CORRESPONDENCE

Conditional expanding post-exposure prophylaxis: a potential new tool for tuberculosis control

To the Editor:

The latest consolidated guideline on tuberculosis (TB) preventive treatment, released by World Health Organization (WHO) in 2020, strongly recommended that children aged <5 years who are household contacts of people with bacteriologically confirmed pulmonary TB and who are found not to have active TB should be recommended for TB preventive treatment even if TB infection testing is unavailable [1]. That means preventative treatment should be administrated to the children aged <5 years once exposure has occurred. The concept of such post-exposure prophylaxis (PEP) has been successfully practised for HIV prevention among at-risk individuals with occupational exposure or non-occupational exposure [2]. For TB, PEP is still a new concept, here we raise a proposal to explore whether PEP could be scaled up to the other high-risk populations as a potential tool to accelerate the achievement of the END TB global goal [3]. The development of a new strategy requires systematic research and sufficient evidence; hence, we are only undertaking some preliminary discussion here.

TB infection is now understood as a dynamic multistate gradient from infection acquisition to subclinical disease and clinically active disease. The outcome of exposure to *Mycobacterium tuberculosis* (MTB) is determined by a complex interaction of bacterial, host and environmental factors [4]. For the host, the initial exposure gradient, such as bacterial load, disease severity of the index case and the closeness and duration of the contact, were directly associated with the risk of developing primary disease [5]. In addition, the endogenous recurrence of TB was found to be mainly associated with weakened immunity of the host [6]. Therefore, due to the high risk of infection after exposure, household contacts and immunocompromised individuals were suggested to be target populations for TB preventive treatment in TB control strategies.

It has been suggested to be good practice to identify recent conversion (TB infection testing from negative to positive) particularly among close contacts when initiating TB preventive treatment [7]. However, imperfect performance of current immunological tests might lead to false-negative results, particularly for young children and immunocompromised individuals, such as people living with HIV (PLHIV) with low CD4 counts [8]. Hence, the updated guidelines strongly emphasised that TB infection testing should not be a prerequisite to start TB preventive treatment in PLHIV and household contacts aged <5 years, particularly in settings with a high TB incidence (*e.g.* >100 TB cases per 100 000 population). Based on the above evidence, we would like to discuss the possibility of PEP for those aged ⩾5 years who were household contacts of bacteriologically confirmed index cases and who were immunocompromised due to disorders other than HIV infection (*e.g.* people who are initiating anti-tumour necrosis factor treatment, receiving dialysis, or who have silicosis). Under the premise of TB exposure, such individuals might also get similar benefit from PEP. It is worth exploring a scoring system in different regions to rank risks of TB infection and disease development in individuals with MTB exposure and to prioritise TB control interventions for people most likely to benefit (figure 1).

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For individuals with high risk of exposure and thereafter developing and transmitting active tuberculosis, conditional post-exposure prophylaxis might be a potential tool for tuberculosis control https://bit.ly/39qHHh4

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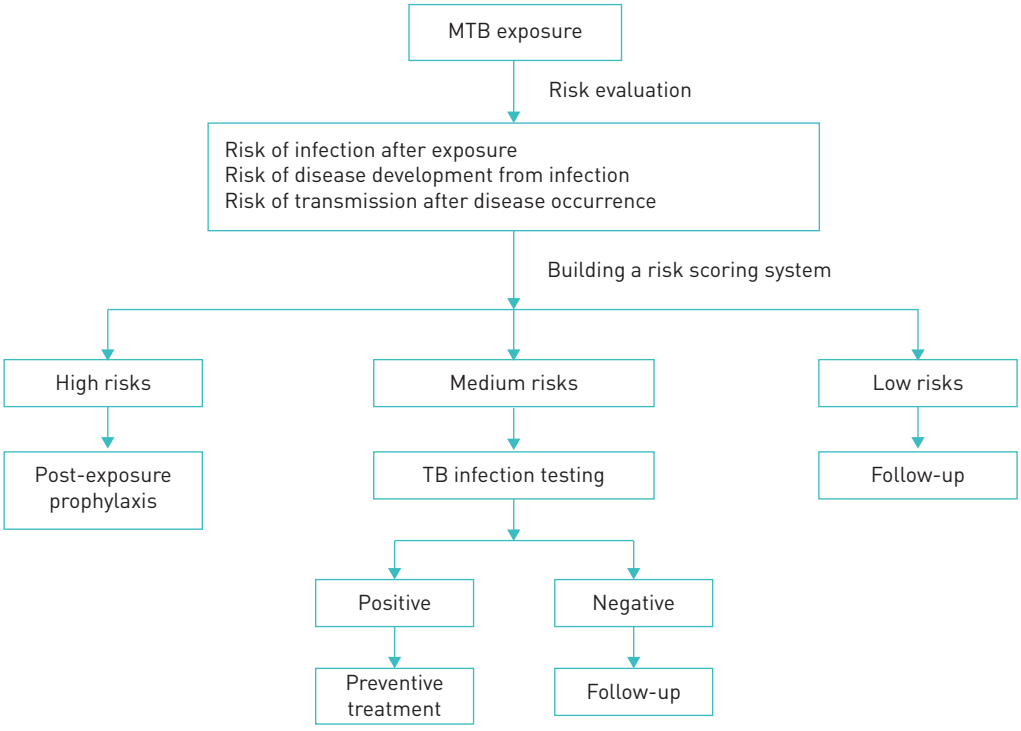

FIGURE 1 Building a risk evaluation system for individuals with *Mycobacterium tuberculosis* (MTB) exposure. For individuals with confirmed MTB exposure, a risk grading system should be built according to their risks of infection after exposure, risks of disease development from infection and risks of transmission after disease occurrence. For those with high grades of risks, post-exposure prophylaxis might be administrated regardless of tuberculosis (TB) infection testing results. For those with medium risks, priorities for preventative treatment should be given to those with positive TB infection testing results. While for those with low risks, regular evaluation and follow-up might be suggested.

In the new era with early initiation of antiretroviral therapy (ART), the risk and benefit of providing TB preventive treatment for all HIV infections should be reconsidered. For example, in addition to the damage caused by ART, long-term anti-TB treatment may bring extra damage to the liver that will subsequently influence the safety and tolerability of ART [9]. Therefore, from our perspective, for HIV infections starting ART at normal immune levels, TB preventive treatment might be considered only in case of exposure occurrence. Case-by-case assessment of the benefit and risk could be conducted to determine targets with HIV infection for TB PEP. Of course, such a personal view should be further discussed and verified by firm evidence.

At present, chemoprophylaxis is the most common tool for TB PEP. Although the efficacy of currently available TB preventive treatment regimens (ranges from 60% to 90%) works well, drug-related adverse events and incompliance should not be ignored [10]. As the potential benefit of preventive treatment should be carefully balanced against the risk for drug-related adverse events, great hopes are placed on immunotherapy which might have better safety and compliance [11]. The Vaccae vaccine is a specified lysate that has been licensed by the China Food and Drug Administration as an immunotherapeutic agent [12]. Currently, it is the only vaccine approved by the WHO that has completed a phase III trial to examine its effectiveness in preventing disease development from infection. It might be an alternative tool for TB PEP. Of course, evidence from clinical trials are needed to support our speculation.

From our perspective, PEP for individuals with MTB exposures and at high risk of infection and developing active disease might be a complement to the TB control strategy. However, as a new attempt, expanding PEP in more target populations still faces multiple challenges, such as establishing an algorithm system to assess exposure gradient, choosing a proper indicator to evaluate the efficacy of PEP and consideration of the balance of risks and benefits.

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