]; the UK childhood immunisation programme is widely recognised

as being one of the foremost worldwide. Although some of the interventions through those years can be clearly linked to specific improvements, in other instances it has proved difficult to pinpoint specific factors that led to improvements.[4] When new vaccines have been introduced, in almost every case this has been done on a campaign basis, usually with some form of catch-up programme to bring the widest benefit to the greatest number of individuals in the shortest time. Each change to the immunisation programme has been accompanied by carefully researched communication initiatives, tested beforehand and evaluated afterwards, and the supply of vaccines has been put on as dependable a basis as possible, acknowledging that vaccines, being biological materials, carry vulnerabilities where consistent manufacturing is concerned. This paper will identify just some of the important initiatives.

New vaccines and campaigns

The list of new vaccines that have been introduced since 1988 is exhausting (Table 1). In each case, the vaccine introduction has involved new national supplies, communication materials, disease surveillance, adverse event surveillance, impact evaluation and adjustment to the programme when necessary. The impacts of these vaccine introductions have been impressive. After the introduction of the measles/mumps/rubella (MMR) vaccine in 1988, coverage rose 10% compared with the previous single measles vaccine, numbers of cases of measles fell considerably, and most importantly, the number of rubella infections in pregnancy fell as pregnant women were no longer infected by their own or their friends' children.[5] Despite a perception that the purpose of the introduction of MMR related to control of measles, the main reason was to interrupt rubella transmission among young children, thereby protecting their pregnant mothers, and this was achieved.

Table 1. Changes to the immunisation programme 1988 to 2008.

1988	Introduction of MMR (measles/mumps/rubella) with catch-up for under-5s
1990	Accelerated immunisation schedule
1992	Introduction of *Haemophilus influenzae* type b vaccine with catch-up for under-4s
1994	MR (measles/rubella) campaign for 5–15s
1996	Second dose MMR and catch-up for 4–6s
1999	Introduction of meningitis C conjugate vaccine with catch-up to 18 years
2001	Catch-up for meningitis C conjugate for up to 25 years
2004	Change to acellular pertussis vaccine and inactivated polio vaccine
2006	Introduction of pneumococcal conjugate vaccine with catch-up for under-2s
2008	Introduction of HPV (human papillomavirus) vaccine with catch-up to 18 years
2008	MMR catch-up programme for 5–18s

The introduction of *Haemophilus influenzae* b (Hib) vaccine was especially challenging since the existence of Hib as a cause of meningitis and other systemic infections was not well known. Nevertheless, high coverage of Hib vaccine was achieved almost immediately, despite a separate injection being required. For the best part of a decade, Hib disease was almost eliminated. When Hib cases started to recur in the early 2000s, catch-up programmes were put in place and Hib is again back at extremely low levels.[6] The development and introduction of meningitis C conjugate vaccine was a world leader for the UK. In the mid-1990s, it was evident that along with high levels of group B meningococcal disease, group C disease was increasing in some European countries, especially the UK.[7] Working with three vaccine manufacturers, a programme of accelerated vaccine development was driven forwards with the result that a full national campaign could be implemented using meningitis C conjugate vaccine – the UK being the first country in the world to do this. The results were spectacular: group C disease melted away, not just in vaccinated individuals but also in non-vaccinated individuals in and outside of the age groups targeted for vaccination.[8] In 1998/9, the year before the campaign was launched, there were 78 deaths in those less than 20 years. In 2006/7 and 2007/8, there was not a single death in that age group. The benefits of this campaign, especially the catch-up programme, are expected to be felt for many years to come.[9] In a similar fashion, the introduction of pneumococcal conjugate vaccine along with its catch-up programme has already impacted significantly on the group targeted for immunisation.[10]

Vaccine supplies

It almost goes without saying that for a vaccine programme to be fully effective, adequate supplies of vaccines must be available. Yet, despite contracts that should assure this, shortages can occur because vaccines are biological products whose consistency of manufacturing cannot be guaranteed. In 1991, some vaccines were purchased centrally by the Department of Health (DH), some were purchased by health authorities against local birth cohort numbers using money devolved by DH against centrally negotiated prices, some were purchased by health authorities on behalf of general practitioners (GPs), some were purchased by practices and some were provided on prescription. In 1992, responsibility for purchasing all childhood vaccines was brought under the DH's control using central funds. Over the last seven years, the US programme has faced numerous 'stock outs' that have on several occasions meant that either schedules had to be changed or complete courses of vaccination could not be achieved[11,12]: during the same time the routine UK childhood programme has had no vaccine shortages that impacted on the ability to vaccinate. In the UK, all childhood vaccines are purchased and supplied centrally. In the USA, half of the childhood vaccines are purchased by the private sector. The UK programme attempts to always maintain a six-month stockpile of vaccines; if shortages are anticipated, central release of vaccine stocks can be managed through a process of 'allocation' by

which all practices get an equal share of stocks according to predefined estimates of their weekly needs, based on patterns of previous use, down to individual practice level. Similarly, in the case of new campaigns, each practice or trust's needs can be fine tuned to match supply and demand. As an example, throughout the complex meningitis C vaccine campaign, no vaccine ordering was necessary by any level. In the USA, frequent stock outs bedevilled the introduction of pneumococcal conjugate vaccine introduction: the UK contract between the DH and the pneumococcal vaccine supplier included penalty clauses that would be invoked in the event of supply failure and there has been none. Currently in the USA, the Hib vaccine schedule has been compromised because of vaccine shortages; a resurgence of cases in Minnesota has been linked to this lack of vaccine.[13]

Communications

The UK immunisation programme has a long history of promotion through different media. In a 1950s information film, the actor John Le Mesurier, smoking a cigarette as he examines a child, berates the parents for not vaccinating their child who has smallpox. In another film from the 1930s, a child with diphtheria is put into the back of a black ambulance and as the door shuts, the voiceover says, 'Every year, tens of thousands of mothers see their child taken away to the fever hospital and every year, three thousand do not come back'. Certainly present day advertising has to be very different both in content and in the routes by which parents are accessed. Seventy per cent of parents obtain information on immunisation from the internet, where material is unregulated and its probity and accuracy hard to establish. Advertising through television has very high penetration to the target audience but is very expensive. We routinely pre-test all communication materials and evaluate their impact through qualitative and quantitative research.[14] In addition to learning about knowledge, attitudes and beliefs about immunisation, such work allows estimates to be made of the relative cost effectiveness of different routes of advertising. For example, the cost of producing paper bags, to be used in pharmacies, that carry advertising on seasonal influenza vaccination, is very cheap compared with television advertising. While the overall impact is smaller, the cost per point of awareness gained is inexpensive compared with each point gained through television advertising.

As infectious diseases become less common and hence awareness of their potential severity becomes a memory only for grandparents, so new fears arise, such as those of vaccine safety. In the absence of disease or its imminent threat, raising fears over disease seriousness is not a useful counter to fears over vaccine safety since such a strategy leaves parents with two fears instead of one. In developing strategies for communicating over vaccine safety, the most effective communicator is the well-informed primary care professional: GPs and practice nurses are consistently rated as highly trusted by their patients.

Challenges

As technological advances bear fruit, there are going to be new vaccines not just against infectious diseases but against malignant disease (we already have hepatitis B and human papillomavirus (HPV) vaccines) and also against chronic diseases and even substance abuse. The immunisation programme will need to change as epidemiological circumstances dictate, and flexibility and responsiveness will be indicators of healthy programmes. Vaccine safety concerns are likely to arise, irrespective of the real risks, and communicating a proper balance of risk and benefit will remain challenging. The UK immunisation programme is well-placed to face the challenges of the future.

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