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## Prevent TB to end TB

Scaling up preventive therapy should be an urgent priority in regions that need it most

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Tuberculosis (TB) is the leading cause of infectious disease deaths globally, killing three people every minute.<sup>1</sup> The World Health Organization (WHO) published its *End TB Strategy*<sup>1,2</sup> in 2015, which set ambitious and laudable targets to reduce global incidence by 90% and deaths from TB by 95% by 2035. When global actors and heads of state convene in New York for the second UN high level meeting on TB on 22 September 2023, however, the scorecard will reflect dismal progress.<sup>3,4</sup> Among the failures, only 12.5 million adults of the 30 million targeted by the political declaration have received TB preventive therapy,<sup>1</sup> despite the original 2021 goal.

TB preventive therapy, long neglected as an effective component of strategies to eliminate tuberculosis,<sup>1</sup> is a course of medication to treat people who are infected with *Mycobacterium tuberculosis* but do not have active TB disease: their immune system is controlling the infection, without eradicating it. This state is often called “latent TB infection” and is usually diagnosed with a tuberculin skin test (Mantoux or Heaf test) or an interferon gamma release assay blood test. Chest radiography must be used to rule out active TB disease.<sup>1</sup>

Preventive therapy eradicates *M tuberculosis*, preventing onward progression to active disease and transmission. Modelling studies show that wider use of preventive therapy is essential alongside intensive active case finding to achieve progress in driving down TB prevalence and incidence.<sup>5-7</sup> Implementation is not a trivial task, but focusing on household contacts with appropriate counselling can achieve high success rates.

In recent years, preventive regimens—which include the drug rifapentine (a long acting rifamycin) and isoniazid given once a week for three months<sup>8</sup> and other variations<sup>6,9-12</sup>—have been studied extensively,<sup>5,6</sup> generating robust evidence of safety and efficacy.<sup>13</sup> These newer, shorter, and safer regimens are endorsed by WHO.<sup>13</sup> Yet roll-out to the people most at risk, especially household contacts of people with active TB, has been sluggish,<sup>13</sup> and preventive therapy is underused globally.

The clearest example of this underuse is from the Indo-Gangetic Plain region, stretching from Pakistan in the west, to Bangladesh in the east, through northern India and the southern Terai area of Nepal. With a population of about 800 million, this region has one of the highest population densities in the world.<sup>14</sup> This is very conducive to transmission of infectious diseases,<sup>15</sup> especially respiratory diseases such as TB and enteric diseases such as typhoid fever. Incidences of both are extremely high in the Indo-Gangetic Plain (approximately 250<sup>1</sup> and 500<sup>16</sup> per 100 000, respectively). TB preventive therapy is

almost completely unused in this region despite strong recommendations from WHO<sup>1</sup> and other international organisations.

Prevention needs to be prioritised and expanded because no effective vaccine for TB exists. The BCG vaccine is widely used, but it is only weakly protective, and new, more effective vaccines are desperately needed. Global efforts, including the landmark TB Vaccine Accelerator Initiative<sup>17</sup> and the critical M72 TB vaccine trial,<sup>18</sup> will help push the vaccine pipeline forward, but as no candidate vaccines are currently more than 50% effective, it is highly unlikely that a truly effective TB vaccine will be found in the next two decades.<sup>19</sup> We cannot afford to wait while millions more people die of a preventable disease.

TB preventive therapy is not a new concept—it was first implemented in the 1960s. Pioneering early studies in Alaska showed that protection after treatment could last at least six years and drive down community TB prevalence substantially.<sup>20</sup> Repeat treatment does not seem to offer additional benefit,<sup>21</sup> although this might depend on both the frequency of TB exposure and individual susceptibility to infection.

The TB community has not paid enough attention to preventive chemotherapy as a strategy, thinking instead that treatment of active disease would be enough to drive elimination. It wasn't. In sharp contrast, the HIV community, driven in large part by patient activists, has embraced the value of preventive treatment and harnessed its potential for disease elimination.<sup>22</sup>

Governments need to accept that TB preventive therapy is a cost effective intervention<sup>6</sup> and urgently prioritise its expanded use, in line with the “key asks” of patient groups at the UN high level meeting.<sup>23</sup> TB elimination is a complex undertaking that will require sustained collective action. All players, including the UN, Unitaid, the Global Fund to Fight AIDS, Tuberculosis, and Malaria, Wellcome Trust, the Bill and Melinda Gates Foundation, and patient advocacy groups, should act now to ensure prevention therapy becomes standard practice in low and middle income countries, as it is in high income countries.<sup>4,13</sup> Cure is crucial, but prevention is always better.

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