Contacts of tuberculosis patients in high-incidence countries

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SUMMARY

The risk of acquiring infection with *Mycobacterium tuberculosis* correlates with duration of exposure to an infectious source of tuberculosis. Contact identification is therefore a comparatively high-yield activity. However, in resource-poor settings tuberculin is rarely available, and even where it is available, non-specific cross-reactions to tuberculin resulting from BCG vaccination complicate the interpretation of tuberculin test results. The identification of a putative infection with *M. tuberculosis* in a contact must result in intervention. Excluding active tuberculosis is mandatory before preventive therapy is provided. This might prove difficult in areas where the most and often only affordable diagnostic means is microscopy. The International Union Against Tuberculosis and Lung Disease (IUATLD) has thus proposed to target preventive therapy to healthy children below the age of 5 years living in the same household as a sputum smear-positive tuberculosis case, with the sole recourse to clinical contact examination. While this approach will lead to treatment of a considerable proportion of uninfected children, the advantages are several-fold: first, these are the easiest identifiable contacts; second, they are particularly prone to progression to disease if infected; third, emerging drug resistance is of little concern at that age; fourth, administration of preventive treatment can be delegated to the source case. This approach is safe, simple, and affordable.

THE RATIONALE for giving high priority to tracing and identification of contacts of newly identified tuberculosis patients lies in the relative ease with which such contacts may be identified and the expected high prevalence of recently acquired infection in this group. However, there are a number of limitations to this active case finding approach. First, the probability of acquisition of infection is not only related to the potential infectiousness of the putative source, but critically dependent on the duration of exposure. Thus, while tracing the closest contacts may be highly efficient, it must be kept in mind that many additional contacts of brief exposure duration may be entirely missed, unless large amounts of resources are invested for a relatively modest yield.

There are four areas that must be addressed when considering contact investigations in countries with high tuberculosis case rates. The first concerns epidemiologic issues, the second the diagnosis of latent infection or tuberculosis, respectively, in contacts, the third the interventions to be chosen, and finally, how an efficient contact investigation scheme can be implemented in a national program.

Epidemiologic issues

It is a widely held conviction that active case finding among contacts of newly identified patients with poten-

tially transmissible tuberculosis is an activity with a high yield. In industrialized countries it has been shown to be a cost-effective intervention. In North America, 2–4% of close contacts are commonly found to have clinically manifest tuberculosis at the point of investigation, and up to one third is found to be latently infected. Much higher prevalences have been reported when tuberculosis was more frequent in industrialized countries and from low-income countries (Table).

Although contacts of newly diagnosed tuberculosis cases can be found across all age groups, the identification of recently acquired infection is more easily distinguished from a long-standing infection in younger rather than older contacts. Thus, although infection among contacts is discussed here for various age groups, the emphasis is on contacts who are children.

In a study in British Columbia and Saskatchewan, Canada, the prevalence of infection among intimate contacts of tuberculosis cases was compared to that in the general population. In white children, the risk of being infected was several times higher than in the general population, particularly among children exposed to sputum smear-positive patients. If only children who were intimate contacts of sputum smear-positive cases were considered, the cases identified amongst them accounted for 3.2% of all tuberculosis
cases found in the period. Thus, examination of a small fraction of the population that was easily accessible produced a considerable proportion of cases and probably a large proportion of all recently infected children.

A study conducted in Kenya in 1959 showed that 30% of children aged less than 6 years who lived in the same household of a sputum smear-positive case had a tuberculin skin test reaction in excess of 8 mm induration. The prevalence of clinically active tuberculosis was several times larger in children who were household contacts compared to the general population.

These findings in Kenya confirm the findings from a survey conducted in Tumkur, India, at about the same time. In the Indian survey, children aged under 5 years who were household contacts of bacteriologically confirmed cases had a prevalence of infection of 12% as compared to 2% in children in households without a case.

While prevalence surveys among contacts provide an indication of the magnitude of transmission and the prevalence of secondary cases at the point of investigation, this underestimates the problem, as cases will continue to emerge over a prolonged period, as shown in a pre-chemotherapy study in the United States. This emphasizes the need to include offering preventive therapy whenever such a screening program is carried out.

While it is well recognized that patients with sputum smears positive for acid-fast bacilli infect a larger proportion of their contacts than sputum smear-negative patients, it is worth noting that the difference in the prevalence of infection by type of index case disappeared in a study in Alabama, USA, if exposure had been sufficiently long.

Most of these contact investigations have centered around patients with potentially the most infectious forms of tuberculosis and contacts living in close proximity with them. It must therefore be kept in mind that, judging from extensive and/or modern approaches to contact tracing, a considerable proportion of persons recently infected by the index case will never be found. Nevertheless, the available data suggest that with some exceptions, investigation of close contacts, particularly children, is a high-yield activity.

### Diagnosis

Identification of latent infection requires tuberculin skin testing. Tuberculin is costly not because of the cost of a single dose, but because the vials that are available contain several doses, most of which must be discarded once the vial is opened. Furthermore, in addition to the requirement of a cold chain, the expiry date of tuberculin is relatively short. In most high-incidence countries, tuberculin is thus not available in peripheral management units. Even if it were, the interpretation of the test result is difficult, as these countries routinely use BCG vaccination.

If children are targeted in a contact investigation scheme, adequately diagnosing active tuberculosis can be very difficult. Various scoring methods have been proposed to diagnose tuberculosis in children. The method perhaps based on the most comprehensive data collection from various countries unfortunately includes tuberculin skin testing results, and is thus unlikely to be widely applicable. The first problem is thus to determine the presence of tuberculosis in a child without tuberculin skin testing. In addition, even if tuberculin skin testing is available, an initially negative test would require continued follow-up examinations subsequent to identification of the index case.

### Table: Prevalence of tuberculous infection and tuberculosis among household contacts of tuberculosis cases in high-incidence settings

<table>
<thead>
<tr>
<th>Study area and time</th>
<th>Index case characteristics</th>
<th>Age group (years)</th>
<th>Number examined</th>
<th>Prevalence of infection n (%)</th>
<th>Prevalence of tuberculosis n (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>India–Madras, 1956–1957*</td>
<td></td>
<td>0–4</td>
<td>101</td>
<td>25 (24.8)*</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5–14</td>
<td>163</td>
<td>15 (9.2)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>India–Tumkur, 1960–1961</td>
<td></td>
<td>0–4</td>
<td>69</td>
<td>8 (11.6)</td>
<td></td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5–9</td>
<td>53</td>
<td>28 (52.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10–14</td>
<td>64</td>
<td>40 (62.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kenya–Kiambu, 1959</td>
<td>Smear-positive</td>
<td>0–5</td>
<td>82</td>
<td>24 (29.3)</td>
<td>10 (12.2)</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6–9</td>
<td>90</td>
<td>54 (60.0)</td>
<td>14 (15.6)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10–14</td>
<td>77</td>
<td>52 (67.5)</td>
<td>10 (13.0)</td>
<td></td>
</tr>
<tr>
<td>Korea–Seoul, 1954</td>
<td>80% smear-positive</td>
<td>0–4</td>
<td>454</td>
<td>62 (13.4)</td>
<td></td>
<td>14</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5–9</td>
<td>470</td>
<td>31 (6.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10–19</td>
<td>865</td>
<td>91 (10.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Norway–Oslo, 1940–1953</td>
<td>76% smear-positive</td>
<td>0–4</td>
<td>1012</td>
<td>490 (48.4)</td>
<td>224 (22.1)</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5–9</td>
<td>607</td>
<td>392 (64.6)</td>
<td>167 (27.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10–14</td>
<td>499</td>
<td>366 (73.3)</td>
<td>83 (16.6)</td>
<td></td>
</tr>
</tbody>
</table>

* Incidence (attack rate) over 5 years of follow-up.
For the identification of cases of active tuberculosis, the only practical means available are clinical examination and sputum smear microscopy, and in some settings chest radiography.

Thus, while contact examinations may be potentially efficient, the practical difficulties are considerable in settings with high incidence rates, as these are usually also those with the least available resources.

**Interventions**

Any contact examination must have therapeutic consequences where indicated, that is either treatment of latent infection or clinically active tuberculosis. Before prescribing preventive therapy, there should be certainty about the absence of clinically active tuberculosis to prevent the emergence of resistance with single-drug therapy. The drug of choice for preventive therapy is clearly isoniazid: it is inexpensive and well tolerated. The disadvantage of isoniazid preventive therapy is the required long duration, which is probably at least 9 months. Cases of active tuberculosis identified during contact investigations should be treated with the recommended national treatment regimen.

**Role of contact examination and implementation of a sensible policy**

High-incidence countries pursue a tuberculosis control strategy which has been defined as a strategy primarily targeted at reducing the incidence of tuberculous infection through identification of potential transmitters of tubercle bacilli in the community, i.e., largely sputum smear-positive cases.

Using sputum smear microscopy among symptomatic contacts of all ages, only 0.8% of cases were found among contacts of sputum smear-positive index cases in a study in eastern Nepal. Contact investigations for such cases is thus not a particularly efficient activity: more than 100 people must be examined to identify a case in a population (contacts) which appears to be at about 10 times the risk of the general population, while only about five to 10 tuberculosis suspects spontaneously presenting with relevant symptoms need to be examined to identify a case. On the other hand, a study in Malawi identified contact tracing as a highly efficient activity for finding other than infectious cases, with a frequency of 7% of cases among contacts of newly identified sources of infection.

Industrialized countries that embark on an elimination strategy must address both reducing the incidence of tuberculous infection, as well as reducing the prevalence of tuberculous infection (i.e., identification of those already infected and providing them with preventive therapy).

A model has suggested that identifying and treating even a moderate proportion of recently infected persons will accelerate the elimination of tuberculosis much more efficiently than preventive therapy of persons with other than recently acquired infection. While this generic model probably holds for both high- and low-incidence countries, the staff in high-incidence countries is often overworked just by the task of controlling active, infectious tuberculosis. Importantly, it will not usually be possible to identify the majority of recently infected persons through simple case finding schemes among readily identified contacts. Adding elements of an elimination strategy, i.e., identifying persons already infected, must thus be considered very carefully. Clearly, any group that is targeted should have an expectedly high prevalence of tuberculous infection, be at particularly high risk of progression to tuberculosis, and be readily accessible to examination.

The International Union Against Tuberculosis and Lung Disease (IUATLD) thus recommends limiting contact tracing to children under the age of 5 years who live in the same household as a sputum smear-positive case. Those found healthy should be given isoniazid and those found ill considered for treatment of active tuberculosis. Nothing other than a clinical examination is recommended. There are several reasons for this recommendation. First, it targets the most vulnerable group, most likely in contact for a prolonged period of time (more so than older children who may be more frequently absent from home). Second, preventive therapy is unlikely to create resistance even if a healthy looking child actually has active tuberculosis, as children of that age as a rule have a small bacillary load. Finally, the index case can be requested to provide preventive therapy to the child. The duration of treatment might pragmatically be for the same period as the index case is being treated. In countries using 8-month regimens, this duration would be close to optimal.

Children in close contact with a sputum smear-positive case are also logistically one of the most easily accessible groups, and one would think that both the index case and the health care provider would agree on the desirability of preventing such children from getting tuberculosis. Although the risk of tuberculosis is higher the more recent the infection, cases may continue to emerge long after the diagnosis in the index case. Thus, reactivation of the infection when such children reach adolescence and adulthood might be successfully prevented through early preventive chemotherapy.

This approach is simple, but it has the distinct disadvantage that up to two thirds of children will receive ‘preventive therapy’, but are actually not infected with *Mycobacterium tuberculosis*. Because the alternative is abstinence from any intervention and children tolerate isoniazid well, this may nevertheless be justifiable.

Experience in IUATLD collaborative programs shows that most national programs have written recommendations in their manuals to offer preventive therapy to children under the age of 5 years who are in close contact with a newly discovered sputum smear-
positive case. Yet, the policy is rarely implemented. Only rarely are children who are household contacts called upon and examined, and preventive therapy in this group is rarely utilized (IUATLD, unpublished data). This rather disappointing observation may reflect the uncertainty about the role and the impracticality of contact investigations in high burden settings. It also indicates that the role of preventive therapy for groups that are more difficult to identify, in whom the risk of tuberculosis is lower or the risk of monotherapy higher, must be relegated to a lower priority for contact investigations as long as the most readily identifiable group, with a high disease risk and low risk of adverse events from the interventions (i.e., small children who are contacts of newly identified cases), is not routinely evaluated and treated.

CONCLUSION

Clearly, the identification of sources of infection and their curative treatment using the approach propagated by the World Health Organization remains the first priority of national tuberculosis control programs. Activities that include elements of contact identification and preventive therapy, particularly for small children, do not contradict such an activity and should be implemented more rigorously.28

References