Tuberculosis (TB) also known as white plague is a major infectious disease and a global emergency. It is one of the oldest recorded human afflictions and still continues to cause widespread morbidity and mortality in children and adults worldwide, despite the extensive use of a live attenuated vaccine and several antibiotics. One third of the world’s population is already infected and about 3 million people die and 8 million people develop the active disease each year\(^1\)\(^-\)\(^2\). In the last decade there is a sharp rise in the cases of TB mainly due to emergence of multi-drug resistant (MTD), extensively drug-resistant (XDR) and totally drug-resistant (TDR) strains of *Mycobacterium tuberculosis*, which are virtually untreatable\(^3\)\(^-\)\(^7\).

In the beginning of the last quarter of the 20th century, there was a glimmer of hope that TB could be brought under control; however, this was dashed with the emergence of HIV/AIDS TB co-infection\(^8\). HIV compromises the immune system, which needs to be competent for control of latent *M. tuberculosis* infection, and hence increases risk of active TB manifold, from 10% risk over a lifetime to 10% risk within of TB is becoming worse day by day. Use of BCG is effective in preventing TB in efficacies. The only approved and currently available vaccine against TB i.e. BCG has young children that too with varied the year of co-infection\(^9\). Despite the fact that highest number of people on the earth has been vaccinated with BCG still scenario been given 4 billion times over the last 100 years since its development; we don’t even understand the precise immune mechanisms that protect BCG vaccinated infants and lacks protection in adults probably due to absence of generating long lasting memory cells. Thus, an effective vaccine for the prevention of pulmonary TB in adolescents and adults, many of whom are latently infected with *M. tuberculosis* in countries in which TB is endemic, is urgently needed to control the TB time bomb.

Immunity to *Mtb* is a two-edged sword: it protects the human host against disseminating infection, but also facilitates transmission of TB to contacts. Therefore, TB vaccines not only need to induce optimal immunity to *Mtb*, but also a balanced response that favors protective and avoids pathogenic mechanisms\(^10\). But the most successful vaccines today target pathogens against which humoral immunity suffices to achieve protection and often sterile eradication but TB vaccines need to drive primarily the cellular arm of the immune system.

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Tuberculosis Timebomb A Global Emergency, Manzoor Ahmad Mir
Tuberculosis Time bomb A Global Emergency, Manzoor Ahmad Mir 85

So the new vaccines candidates are needed which are better than BCG and must protect not only toddlers but also adults; be effective when administered pre-exposure and post-exposure with M. tuberculosis; and ultimately the next-generation candidates should be capable of eradicating or preventing infection with M. tuberculosis, while current vaccine candidates are aimed at preventing active TB disease by controlling latent M. tuberculosis infection(5). Currently extensive efforts are being put into the development of a better vaccine. Some of the live vaccine alternatives are quite promising for prevention of primary disease. The development of new TB vaccines should follows two basic
avenues; the first aims at replacing BCG either by genetically attenuated \( Mtb \) or by improved recombinant (r)BCG. And in both the cases the vaccine should be: more immunogenic, capable of inducing long lasting protection; safer for human use and should also induce protection against highly virulent clinical isolates such as MDR, XDR, TDR and \( Mtb \) Beijing strains.

The promising alternatives are recombinant BCG expressing listeriolysin from Listeria monocytogenes, over-expression of antigen 85B in BCG or recombinant BCG expressing cytokines like IL-18 and IFN-\( \gamma \) for more profound
Th1 cell polarization\textsuperscript{(10,11)} and deletion of antiapoptotic genes to facilitate cross-priming, introduction of genes encoding dormancy antigens such as the DosR-regulated gene products for postexposure vaccination of latently infected individuals\textsuperscript{(12)}, subunit vaccines of fused MTB proteins with novel adjuvants, heterologous vectors such as modified vaccinia Ankara or adenovirus expressing MTB proteins; attenuating MTB by removing virulence genes such as secA. One more way to improve BCG is either by introducing immunodominant \textit{Mtb}-specific antigens that are absent from BCG, such as RD1 locus-encoded antigens (ESAT6, CFP10)\textsuperscript{(13-17)}; or by over-expressing antigens that BCG already expresses by itself (cognates of Ag85 complex), but probably not sufficiently high throughout all phases of infection. Another way to improve BCG is by introducing genetic modifications for superior targeting of essential immune pathways, for example, by enhancing or facilitating cross-priming; and to inhibit its ability to neutralize phagosomal maturation. The second major avenue to develop better TB vaccines relies on the development of subunit vaccines which are non-live, or in the case of viral vectors, non-replicating vaccines, which can be delivered safely into the human host regardless of immune-competence. Researchers are now able to exploit cutting edge technologies in designing the most potent vaccine combination by using the prime BCG vaccine with super BCG (a rBCG vaccine that expresses listeriolysin) followed by booster doses with a super subunit vaccine\textsuperscript{(18)}. This logical approach of boost vaccination by introducing a second vaccine different from BCG at a later time point to use a heterologous prime–boost strategy for prevention of TB is also of high importance.

A booster dose may be used for two purposes, to strengthen the immunity of the BCG to prevent primary disease and to strengthen the immunity in individuals with latent infection with \textit{M. tuberculosis}\textsuperscript{(19)}. These vaccines would contain antigens secreted by metabolically active \textit{Mtb} as well as dormancy antigens. However the first attempt might be to combine current vaccine candidates to

### Tuberculosis in different phases of clinical trials

<table>
<thead>
<tr>
<th>Type of Vaccine</th>
<th>Candidate</th>
<th>Description</th>
<th>Clinical trial status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fusion protein in adjuvant for pre-exposure booster vaccination</strong></td>
<td>Hybrid 1+IC31</td>
<td>Fusion of Ag85B and ESAT-6 in adjuvant IC31</td>
<td>Phase I completed</td>
</tr>
<tr>
<td></td>
<td>Aerias-404:Hyvac+4+IC31</td>
<td>Fusion of Ag85B and TB10.4 in adjuvant IC31</td>
<td>Phase I ongoing</td>
</tr>
<tr>
<td></td>
<td>M72AS01 or AS02</td>
<td>Fusion of Rv1196 and Rv0125 in Adjuvant AS01 or AS02</td>
<td>Phase II ongoing</td>
</tr>
<tr>
<td></td>
<td>Hybrid 1+CAF01</td>
<td>Fusion of Ag85B and ESAT-6 in Adjuvant CAF01</td>
<td>Phase I ongoing</td>
</tr>
<tr>
<td></td>
<td>Hybrid 56+IC31</td>
<td>Fusion of Ag85B, ESAT-6 and Rv2660c in adjuvant IC31</td>
<td>Phase I ongoing</td>
</tr>
<tr>
<td><strong>Recombinant BCG for pre-exposure prime vaccination</strong></td>
<td>rBCG30</td>
<td>rBCG-expressing Ag85B</td>
<td>Phase I completed</td>
</tr>
<tr>
<td></td>
<td>VPM 1002</td>
<td>rBCG-expressing listeriolysin and urease deletion</td>
<td>Phase II ongoing</td>
</tr>
<tr>
<td></td>
<td>Aerias-422</td>
<td>rBCG-expressing listeriolysin</td>
<td>Phase I terminated</td>
</tr>
<tr>
<td><strong>Viral-vectors for pre-exposure booster vaccination</strong></td>
<td>AdAg85A</td>
<td>Replication deficient adenovirus 5 expressing Ag85A</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>Crucell Ad35/Aeras-402</td>
<td>Replication deficient adenovirus 35 expressing Ag85A, Ag85B, TB10.4</td>
<td>Phase II ongoing</td>
</tr>
<tr>
<td></td>
<td>Oxford MVA85A/Aeras-485</td>
<td>Modified vaccinia Ankara expressing Ag85A</td>
<td>Phase II ongoing</td>
</tr>
<tr>
<td><strong>Whole bacterial cell vaccine for therapeutic vaccination</strong></td>
<td>M. vacca</td>
<td>Inactivated M. vacca</td>
<td>Phase II completed</td>
</tr>
<tr>
<td></td>
<td>RUTI</td>
<td>Detoxified M. tuberculosis in liposomes</td>
<td>Phase II ongoing</td>
</tr>
</tbody>
</table>
achieve sterile eradication of the pathogen, i.e., prime with the best BCG replacement vaccine followed by a selection of subunit boosters. Further the tremendous progress in standardizing animal models of MTB infection has allowed complete comparison of genetically manipulated mycobacteria and new TB vaccines across the research centres around the world\textsuperscript{(20-23)}.

In the near future with little bit of focus, we may be ready to reap the fruits of the efforts of decades of research in developing one or two vaccines with proven protective efficacy and safety but this by no means signals the end of scientific efforts. In fact, an emerging bottleneck may not be the number of pre-clinical TB vaccine candidates that TB researchers can produce, but rather the number of vaccines that can be Table 2: Most Advanced vaccine candidates against tested clinically in efficacy trials, given the limited clinical trial capacity worldwide, i.e., a shortage that exists not only in Africa but also in Asia. Finally, the identification of TB surrogate end-point biomarkers or “correlates of protection” may drastically reduce the need for the current long-term large-scale clinical trials, and thus will speed up TB vaccine discovery and clinical testing. But this all needs a special focus on the TB research funding and fortunately the European Commission, the National Institutes of Health, and private foundations like the Bill and Melinda Gates Foundation, have instigated several mechanisms to support TB-oriented research and clinical trials \textsuperscript{(24–25)}.

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