Resurgence of tuberculosis and the impact of HIV infection

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Tuberculosis is increasing in many countries. In some areas the major influences on tuberculosis trends are the traditional ones: poverty, failures in the treatment system, and immigration. In others, and increasingly, the HIV epidemic is having a huge impact. HIV infection increases the risk of tuberculosis approximately 7-fold, though this may vary with the stage of the HIV epidemic, the prevalence of tuberculosis, and the age groups considered. Dually-infected individuals develop tuberculous disease at a rate of 5-10% per year. HIV also increases the risk of disease following recent infection, which makes a major contribution to the tuberculosis burden in some settings. HIV-infected individuals may transmit Mycobacterium tuberculosis less than do HIV-negative individuals, but the extra cases will add to the transmission overall, and evidence of HIV-attributable increases in the annual risk of infection is beginning to be seen.

In 1993, the WHO took the unprecedented step of declaring tuberculosis to be a ‘Global Emergency’. This action was stimulated both by the magnitude of the tuberculosis problem – an estimated 8 million cases and 3 million deaths each year1 – and by recent changes in tuberculosis incidence. In many countries tuberculosis case rates, which had been declining for decades, were reported to be increasing, or at least to have stopped decreasing. That this was happening worldwide was remarkable, not least because the underlying causes of the increase varied from place to place.

In the US, there was an estimated 13% increase in the case rate between 1985 and 19922. In many countries of Western Europe case rates stopped falling or started to rise in the mid to late 1980s3. Dramatic increases have been reported from Eastern Europe since 19894-6. Estonia recorded an 80% increase in incidence between 1982 and 19865. Rises in childhood tuberculosis are particularly worrying6,7, as these are likely to reflect increased transmission of infection, not just an increase in re-activation disease. In Russia, incidence in children increased by almost 80% between 1989 and 19957. Most countries in
Africa, for which sufficient data are available, show increases since the mid 1980s, some of more than 10% per year. In Asia, rates increased from 1985 to 1990 and further increases are predicted.

**Increases in data or in disease?**

Three sorts of data are used to estimate trends in tuberculosis in a population: (i) incidence rates of all or selected types of disease; (ii) mortality rates; and (iii) estimates of the annual risk of infection. Some forms of tuberculosis are notoriously difficult to diagnose accurately, and good diagnostic facilities are often lacking. There was no change in case definition that would have accounted for the trends, but the completeness of case finding and notification may well have improved in some countries. The proportion of cases found is very difficult to estimate. Many tuberculosis programmes have used a 'rule', based on estimates from survey data, that for each 1% annual risk of infection there should be about 50 smear positive tuberculosis cases per 100 000 population. Using this rule, case finding is often thought to be poor, perhaps as low as 30% in some areas, so that even the WHO goal for case finding is only 70%. This simple rule has been criticized and is no longer valid. The annual risk of infection is subject to considerable error in measurement, particularly in the presence of neonatal BCG vaccination and exposure to non-tuberculous mycobacteria. Furthermore, the presence of HIV infection, which increases the progression from infection to disease, changes the relationship between the annual risk of infection and disease incidence.

'Case rates' may refer to both new and relapse cases and are often crude rates, not adjusted for the age and sex structure of the population. Demographic changes may lead to changes in crude rates, although the age-specific rates are stable. Interactions with age are complex, older individuals having a higher risk of disease following infection than do younger individuals. As the annual risk of infection falls, the average age at infection rises, which could cause a paradoxical increase in disease.

Tuberculosis mortality rates reflect the efficiency of diagnosis and treatment as well as the incidence of tuberculosis, so also need to be interpreted cautiously. Many deaths from tuberculosis may be misdiagnosed, particularly in HIV-positive patients.

Although it is difficult to measure, much of the recorded increase probably reflects real changes in the incidence of tuberculosis. The increase is due both to 'traditional' factors which have been influencing tuberculosis trends for decades (immigration, poverty and failures in the treatment system), and to HIV.
‘Traditional’ influences on tuberculosis trends

Immigration

In some countries, much of the rise in tuberculosis cases can be attributed to recent immigration. In the US, foreign-born cases accounted for 60% of the increase in tuberculosis seen between 1986 and 1992. In The Netherlands, the incidence of tuberculosis in the native-born population has continued to fall, though the total incidence rate increased since 1987. The extent of spread of tuberculosis from the immigrant communities to the general population has been studied in The Netherlands using DNA fingerprinting techniques. Much of the transmission occurred within each immigrant community, though the extent of this varied by nationality. Among tuberculosis cases in Dutch nationals, 17% (about half of those thought to be due to recent infection) were attributed to transmission from non-Dutch nationals.

Poverty and living conditions

Tuberculosis has traditionally been linked to poverty, though the relative roles of the different aspects of poverty which may be responsible, for example nutrition and overcrowding, are not well defined. Increases in inner city poverty and homelessness have been blamed for some of the increases in tuberculosis seen in high income countries. Sometimes this effect is direct, with transmission occurring in shelters for the homeless. Poverty is also a factor in the high rates of tuberculosis seen in immigrants. The displacement of populations due to war or natural disasters leads to crowding and malnutrition which are likely to foster tuberculosis. High rates of tuberculosis, often in association with HIV, have also been found in prisons.

Collapse of treatment systems, and drug resistance

The duration of tuberculosis treatments (‘short course’ regimens are at least 6 months long) bring particular problems to both health services and patients. Treatment failure can have many causes: inappropriate regimens may be prescribed; drugs may be unavailable; the patient may have insufficient access to the health service; or may default even if drugs are available. Sub-optimal prescribing is a particular problem where tuberculosis services are not centralised, for example in populations where many patients are treated privately. Failures in drug supply can occur in any underfunded or neglected system. Failures of patients to

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collect or take drugs may be linked to costs (direct or indirect, particularly if travel is involved) or lack of understanding of the importance of continuing treatment beyond the acute phase of illness. Drop out rates can be very high: of a group of patients in Harlem, New York, many of whom were drug users or alcoholics, 89% failed to complete treatment. In a study in Madras, only 42% of smear positive patients on short course therapy completed at least 80% of their treatment and, of these, 22% remained sputum positive. The inevitable consequence of these failures is a rise in drug resistance, first acquired resistance, and then, with subsequent spread, primary resistance. Published rates of drug resistance have recently been reviewed. Multidrug resistance was uncommon in new patients (less than 1% in most studies), but was much more common (over 10% in some areas) among patients with a history of previous treatment. The impact of drug resistance on tuberculosis is covered by Eltringham in this issue.

**HIV**

Whereas the factors discussed above have been influencing tuberculosis trends for some time, and we can predict their impacts, even if not always deal effectively with them, the full impact of HIV has yet to be felt. There is no doubt that HIV infection increases the risk of developing disease among individuals infected with *M. tuberculosis*. HIV infection may not increase the risk of infection in those exposed, though this is difficult to study since delayed type hypersensitivity reactions to tuberculin are lost as HIV infection progresses, and testing for anergy can give inconsistent results.

**The association between HIV and tuberculosis**

The relative risk of tuberculosis disease in individuals infected with HIV, compared to those not infected, has frequently been studied. Cohort studies, and case-control studies that have used community controls and have adjusted at least for age and sex are shown in Figure 1. Many other studies of the relationship between HIV and tuberculosis have been reported, but have used inappropriate comparison groups, or have made no adjustment for confounders. For case-control studies, it is difficult to define suitable controls. Tuberculosis cases are usually identified in hospital settings, but hospital controls are rarely appropriate since HIV is associated with many different diseases, and referral patterns vary for different conditions. Blood donors have been used, but are unlikely to be representative of the general population as they will be...
Fig. 1: Relative risk of TB in HIV-positive and HIV-negative individuals. Rate ratios are presented for the cohort studies and odds ratios for the case-control studies. In addition to those shown, a cohort study among tuberculosis-positive drug users in New York found 7 cases of tuberculosis in 49 HIV-positives and none in 62 HIV-negatives. In Nairobi, a cohort study of commercial sex workers found tuberculosis in 49/587 HIV-positives and 0/132 HIV-negatives.
healthy and may have been preselected, and in some countries are paid to donate. Health care workers\textsuperscript{46} are also unrepresentative.

Even among the selected studies, there is a large variation in estimates of the relative risk. Most are consistent with a relative risk of around 7, but the relative risk may not be the same in different situations. The relative risk should increase as the HIV epidemic progresses, as a higher proportion of HIV-infected individuals develop more advanced levels of immunosuppression. Several studies have found variations with age, with higher relative risks in younger adults than in older adults\textsuperscript{34,41,43–45,47}. The relative risk may vary with the incidence and prevalence of \textit{M. tuberculosis} infection in the population, since the relative risks of primary, re-activation and re-infection disease may not be the same. The relative importance of these different types of disease may explain any variations found with age, since disease in a young adult is more likely to be due to recent infection than is disease in an older adult.

\textit{Incidence of tuberculosis in HIV-infected individuals: re-activation or re-infection?}

The absolute incidence of tuberculosis in HIV-positive individuals depends on the prevalence of previous \textit{M. tuberculosis} infection, the current risks of infection, the extent of immunosuppression\textsuperscript{48} and the use of antimicrobial (usually isoniazid) prophylaxis. In studies of incidence, tuberculin testing, usually taking a cut-off of \textgreater{} 5 mm, has been used to distinguish those thought to have previous infection. The extent of immunosuppression and the current risk of infection depend on the patient groups included and the setting of the study. Studies excluding sicker patients and those with a history of previous tuberculosis, and studies with stricter criteria for diagnosing tuberculosis, will tend to find lower incidences of disease. Table 1 shows estimates of tuberculosis incidence for 12 studies in which data were available for HIV-infected patients with known previous positive tuberculin tests who had not received isoniazid prophylaxis. The settings, exclusion and diagnostic criteria are shown. The rates of tuberculous disease of 5–10% per year in dually infected persons compare with an estimated lifetime risk of 10% in those without HIV infection\textsuperscript{58}.

The appropriateness of the 5 mm induration cut-off as an indicator of \textit{M. tuberculosis} infection will vary from setting to setting, its specificity being lower in areas with higher rates of infection with environmental mycobacteria, and those with widescale BCG use. This, and the multiple exclusion criteria which will have resulted in a cohort of relatively newly HIV infected patients, may explain the low incidence found in the recent Ugandan study\textsuperscript{57} (Table 1).
# Table 1 Incidence of tuberculosis (TB) in HIV-positive individuals with tuberculin reactions of at least 5 mm who had not received isoniazid

<table>
<thead>
<tr>
<th>Ref Place</th>
<th>Year</th>
<th>Patient group</th>
<th>Median CD4 count x10^4</th>
<th>Exclusion criteria</th>
<th>All culture confirmed?</th>
<th>Estimated length of follow-up (years)</th>
<th>Risk n/n</th>
<th>Rate/100 person years at risk (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>49 Port-au-Prince, Haiti</td>
<td>86–92</td>
<td>Symptom-free, newly diagnosed</td>
<td>49</td>
<td>Previous TB, abnormal chest X-ray, abnormal LFTs</td>
<td>No</td>
<td>2 4</td>
<td>6/25</td>
<td>10 0 (3 6–21 4)</td>
</tr>
<tr>
<td>39 New York, USA</td>
<td>85–88</td>
<td>IVDUs in methadone maintenance programme*</td>
<td>39</td>
<td>? None</td>
<td>Yes</td>
<td>1 8</td>
<td>7/36</td>
<td>10 8* (4 3–22 2)</td>
</tr>
<tr>
<td>32 New York, USA</td>
<td>88–90</td>
<td>IVDUs in methadone maintenance programme</td>
<td>560</td>
<td>Documented previous TB</td>
<td>No</td>
<td>1 7</td>
<td>4/25</td>
<td>9 7 (2 6–24 7)</td>
</tr>
<tr>
<td>50 Hartford, USA</td>
<td>84–92</td>
<td>IVDUs seen as in or outpatients</td>
<td>50</td>
<td>? None</td>
<td>No</td>
<td>3 8</td>
<td>2/18</td>
<td>2 9 (0 4–10 6)</td>
</tr>
<tr>
<td>51 6 cities, USA</td>
<td>88–94</td>
<td>Mixed 23% IVDUs No or &lt; 6 months isoniazid</td>
<td>51</td>
<td>TB in last 12 months, acute pulmonary disease, AIDS</td>
<td>No</td>
<td>73 8</td>
<td>7/34</td>
<td>4 5 (1 6–9 7)</td>
</tr>
<tr>
<td>52 Madrid, Spain</td>
<td>85–94</td>
<td>Referred patients, 90% IVDUs</td>
<td>52</td>
<td>Previous or active TB</td>
<td>No</td>
<td>2 8</td>
<td>24/84</td>
<td>10 4* (6 7–15 5)</td>
</tr>
<tr>
<td>53 Madrid, Spain</td>
<td>89–92</td>
<td>Newly diagnosed, refused, or discontinued isoniazid</td>
<td>53</td>
<td>Previous or active TB</td>
<td>No</td>
<td>1 7</td>
<td>43/92</td>
<td>9 4 (6 8–12 7)</td>
</tr>
<tr>
<td>48, Italy</td>
<td>90–93</td>
<td>In and outpatients, 73% IVDUs</td>
<td>48</td>
<td>TB in last 18 months</td>
<td>Yes</td>
<td>1 4</td>
<td>15/197</td>
<td>5 4 (3 0–9 0)</td>
</tr>
<tr>
<td>55</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40 Nairobi, Kenya</td>
<td>89–92</td>
<td>Commercial sex workers</td>
<td>40</td>
<td>Previous TB</td>
<td>No</td>
<td>2 4</td>
<td>11/69</td>
<td>6 7 (3 3–11 9)</td>
</tr>
<tr>
<td>56 Nairobi, Kenya</td>
<td>92–94</td>
<td>Commercial sex workers and clinic attenders</td>
<td>56</td>
<td>Previous TB, possible current TB, abnormal LFTs, pregnant, life-threatening illness</td>
<td>No</td>
<td>1 8</td>
<td>10/69</td>
<td>8 0 (3 9–14 8)</td>
</tr>
<tr>
<td>57 Kampala, Uganda</td>
<td>92–95</td>
<td>Clinic attenders</td>
<td>57</td>
<td>Previous TB, active TB, white cell count &lt; 3000/mm², Hb &lt; 80 g/l, abnormal LFTs, pregnancy, advanced HIV disease, major underlying illness</td>
<td>No</td>
<td>1 3</td>
<td>21/464</td>
<td>3 4 (2 1–5 2)</td>
</tr>
<tr>
<td>f Lusaka, Zambia</td>
<td>92–96</td>
<td>Clinic attenders, referrals from blood bank and voluntary testing centres</td>
<td>f</td>
<td>Previous TB, possible current TB, abnormal LFTs, pregnancy, life-threatening illness</td>
<td>No</td>
<td>1 6</td>
<td>9/60</td>
<td>9 2 (4 2–17 4)</td>
</tr>
</tbody>
</table>

**IVDU = intravenous drug user, LFT = liver function test, Hb = haemoglobin, CI = confidence interval,**

*Previous TB, abnormal chest X-ray, abnormal LFTs

**Without isoniazid Rate estimated assuming length of follow up same as for whole group,**

*Same rate for culture confirmed, *Includes new converters,

*And unpublished data, *Unpublished data from Zambart Project (isoniazid prophylaxis trial)
### Tuberculosis incidence in HIV-positive patients who did not receive isoniazid, by initial tuberculin reaction

<table>
<thead>
<tr>
<th>Ref</th>
<th>Setting</th>
<th>Patient group</th>
<th>Risk n/l</th>
<th>Rate/100 person years at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>23 hospitals in Italy 1990-93 In and outpatients, 73% IVDUs, 73% male, mean age 29</td>
<td>Tuberculin positive</td>
<td>15/197</td>
<td>5.4 (3.0-9.0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anergic</td>
<td>62/1649</td>
<td>3.0 (2.3-3.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tuberculin negative, non anergic</td>
<td>6/849</td>
<td>0.45 (0.16-0.97)</td>
</tr>
<tr>
<td>52</td>
<td>Madrid, Spain 1985-89 Patients referred to one hospital (including referrals from prison hospital), 78% IVDUs, 73% male, mean age 27</td>
<td>Tuberculin positive</td>
<td>24/84</td>
<td>10.4 (6.7-15.5)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anergic</td>
<td>20/112</td>
<td>12.4 (7.6-19.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tuberculin negative, non anergic</td>
<td>19/151</td>
<td>5.4 (3.3-8.4)</td>
</tr>
</tbody>
</table>

In both studies, initial CD4 counts were similar in the tuberculin positive and tuberculin negative, non anergic groups, and much lower in the anergic patients.

Tuberculin tests may be negative because the cut-off is too high, because the individual is not infected with *M. tuberculosis*, or because of a failure of the delayed type hypersensitivity response (anergy). Some studies have used skin tests with additional antigens in order to distinguish anergic from tuberculin negative, non anergic individuals. Incidence rates of tuberculosis in HIV-positive individuals may be lower in those who are anergic than in those who are tuberculin positive, since only a proportion of the patients will be infected with *M. tuberculosis*, or may be higher, since anergy is correlated with degree of immunosuppression. Among HIV-positive individuals in Italy, lower rates of tuberculosis were found in anergic individuals than in those who were tuberculin positive; in Spain and New York (mainly among intravenous drug users), and Uganda, rates were similar in the two groups, presumably reflecting higher background prevalence rates of *M. tuberculosis* infection.

The incidence of tuberculosis in HIV-infected individuals who are tuberculin negative but not anergic at the start of a study, compared to that in those who are tuberculin positive, gives an indication of the proportion of disease due to recent infection. Unfortunately this information is rarely available (Table 2) and, given the apparent success of isoniazid prophylaxis, further studies without prophylaxis are unlikely. The higher rates in Spain than in Italy fit with the reported prevalence of tuberculosis in the two countries. The data suggest that most of the disease seen in Italy in those previously infected (tuberculin positive) is a re-activation of the previous infection, whereas in Spain perhaps half is due to a new infection. However, this interpretation assumes that the tuberculin test is an accurate reflection of previous infection, and that the risk of becoming re-infected and developing disease is the same as the risk of being infected and developing disease for the first time, which is unlikely to be true. 

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*Resurgent/emergent infectious diseases*
Incidence studies based on outbreaks with known index cases in defined settings, such as HIV care facilities, suggest that infection and disease rates in HIV-positive individuals can be very high and that the incubation period can be very short. These findings need to be interpreted cautiously. Large, dramatic outbreaks will be investigated and reported preferentially. Indeed 'outbreaks' where no secondary cases are seen will be missed altogether although some transmission of *M. tuberculosis* may have occurred. Occasional dramatic outbreaks were also reported in the pre-HIV era.

An indirect method for estimating the proportion of disease due to recent infection is provided by DNA fingerprinting studies. Groups of patients with strains of *M. tuberculosis* with identical fingerprints, usually defined by restriction fragment length polymorphism of the IS6110 insertion sequence, are said to be 'clustered' and the strains (or at least all but one of a cluster) are assumed to have been recently transmitted. The proportion of tuberculosis patients in a population who are in clusters is used as an indication of the amount of recent transmission of tuberculosis. Estimates of 30–40% clustering have been made in studies in the US and South Africa. However, the interpretation of proportion clustered as a measure of recent transmission depends on the molecular clock of the marker system, which is as yet not known, and on the sampling of the population. Random incomplete inclusion of cases will underestimate clustering, but non-random inclusion, for example contact tracing, will tend to increase it.

The proportion clustered has been found to be higher among HIV-positive patients than among HIV-negative patients in some settings, and similar in others. This is likely to reflect the relative exposure, and perhaps susceptibility, to infection of HIV-positives and negatives, but other considerations are also important. Relative clustering will be influenced by the higher risk of progression to disease and shorter incubation periods of HIV-positive individuals compared with HIV-negatives, which apply, though not necessarily equally, to both recent and past infection. The amount of transmission of *M. tuberculosis* from HIV-positives and HIV-negatives will also influence the clustering seen, as this determines the chance of being the index case of a cluster.

**The impact of HIV on tuberculosis: direct and indirect effects**

It was initially feared that HIV-infected tuberculosis patients could be more infectious than HIV-negative patients, since the lack of cell-mediated immunity would encourage multiplication of the bacilli. On the other hand, more HIV-infected tuberculosis patients than HIV-negative tuberculosis patients have extrapulmonary disease, and those...
with pulmonary disease are less likely to have cavities. Several studies have measured tuberculous infection and disease in household contacts of HIV-positive and negative pulmonary tuberculosis patients. In Nairobi among HIV-negative contacts, and in Kinshasa among all contacts, the patterns of tuberculin positivity in the contacts of HIV-positive and HIV-negative index cases were very similar. In Lusaka, HIV-negative contacts of HIV-positive patients were less likely to be tuberculin positive than were similar contacts of HIV-negative patients, even after adjustment for smear positivity. In all three studies, background BCG coverage and tuberculosis infection rates were high, making any difference between the two sets of contacts hard to detect. No differences in disease rates among contacts by HIV status of the index case were found in any of these studies, but numbers were small. A study in Florida, where BCG is not routinely used and background infection rates are low, found lower risks of tuberculin positivity in contacts of HIV-positive cases than of HIV-negative cases, and this persisted after restricting the analysis to contacts aged 5-14 years (who are unlikely to be HIV-infected) and adjusting for smear positivity of the index case. A preliminary report from Rio de Janeiro also found lower proportions tuberculin positive among contacts of HIV-positive than of HIV-negative index cases. Outside a study setting, transmission from HIV-positive cases may be less than that from HIV-negative cases, simply because undiagnosed and untreated HIV-positive cases have a higher mortality rate than HIV-negative cases and so have less time in which to transmit.

Most estimates of the impact of HIV on tuberculosis at the population level have considered the direct effect, for example in terms of the population attributable fraction (PAF). PAFs of 30-40% have been measured in various studies in sub-Saharan Africa – sufficient to account for all the observed increase in tuberculosis cases in these areas. Worldwide, it is estimated that about 14% of tuberculosis cases will be directly attributable to HIV by the year 2000. Even if HIV-infected tuberculosis patients give rise to fewer secondary cases than do HIV-negative cases, any increase in the number of infective cases must increase *M. tuberculosis* infection above what it would have been without them (an indirect effect). If transmission were equal, and population mixing random, the annual risk of infection in the short-term would be expected to increase by the same factor as the increase in tuberculosis cases due to the direct effect of HIV. This factor is given by the ratio of the risk of tuberculosis in the general population to the risk of tuberculosis in the HIV-negative part of the population, or 1/(1-PAF). Using this formula, PAFs of 30-40% translate into expected increases in the annual risk of infection of 40-70% above what they would have been in the absence of HIV. In the longer term, there would be a further increase due to transmission from the extra second generation cases.
More complex models have been developed to try and estimate this impact, some principally to estimate the effect of various interventions. All models are constrained by the validity of their assumptions, and these seem to have (implicitly) assumed identical transmission probabilities from HIV-positive and HIV-negative tuberculosis cases.

It was initially unclear whether the impact of HIV would be sufficient to reverse the long-term downward trend in the annual risk of infection. It now appears that it may be. In the US, increases of 10% per year in the risk of infection between 1987 and 1990 have been estimated from the documented increase in tuberculosis cases in children under 5 years, though not all of this can be attributed to HIV. Preliminary results from Kenya show that the annual risk of infection calculated from tuberculin surveys in children has increased over the past decade in some districts, and that this correlates with the HIV prevalence in those districts.

**Conclusions**

There are multiple causes of the resurgence of tuberculosis, and the predominant factors vary between different parts of the world. In sub-Saharan Africa there is no doubt that HIV is of over-riding importance. In Eastern Europe it is probably a combination of poverty and deteriorating health care. In parts of Western Europe immigration is the key factor. Immigration and HIV have probably contributed similar amounts to the increase in the US.

The HIV epidemic presents new challenges in tuberculosis control, and the situation is likely to get worse. It is estimated that two-thirds of the world's *M. tuberculosis*-infected population live in Asia, many in areas where the HIV epidemic is still in its early stages. Apart from measures to control HIV, the response depends on vaccination, prophylaxis, and efficient case finding and treatment. The only available vaccine, BCG, is already widely used but is ineffective in many areas. Prophylaxis with isoniazid in dually-infected individuals has been shown to be effective in most studies, at least in the short term and has been recommended, but has yet to be widely implemented. Safe use requires exclusion of active tuberculosis in recipients, which is difficult on a large scale; without this precaution the result will simply be an increase in isoniazid resistance. Where much disease is due to recent infection, short term prophylaxis in known infected individuals can have only limited impact.

Currently the main emphasis in control programmes is on efficient treatment following the WHO DOTS (directly observed therapy, short-course) strategy. This aims to reduce transmission and hence the next
generation of cases. While it is possible to reverse upward trends in failing programmes\textsuperscript{14}, and DOTS can be implemented on a mass scale\textsuperscript{12}, success becomes increasingly difficult in the face of high HIV prevalence\textsuperscript{8}.

Acknowledgements

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