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A Review on Recent Updates in the Management of Tuberculosis (Mdr/Xdr): New Treatment Regimens and Progress of Vaccination in Clinical Evaluation

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ABSTRACT

Tuberculosis (TB) is a severe infectious disease worldwide. The increasing emergence of drug-resistant Mycobacterium tuberculosis (Mtb) has markedly hampered TB control. In 2019 there were an estimated 500,000 cases of multidrug resistant TB (MDR-TB) of which only 186,772 MDR-TB cases were diagnosed, and positive treatment outcomes were achieved in 57% of them. These data highlight the need for accelerating and improving MDR-TB screening, diagnostic, treatment and patient follow-up services. The last decade has seen three new TB drugs being licensed; Bedaquiline, Delamanid and Pretomanid, and combinations these new, existing and repurposed drugs are leading to improved cure rates. Investing more in development of new TB drugs and vaccines shorter MDR-TB treatment regimens is required in anticipation of emerging drug resistance to new TB drug regimens. The WHO 2020 global report estimates thatTuberculosis (TB) is the leading killer among all infectious diseases worldwide despite extensive use of the Mycobacterium bovis bacille Calmette-Guérin (BCG) vaccine. A safer and more effective vaccine than BCG is urgently required. More than a dozen TB vaccine candidates are under active evaluation in clinical trials aimed to prevent infection, disease, and recurrence. After decades of extensive research, renewed promise of an effective vaccine against this ancient airborne disease has recently emerged. In two innovative phase 2b vaccine clinical trials, one for the prevention of Mycobacterium tuberculosis infection in healthy adolescents and another for the prevention of TB disease in M. tuberculosis-infected adults, efficacy signals were observed.

I. INTRODUCTION

Tuberculosis (TB) is a respiratory infectious disease caused by Mycobacterium tuberculosis (Mtb). The World Health Organization (WHO) reported approximately 9.9 million incident cases and 1.28 million deaths related to TB in 2020. Although a declining trend in the incidence and mortality of TB has been observed since 2010, the global TB burden remains a challenge. In addition, multi drug resistant (MDR)-TB poses a threat to TB control. For more than 10 years, approximately 3-4% of new TB cases and 18-21% of patients with TB with retreatment had MDR-TB or rifampicin (RFP)-resistant TB (RR-TB). Therefore, the importance of preventing Mtb transmission and identifying treatments for MDR-TB and XDR-TB must be recognized and addressed. Effective anti-TB regimens kill Mtb, improve the clinical symptoms of TB, and prevent the malignant development of the disease. The current standard treatment for drug sensitive TB is a combination of a short-course chemotherapy regimen under direct supervision recommended by the WHO, which uses four first-line drugs [isoniazid (INH), RFP, ethambutol (EMB), and pyrazinamide (PZA)] in the first two months of development, followed by INH and RFP in the last four months of consolidation. At present, there are limited varieties of anti-TB drugs in clinics, leaving clinicians with limited options. Therefore, there is an urgent need to develop new drugs with novel mechanisms to cure TB or shorten the treatment time for MDR-TB and provide effective support

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for TB control. Here, we reviewed the 45targets of drug action on Mtb and reported the corresponding newly developed drugs in recent years. These new drugs showed excellent anti-TB activity due to their action on different new targets, improved the cure rate of patients with MDR/XDR-TB, and significantly reduced the total mortality;however, some new drugs were more toxic than existing anti-TB drugs. Clearly, the rational and eff ective implementation of new drug regimens will overcome the "barrier" of drug-resistant TB and provide strong support for the goal of ending TB globally. Rifapentine half-life is five times longer than that of rifampin. However, once-weekly treatment with rifapentine (600mg) and isoniazid during the continuation phase of treatment, while effective, is inferior to twice- or thrice- weekly treatment with rifampin (600mg) and isoniazid in patients at high risk of treatment failure. Rifapentine is well tolerated when administered once-weekly at doss of up to 600mg. The tolerability and safety of higher and more frequent doses have not been rigorously assessed. On the other hand, there is reluctance to use rifampin at doses higher than 600 mg. Substitution of moxifloxacin for isoniazid substantially increases the bactericidal activity of rifamycin based regimens. We also assessed the treatment-shortening potential of daily and intermittent treatment regimens with more frequent administration of rifapentine to significantly increase rifamycin exposure.

Vaccines are the victories of immunology. Yet the development of effective vaccines that can provide lifelong protection against three of the most-deadly infectious diseases, tuberculosis (TB), human immunodeficiency virus (HIV)/AIDS, and malaria, has so far eluded vaccinologists. Pathogen evasion of the host immune response is the shared trait of these diseases. With1.6 million deaths annually, TB, an ancient airborne disease caused by Mycobacterium tuberculosis, is the top killer among all infectious diseases worldwide. Unfortunately, the current plan of actions are-not enough to achieve TB elimination in this century. Increases in the number of drug-resistant TB cases and converging syndemics of TB, HIV, and type 2 diabetes warrant novel prevention and control measures. Without effective TB vaccines, shorter treatment regimens, and improved point-of-care diagnostics, we will not be able to end the global TB epidemic.

Historical efforts to develop an effective TB vaccine are long-standing, going back to the 1800s, yet Mycobacterium bovis bacille Calmette-Guérin (BCG), a partially effective vaccine developed in 1921, remains the only licensed vaccine against TB. BCG is a part of the World Health Organization's Expanded Program on Immunization (EPI) and is listed on the WHO's list of essential medicines (233). Even though time-tested and most widely used, BCG has major limitations. Its efficacy against severe and extrapulmonary forms of pediatric TB is well recognized, but highly variable and poor protection at all ages against pulmonary TB remains a major concern. Despite the widespread use of BCG, it is estimated that around one-quarter of the world's population currently harbors a latent TB infection (LTBI), and around 3 in every 1,000 people globally carry latent multidrug-resistant M. tuberculosis infection. Although LTBI is by definition clinically asymptomatic and approximately 90% of individuals with LTBI will not progress to disease, this state in the spectrum of infection is a potential source of disease reactivation and remains a major impediment to TB elimination. A new TB vaccine that has greater protective efficacy than BCG and that can prevent disease in adolescents and adults, thereby interrupting M. tuberculosis transmission, is essential for global TB elimination and for achieving the WHO's "End TB" goals of 90 to 95% reductions in TB cases and associated deaths by 2035. The development of a safer and highly efficacious TB vaccine therefore should hold a top-priority position on the global research schedule. In the last 2 decades, over 20 vaccine candidates have progressed through clinical studies, and 14 are under active evaluation in clinical trials. Unfortunately, several candidates will not advance through clinical development, as vaccine development has historically been an empirical process. Disappointing results, as exemplified by setbacks in the MVA85A and AERAS-422 trials, highlight our incomplete understanding of the complexity of the host immune responses to M. tuberculosis and challenges associated with developing a vaccine that can elicit lifelong protective immunity. These trials highlight the gap in our knowledge of the correlates of protection or biomarkers that can predict who will control infection and who will develop the disease. However, results from recent path-breaking vaccine trials, together with recent advances in the identification of host biomarkers that have improved our understanding of the spectrum of M. tuberculosis infection, disease pathogenesis, and disease progression, promise that effective TB vaccines remain an attainable goal.

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In this review article, we discuss some of the challenges faced by current TB drug regimens and vaccine concepts, the progress of current vaccine candidates in clinical trials, potential avenues to build on recent successes and accelerate the TB vaccine research and-development (R&D) trajectory.

II. MATERIALS& METHODS:

METHODS IN THE DEVELOPMENT OF NEW DRUG REGIMENS AND VACCINES AGAINST ACTIVE TB.

METHODS:

It is believed that the pharmacodynamic response of TB infection to treatment is nonuniform, based on the efficacy of different drugs against sub-populations of M tuberculosis bacilli in varying metabolic states. Quantitative sputum colony counting studies in DS-TB support a biphasic model of bacillary elimination comprising a 5-7 day "Early Bactericidal Phase" during which replicating organisms are killed by isoniazid and a prolonged "Sterilisation Phase" when metabolically quiescent "persisters" are eradicated more slowly.

Rifampicin and pyrazinamide are currently the best first-line sterilising drugs but it seems that faster Sterilisation Phase activity is essential for shorter regimens. For this reason, compounds with strong bactericidal activity against dormant/non-replicating M. tuberculosis cultures and treatments which accelerate bacillary clearance in animal models are of particular interest. Drugs with these characteristics may proceed to efficacy trials in patients with pulmonary TB. Phase IIa extended Early Bactericidal Activity (EBA) studies are often used to measure the fall in log10 colony forming units (CFU)/ ml of sputum achieved by new compounds compared to standard rifampicin-isoniazid-pyrazinamide-ethambutol (RHZE) therapy over 7-14 days. This provides a rapid assessment of potency but it is unclear whether studies of less than 2 weeks duration accurately reflect Sterilisation Phase activity. Phase IIb trials of 8 weeks duration are a better test of new drug combinations but the most suitable microbiological endpoints for these are unclear. Ultimately, new DS-TB regimens require evaluation in Phase III trials with a clinical end-point of post-treatment relapse. This means approximately 500 patients per arm on study for 18-30 months. MDR- and XDR-TB trials require multi-site recruitment and even longer treatment and follow-up. Improved standardisation and validation of the surrogate endpoints used in Phase IIb studies is needed to ensure that candidate regimens taken forward to Phase III trials have the highest chance of success.

TRIAL DESIGN AND OUTCOME

The Tuberculosis trials association study 31/AIDS Clinical Trials GroupA5349 was an international, multicenter, randomized, open label, phase 3, nonferiority trial conducted at sites of the Centers for Disease Control and Prevention (CDC) tuberculosis Trials association and the National Institutes of Health AIDS Clinical Trials Group. Full details of the design and implementation of the trial has been previously published. Members of the protocol team from the Tuberculosis trials Association and AIDS Clinical Trial Group designed and implemented the trial and collected and analyzed the data. Protocol team included some of the authors. The first order of the document was written by the first corresponding authors. The authors verify the accuracy and completeness of the data the preparation of document to submit for publication. The trial was conducted in accordance with the principles of International Council for Harmonization Good Clinical Practice guidelines, Declaration of Helsinki and applicable regulatory requirements.

PARTICIPANTS:

The participants were persons with human Immunodeficiency Virus (HIV) infection were required to have a CD4 T-cells count of at least 100 cells per cubic millimeter and were enrolled to drug- drug interactions between rifapentine, 1200 mg once daily, and efavirenz. Participants were required to have at least one sputum specimen that was fast for acid fast bacilli on smear microscopy or M. tuberculosis on a rapid nucleic acid amplification test with a semi-quantative result of medium or high which appropriately matches the criteria for positive smear. The participants were 12 years of age or older and had newly diagnosed pulmonary tuberculosis that was confirmed on culture to be susceptible to isoniazid, rifampin and fluoroquinolones. Full details of criteria for eligibility are provided in the protocol.

RANDOMIZATION AND TREATMENT

The participants were randomly assigned in a 1:1:1 ratio to one of three regimens with the use of a central web-based system and the big stick. Randomization was stratified according to trial site, the control rule involved 8weeks of once daily rifampin, isoniazid, pyrazinamide, and ethambutol followed by 18 weeks of once daily rifampin and

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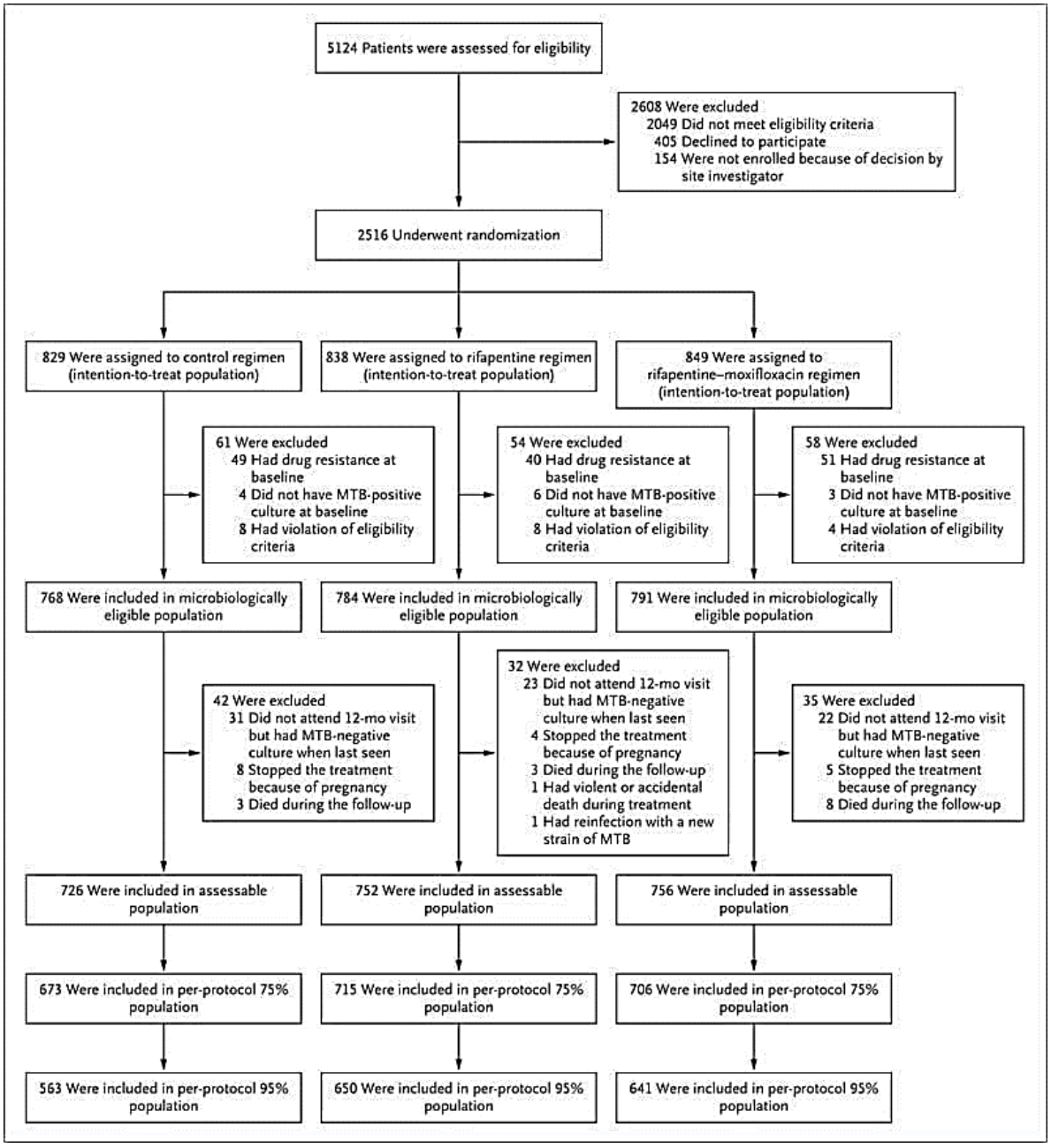
isoniazid. Rifapentine rule involved 8 weeks of once daily rifapentine, isoniazid, pyrazinamide and ethambutol followed by 9 weeks of once daily rifapentine and isoniazid. The rifapentine-moxifloxacin rule involved 8 weeks of once daily rifapentine, isoniazid, pyrazinamide and moxifloxacin followed by 9 weeks of once daily rifapentine, isoniazid and moxifloxacin. Moxifloxacin was administered at a daily dose of 400mg and rifapentine at a daily dose of 1200mg. According to body weight other drugs were administered at standard doses. Because food effect the absorption of rifapentine and rifapentine differently. Rifampin was administered on an empty stomach and rifapentine was administered within 1hour after eating food. The medication in each rule were administered 7 days per week, including at least 5 days of oneself directly observed therapy per week.



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TRIAL OUTCOME

The primary successful outcome was survival free of tuberculosis at 12 months randomization. The total duration of follow-up was 18 months. A secondary successful outcome of tuberculosis at 18 months has not been performed. The status with respect to primary outcome was determined for each patient (favorable, unfavorable or not assessable). Favorable position attribute if a patient was alive and free of tuberculosis at 12 months. Unfavorable position was determined if a participant had M. tuberculosis-positive obtained at or after week 17.

Status was not assessable if a participant did not already have an unfavourable outcome.

Table 2. Primary Efficacy Analysis in the Microbiologically Eligible and the Assessable Populations.*

Outcome	Microbiologically Eligible Population				Assessable Population			
	Control (N=768)	Rifapentine–Moxifloxacin (N=791)	Rifapentine (N=784)	Total (N=2343)	Control (N=726)	Rifapentine–Moxifloxacin (N=756)	Rifapentine (N=752)	Total (N=2234)
Favorable								
Participants with outcome — no. (%)	656 (85.4)	668 (84.5)	645 (82.3)	1969 (84.0)	656 (90.4)	668 (88.4)	645 (85.8)	1969 (88.1)
Adjusted difference from control — percentage points (95% CI)	NA	1.0 (-2.6 to 4.5)	3.0 (-0.6 to 6.6)	NA	NA	2.0 (-1.1 to 5.1)	4.4 (1.2 to 7.7)	NA
Participant had negative culture at month 12 — no. (%)	643 (83.7)	656 (82.9)	636 (81.1)	1935 (82.6)	643 (88.6)	656 (86.8)	636 (84.6)	1935 (86.6)
Participant was seen at month 12 but no sputum was produced or cultures were contaminated but without evidence of *M. tuberculosis* — no. (%)	13 (1.7)	12 (1.5)	9 (1.1)	34 (1.5)	13 (1.8)	12 (1.6)	9 (1.2)	34 (1.5)
Unfavorable								
Participants with outcome — no. (%)	112 (14.6)	123 (15.5)	139 (17.7)	374 (16.0)	70 (9.6)	88 (11.6)	107 (14.2)	265 (11.9)
Outcome related to tuberculosis — no. (%)	24 (3.1)	45 (5.7)	75 (9.6)	144 (6.1)	24 (3.3)	45 (6.0)	75 (10.0)	144 (6.4)
Two consecutive positive cultures at or after week 17†	11 (1.4)	34 (4.3)	63 (8.0)	108 (4.6)	11 (1.5)	34 (4.5)	63 (8.4)	108 (4.8)
Participant not seen at month 12 but had positive culture when last seen	11 (1.4)	3 (0.4)	4 (0.5)	18 (0.8)	11 (1.5)	3 (0.4)	4 (0.5)	18 (0.8)
Clinical diagnosis of tuberculosis recurrence and treatment restarted	2 (0.3)	8 (1.0)	8 (1.0)	18 (0.8)	2 (0.3)	8 (1.1)	8 (1.1)	18 (0.8)
Outcome not related to tuberculosis — no. (%)	46 (6.0)	43 (5.4)	32 (4.1)	121 (5.2)	46 (6.3)	43 (5.7)	32 (4.3)	121 (5.4)
Consent withdrawn during treatment period with no adverse event reported	14 (1.8)	15 (1.9)	11 (1.4)	40 (1.7)	14 (1.9)	15 (2.0)	11 (1.5)	40 (1.8)
Change in treatment because of adverse event	8 (1.0)	16 (2.0)	9 (1.1)	33 (1.4)	8 (1.1)	16 (2.1)	9 (1.2)	33 (1.5)
Death during treatment period	7 (0.9)	3 (0.4)	3 (0.4)	13 (0.6)	7 (1.0)	3 (0.4)	3 (0.4)	13 (0.6)
Loss to follow-up during treatment period	8 (1.0)	2 (0.3)	2 (0.3)	12 (0.5)	8 (1.1)	2 (0.3)	2 (0.3)	12 (0.5)
Consent withdrawn during treatment period after occurrence of adverse event	2 (0.3)	3 (0.4)	3 (0.4)	8 (0.3)	2 (0.3)	3 (0.4)	3 (0.4)	8 (0.4)
Treatment changed or restarted for other reasons	7 (0.9)	4 (0.5)	4 (0.5)	15 (0.6)	7 (1.0)	4 (0.5)	4 (0.5)	15 (0.7)
Not assessable								
Participants with outcome — no. (%)	42 (5.5)	32 (4.0)	35 (4.5)	109 (4.7)	NA	NA	NA	NA
Participant not seen at month 12 but had negative culture when last seen	31 (4.0)	22 (2.8)	23 (2.9)	76 (3.2)	NA	NA	NA	NA
Treatment discontinued because of pregnancy	8 (1.0)	5 (0.6)	4 (0.5)	17 (0.7)	NA	NA	NA	NA
Death unrelated to tuberculosis during follow-up	3 (0.4)	8 (1.0)	3 (0.4)	14 (0.6)	NA	NA	NA	NA
Violent or accidental death during treatment period	0	0	1 (0.1)	1 (<0.1)	NA	NA	NA	NA
Exogenous reinfection confirmed on WGS	0	0	1 (0.1)	1 (<0.1)	NA	NA	NA	NA

* The assessable population included the participants in the microbiologically eligible population who met the criteria for favorable or unfavorable status with respect to the primary outcome. NA denotes not applicable, and WGS whole-genome sequencing.

†Among the participants who had a microbiologically unfavorable outcome, one in the rifapentine–moxifloxacin group had an isolate of recurrent *Mycobacterium tuberculosis* that showed phenotypic evidence of resistance to isoniazid plus rifampin but was susceptible to isoniazid and rifampin on line-probe molecular testing (WGS results were not available) and three in the rifapentine group had isolates of recurrent *M. tuberculosis* that showed evidence of resistance to isoniazid plus rifampin (WGS results were not available).

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III. STATISTICAL ANALYSIS

Expecting that 15% of the volunteers who could be assessed would have an unfavorable outcome, that an additional 12% would reject from the microbiologically eligible population and that further 12% would have an outcome status that could not be assessed. To test the primary hypotheses that the 4-month rifapentine-moxifloxacin regimens would be noninferior to the 6 months standard control regimen, with a noninferiority margin of 6.6%points. Noninferiority was shown if the upper boundary of the 95% confidence interval around the difference was 6.6% or less in both the microbiologically eligible and the assessable population. To report for scores, a graded ordering hypotheses was prespecified in the protocolthe rifapentine-moxifloxacin group was compared with the controlled group first, and if noninferiority was demonstrated, the rifapentine group was compared with the control group.

IV. DISCUSSION

In this phase 3 trials, the efficacy of the 4-month rifapentine regimen containing rifapentine and moxifloxacin was noninferior to that of standard 6 months regimen. The efficacy of the 4-month regimen containing rifapentine without moxifloxacin did not meet the criteria for noninferiority. Adverse events are similar in both the rifapentine-moxifloxacin and control group and was slightly lower in the rifapentine group. In view of the possibility of using the rifapentine-moxifloxacin regimen in national tuberculosis programs, various issues are related. First, rapid drug susceptibility testing to fluoroquinolones and isoniazid should be performed in addition to the widely available rapid molecular drug liability testing for rifampin. Second, rifapentine absorb fast in the presence of high-fat food. Finally, drug costs maybe higher for the rifapentine-moxifloxacin regimen than the standard 6 months' regimen. In this trial, 4 months' regimen that included rifapentine at a daily dose of 1200 mg and moxifloxacin at daily dose of 400mg had an efficacy that was noninferior to that of the standard 6-months regimen across the primary, secondary and sensitivity analysis population.

V. RESULTS

Among 2516 participants who have gone randomization, 2343 had a positive for M. tuberculosis that was not resistant to isoniazid, rifampin or fluoroquinolones of whom 194 were coinfected with HIV and 1703 cavitation on chest radiography. A total of 2234 participants assessed for the primary outcome. Rifapentine-moxifloxacin was noninferior to the control in the microbiologically eligible population. Adverse events of grade 3 occurred during thetreatment period in 19.3% of participants in the control group, 18.8% in the rifapentine-moxifloxacin group, and 14.3% in the rifapentine group.

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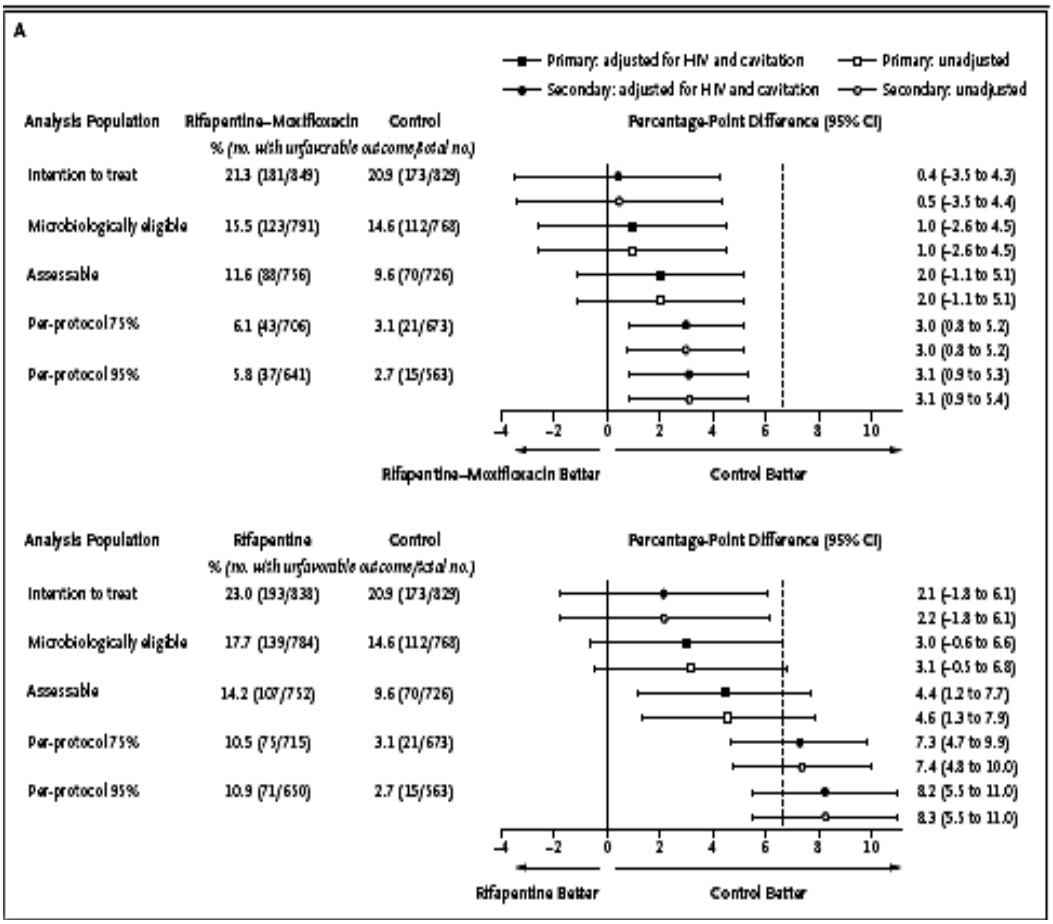

VACCINES:

Given the current commonness of TB infection, with the associated lifetime risk of progressing to active disease, it is most important that we protect future generations from this burden by halting transmission entirely. With greater understanding of the cellular processes involved in MTB susceptibility and pathogenesis, scientists have been able to identify various potential targets with a role in vaccination. Central to this is the cellular immune response, with a need to over express T-helper cell (Th)1, and downregulate Th2 and regulatory T-cell responses. It appears that MTB has also recognised the need to adapt to this

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hypo-inflammatory phenotype with more modern strains displaying shorter latency and higher virulence than previously seen.

TB VACCINE DEVELOPMENT

The human immune system can contain M. tuberculosis infection in most cases, and only 5 to 15% of people with latent tuberculosis infection progress to Tuberculosis disease during their lifetime. These figures, along with the evidence that some people remain negative by M. tuberculosis infection tests despite repeated M. tuberculosis exposures and that some individuals change back to being test negative after initially testing positive, suggest that humans can clear M. tuberculosis to avoid or abort infection. Furthermore, established latent tuberculosis infection seems to confer protection against subsequent tuberculosis disease upon reinfection in a proportion of individuals, strongly suggesting that infected humans mount protective immunity against M. tuberculosis, which can drive "natural-immunity-guided" vaccine development. Likewise, prior infection appears to be protective against reinfection in some animal models. This natural immunity to reinfection, termed concomitant immunity, likely requires clear immune responses other than the long-lived memory immune responses usually targeted by conventional vaccination strategies. It may also require natural myeloid cell activation elicited by prior infection or established latent tuberculosis infection. Furthermore, in the pre-antibiotic era, self-healing was reported for some pulmonary Tuberculosis patients, suggesting that the natural immune response can successfully heal or provide long-term control of clinical disease without antibiotics in some individuals. Long-term immunity against M. tuberculosis is clearly cell mediFIG 2, Current global clinical pipeline of Tuberculosis vaccine candidates. The 2019 global clinical portfolio of Tuberculosis vaccine candidates includes mycobacterial killed, whole-cell, or extract vaccine candidates (Vaccae, MIP, DAR-901, and RUTI); live-attenuated mycobacterial vaccine candidates (VPM1002, BCG revaccination, and MTBVAC). However, there is mounting evidence for a possible role of antibodies in protection. Antibodies that may contribute to protection have recently been identified in some individuals who remain healthy despite long-term, heavy M. tuberculosis exposures, with or without exhibiting signs of latent tuberculosis. These findings collectively offer potential evidence for the existence of natural immunity in those immunologically sensitized by M. tuberculosis infection and those not sensitized by M. tuberculosis infection. Although natural immunity might not be widely generalizable, it clearly can occur in some people (termed "resisters") and may inform rational tuberculosis vaccine design. These resisters, who persistently test negative by M. tuberculosis infection tests such as the tuberculin skin test (TST) and interferon gamma (IFN) release assays (IGRAs) despite heavy M. tuberculosis exposure, harbor antibody responses and non-IFN- T-cell responses to M. tuberculosis-specific proteins, suggesting that they may have in fact once been infected (or may still be infected) with M. tuberculosis. Therefore, understanding the immunological footprint and specificity of antigen recognition in these populations, including various high-exposure cohorts of resisters, and improved insights into M. tuberculosishost biology are vital for developing an effective vaccine.

BCG, A FRAMEWORK TO UNDERSTAND TB IMMUNITY

The principle behind BCG vaccination entails priming "natural immunity" to mycobacterial antigens, mimicking natural infection of the host, to generate immunological memory that ensures accelerated responses after exposure to M. tuberculosis. However, in spite of inducing a strong TH1 response, this vaccine has proven insufficient to control global TB epidemics, most likely because BCG does not usually protect against pulmonary TB. Early studies investigating BCG-elicited protection informed us about T-cell-based mechanisms of immunity. More recently, we have learned about the non-specific protection that it provides against general morbidity and mortality in infants from resource-limited counties. This heterologous beneficial effect against non-targeted diseases has been assign to effects on innate immune cell function, termed "trained immunity." It relies, in part, on the epigenetic imprinting of stem cells and innate immune cells, such as monocytes and NK cells, that exhibit memory-like attributes, providing evidence for innate-immunity-mediated protection.

TB VACCINES AND DESIRED IMMUNE RESPONSES

TB vaccines must induce responses to antigens that are expressed and presented during initial and later stages of M. tuberculosis infection. These responses must also reside in the appropriate tissue locations during the relevant infection stages. Unlike HIV and influenza virus, for which antigen

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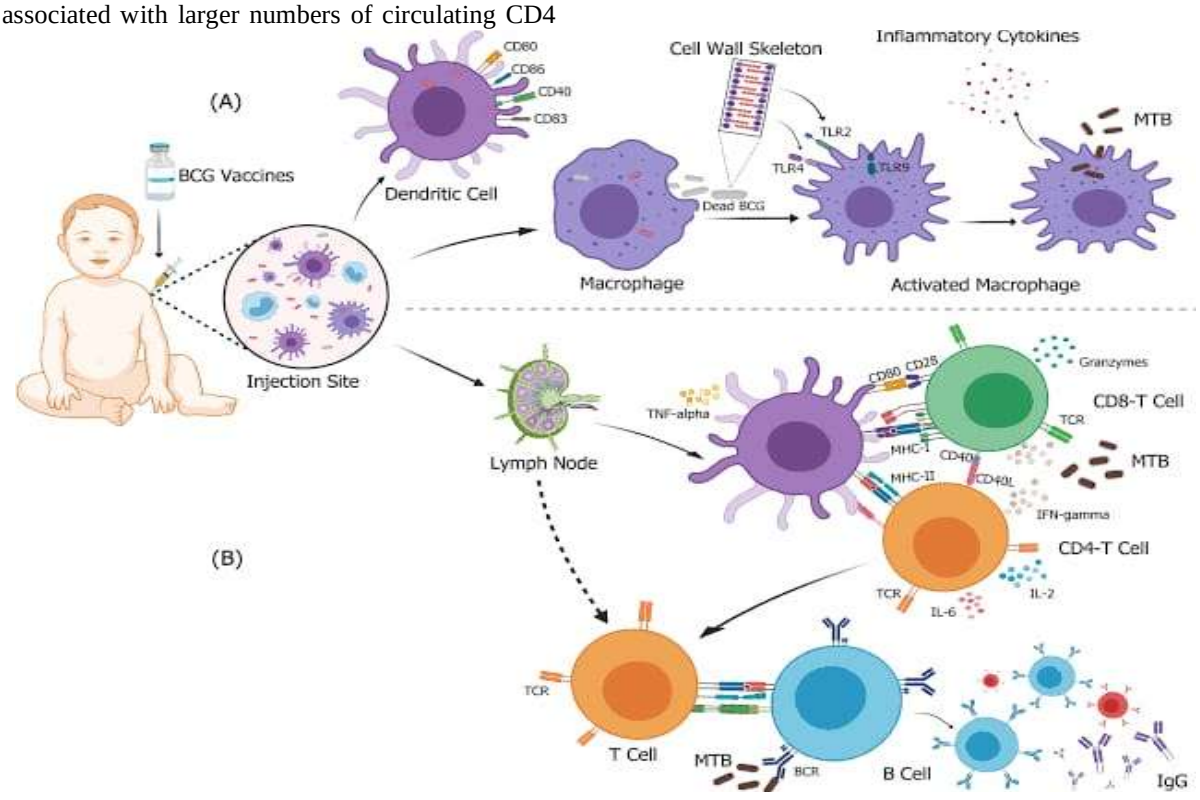
variation is a major vaccination challenge, M. tuberculosis proteins that comprise the main targets of human T cells do not exhibit significant sequence variation. The implications of the conservation of T-cell epitopes for vaccine development are not fully understood. Yet this phenomenon has fueled the theory that these immunodominant antigens deliberately drive persistent, robust T-cell responses which may act as "decoys" and divert the response from targeting the critical antigens. Exaggerated TH1 responses may also benefit M. tuberculosis, the theory suggests, by promoting an inflammatory environment that facilitates tissue damage, expectoration, and aerosolization of the pathogen to drive transmission. In HIV-M. tuberculosis-coinfected individuals, the occurrence of cavitary disease is associated with larger numbers of circulating CD4 T cells, supporting **this** possibility. This hypothesis must be considered in light of the knowledge that most M. tuberculosis-infected people have strong TH1-cell responses to the same immunodominant T-cell epitopes, which do not appear to drive pathogenesis. Taken together, our understanding of the T-cell responses required for effective control of M. tuberculosis, while avoiding immunopathology, has advanced considerably in recent years. To achieve control of M. tuberculosis, rational vaccine design should aim to elicit a balanced immune response that encompasses multiple components of pulmonary mucosal and systemic responses Since a single vaccine may not possess all "desired" attributes, multiple vaccines and combination approaches, such as heterologous boosting, may be required.



CURRENT TB VACCINE DEVELOPMENT APPROACHES

TB vaccine approaches can be broadly divided into prevention-of-infection (POI), prevention-of-disease (POD), prevention-of-recurrence (POR), or therapeutic vaccines to treat M. tuberculosis infection or TB disease. They are divided into live mycobacterial vaccines, subunit vaccines, and killed mycobacterial vaccines based on the platform used.

POI Vaccines

The POI vaccine, given preexposure, can prevent initial or sustained infection and is therefore thought to also protect against disease. As discussed above, several lines of evidence suggest that some people can resist infection despite repeated intense exposures, while BCG may also offer partial protection against infection, providing the rationale for the POI approach. POI trials are smaller, shorter, and FIG 3 (Continued) TRM cells at submucosa may act as sensory cells, recruit

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memory T cells, and/or act as early effectors to increase the kinetics of killing of M. tuberculosis-infected cells, leading to abortion of infection. Nevertheless, immune evasion strategies employed by M. tuberculosis likely present challenges for the prevention of infection, resulting in the establishment of infection in the interstitium. Induction of lymphoid follicles, as a local antigen presentation site, may be a desired feature of vaccination to reduce the bottleneck in delayed antigen presentation in draining LNs and impediment in the activation of TRM and TEM cells. Activated dendritic cells and other antigen-presenting cells during recall responses may rapidly initiate the activation of TCM cells and memory B cells. TB vaccines will need to elicit long-lived memory T cells, and these memory T cells will need to rapidly expand and generate secondary effectors with a sustained proliferative and "functional" capacity. Primed effectors will need to be specific to critical antigens in the life cycle of M. tuberculosis, possess lung-homing potential, traffic to the infection site, recognize M. tuberculosis-infected cells, and resist terminal differentiation or exhaustion. Mucosal antibodies may prevent infection or reduce the severity of infection, host-damaging effects, and systemic dissemination. Effector T-cell responses must be capable of eliminating infection, or at least enforcing lifelong control of infection, while preserving delicate anatomical structures. This necessitates appropriately placed, tightly regulated, and highly balanced pro- and anti-inflammatory responses. Although pulmonary mucosal vaccination appears to be capable of inducing a protective local immune response, it must be safe for administration. (C) Desired attributes of immune responses (portrayed and listed in panel B) to be elicited by a "modern TB vaccine.". less costly than POD trials, owing to the 8- to 10-fold-higher annual infection rates than TB disease rates in high-transmission setting. Such trials thus provide opportunities to study mechanisms of vaccine efficacy signals directly in humans, providing a platform to select lead candidates for further testing. A major challenge is that no tests are available to measure the acquisition, persistence, and clearance of asymptomatic M. tuberculosis infection directly. Current methods therefore rely on the detection of T-cell responses induced by infection, a process that takes 4 to 8 weeks. Furthermore, commercial IGRAs suffer from assay variability and uncertainty regarding the most effective assay cutoff. In addition, a vaccine candidate that cannot prevent infection might still protect against disease progression by inducing successful control of M. tuberculosis replication and would have a major impact on TB prevention. Conversely, a candidate that prevents infection in those individuals who, if infected, would in any case not progress to TB disease would have no or little impact on disease, transmission, and the TB epidemic. Despite these challenges, a recent landmark POI trial tested the ability of BCG revaccination or H4:IC31 subunit vaccination to prevent M. tuberculosis infection in healthy South African adolescents. H4:IC31 consists of a recombinant fusion protein (Hyvac-4) of TB10.4/EsxH and antigen 85B (Ag85B) in the IC31 adjuvant that signals through Toll-like receptor 9 (TLR9). Although neither vaccine showed efficacy based on the primary endpoint, namely, prevention of initial infection (QuantiFERON-TB gold in-tube [QFT] conversion at the manufacturer's cutoff), BCG revaccination significantly reduced the rate of sustained infection (QFT conversion followed by two consecutive QFT-positive results, 3 months apart, as a secondary endpoint), with an efficacy of 45.4% (95% confidence interval [CI], 6.4 to 68.1%), which might indicate the ability to help control or clear infection. BCG revaccination also showed an efficacy of 45.1% in preventing initial infection at a higher QFT cutoff of 4 IU/ml. Since QFT values above 4 IU/ml have been associated with a very high risk of TB disease in infants and adults, this result further supports the hypothesis that BCG-induced immune responses might have promoted improved control of M. tuberculosis replication or perhaps even sterilization. H4:IC31 vaccination showed an efficacy of 30.5% (95% CI, 15.8 to 58.3%) in preventing sustained infection, which did not differ significantly from that of the placebo group. Therefore, H4:IC31 is no longer in further clinical evaluation. These results encourage POI trials of other candidates in the pipeline and warrant further evaluation of BCG revaccination in M. tuberculosis-uninfected individuals to determine if prevention of infection and subsequent progression to TB disease can be achieved. Potential barriers to BCG revaccination include existing contraindication in HIV-infected individuals and interference by prior NTM exposures in some settings

POD Vaccines

A POD vaccine is given pre- and postexposure to protect against progression to TB disease. Epidemiological modeling suggests that an effective POD vaccine given to adolescents or

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young adults will have the fastest and largest impact on the global TB epidemic by interrupting transmission. Although most candidates in ongoing clinical trials aim to prevent TB disease, POD trials are larger, longer, and more costly than POI trials, owing to the lower rate of TB disease endpoints. To address this, the recent phase 2b POD trial of the candidate M72:AS01E subunit vaccine in South Africa, Kenya, and Zambia was conducted only with IGRA-positive individuals, a population with enriched TB case accrual. In an endpoint-triggered interim analysis of this trial, comprising 3,283 adults, the incidence of pulmonary TB was significantly lower in the M72:AS01E group than in the placebo group after a mean follow-up period of 2.3 years. The 54% vaccine efficacy reported in this trial establishes for the first time the proof of principle of vaccine-induced protection against clinical TB disease among persons already infected with M. tuberculosis. Although the observed confidence intervals are wide (95% CI, 2.9 to 78.2%), this proof-of-concept study supports further evaluation of M72:AS01E. These results defy widespread doughtfulness of the feasibility of such a vaccine for the POD indication in IGRA-positive people and represent an important advance. The final analyses of clinical data from this trial are slated to be released in late 2019. Because this trial included M. tuberculosis-infected adults who were predominantly BCG vaccinated, it was not possible to determine the extent to which infection-generated or childhood BCG vaccination-elicited responses influenced vaccine efficacy; additionally, the trial was not designed to determine whether M72: AS01E can protect against M. tuberculosis infection. The global vaccination strategy would ideally target both M. tuberculosis-infected and -uninfected individuals, avoiding the need for IGRAs. Because the lack of efficacy among IGRA-positive individuals might halt further clinical development of candidates in the pipeline with potential efficacy against infection, inclusion of both uninfected and infected individuals in future trials would be necessary.

POR Vaccines and Therapeutic Vaccines

Vaccines that aim to prevent recurrent TB (POR vaccines) are administered during or after TB treatment to prevent recurrence after cure. Therapeutic vaccines are administered as an adjunct to drug treatment to increase the effectiveness of treatment and shorten the duration of TB treatment. Since treated TB patients are at a severalfold higher risk of recurrent TB disease than matching community controls, the POR design achieves endpoint accrual with a much smaller sample size, providing a compelling rationale for POR vaccines. TB recurrence occurs in about 2 to 8% of TB patients after completion of treatment by relapse or reinfection, depending on the treatment effectiveness and transmission rates, and 70 to 90% of this recurrent disease occurs within 1 year of treatment completion. As recurrent disease accrual is greater and faster, POR trials are usually smaller and shorter than POD trials, but these trials are complex in design. TB treatment is 6 to 24 months long, arduous, and very costly, depending on drug-susceptible or -resistant disease. Furthermore, as an immunotherapeutic adjunct to chemotherapy, POR vaccines may simplify, increase the effectiveness of, or possibly shorten the duration of TB treatment. A therapeutic vaccine may also ameliorate disease severity, reduce treatment failures, and have a major impact on the personal, logistical, and financial burden of TB treatment. POR candidates that prevent relapse and reinfection may also prevent reactivation and could signal an expansion of testing from a POR trial into a larger POD trial. Candidates currently being tested for POR include the H56:IC31 and ID93:GLA-SE subunit vaccines, which were shown to prevent reactivation or limit disease severity in nonhuman primates (NHPs), as well as the rBCG vaccine candidate VPM1002. They are currently in phase 2 or 3 POR trials in TB patients during or after completion of treatment.

Killed Mycobacterial Vaccines

Killed mycobacterial vaccine preparations in clinical trials include RUTI, DAR-901, Mycobacterium vaccae, and Mycobacterium indicus pranii (MIP). RUTI is a liposomal formulation containing fragmented, detoxified M. tuberculosis grown under stress. As a potential therapeutic vaccine, it was found to be safe and immunogenic in persons with LTBI when administered 1 month after isoniazid treatment. It is under evaluation in HIV-infected and non-HIV infected persons with LTBI for POD, and an additional trial in persons with multidrug-resistant TB is planned. DAR-901, a broth-grown preparation of Mycobacterium obuense, is currently in a phase 2b POI trial in BCG-vaccinated adolescents in Tanzania. The efficacy data from this trial are expected in 2020. It is also under evaluation in HIV-infected TB patients as a therapeutic vaccine. SRL172, an earlier agar-grown M. obuense preparation, was evaluated in the first phase 3 efficacy trial conducted since BCG. Results of this trial suggested that multidose SRL172

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vaccination provides some protection against HIV-associated TB (39% reduction in culture-confirmed cases; hazard ratio, 0.61 [95% CI, 0.39 to 0.96]) in BCG-vaccinated adults. Yet the development of SRL172 faced challenges due to non-scalability. Several studies have also investigated killed M. vaccae and lysates thereof as an adjunct to antibiotic treatment, including in HIV-coinfected persons, and M. vaccae and MIP preparations are currently in phase 3 POD trials in China and India, respectively. Although efficacy data from the multidose M. vaccae (Vaccae) vaccine trial in TST-positive adults were expected in 2016, the status of this trial has not been verified in 2 years. While M. vaccae is already licensed as an adjunctive therapeutic vaccine in TB patients in China, MIP is licensed as a leprosy vaccine in India.

A clinical trial of MIP in household contacts of TB patients for POD indication is under way in India. However, efficacy signals provided by M. vaccae and MIP preparations as therapeutic vaccines are not definitive, and results from ongoing trials are eagerly anticipated.

Subunit Vaccine

Subunit vaccine candidates aim to boost BCG-primed responses and include virusvectored or adjuvanted recombinant proteins. The first subunit candidate to enter clinical trials was MVA85A, which delivered immunodominant M. tuberculosis Ag85A via a modified vaccinia virus Ankara (MVA) vector. Despite being safe and immunogenic in different populations and age groups in early trials, phase 2b efficacy trials of MVA85A did not demonstrate vaccine efficacy. In the first efficacy trial carried out in BCG-vaccinated South African infants, boosting with MVA85A did not show significant improvement over BCG in preventing M. tuberculosis infection or TB diseasedespite inducing Ag85A-specific TH1 and TH17 responses. MVA85A-induced TH1 responses were later found to persist for over 6 years, indicating a highly enduring response. In the second efficacy trial carried out with HIV-infected adults, MVA85A also enhanced Ag85A-specific TH1 responsebut yet again showed no efficacy against M. tuberculosis infection or disease compared to placebo. However, the latter trial was stopped early in light of the infant trial results and thus did not accrue the endpoints required for necessary statistical power. Several factors are speculated to have contributed to the failure of MVA85A to provide protection, including the use of a single antigen, hypo-immune responsiveness in infants, immunological interference by EPI vaccines, boosting at the peak of the BCG response, immunosuppression in HIV-infected adults, decreased Ag85A expression after M. tuberculosis infection, and reduced Ag85A availability in the lungs during chronic infection. Nonetheless, these results ignited intense and valuable debate in the TB field surrounding prevalent paradigms of protective immunity and vaccination strategies for TB. This led to the reconsideration of boosting prior IFN-/TH1 responses with newer TB vaccines and emphasized the need for more-stringent preclinical efficacy data for advancing only “best-in-class” candidates to late-stage clinical trials. Of significance is that it shifted the focus within the vaccine development community to preventing reactivation TB in adolescents/adults, to interrupt M. tuberculosis transmission. Additional clinical trials that will address some of these questions are under way, including combination boosting using simian adenovirus (Ad)- and MVA-vectored Ag85A vaccines by the aerosol route. Combination boosting by the systemic route using simian adenovirus- and MVA-vectored Ag85A vaccines (ClinicalTrials.gov identifier NCT01829490) and alternate aerosol and systemic immunizations using an MVA-vectored Ag85A vaccine (ClinicalTrials.gov identifier NCT01954563) were found to be safe and immunogenic in healthy BCG-vaccinated adults. Since BCG elicits a weak CD8 T-cell response, dominant CD8T-cell-response-inducing replicationdeficient adenovirus vector platforms also underwent clinical evaluations as novel BCG booster vaccines. These candidates include adenovirus serotype 35 (Ad35) expressing M. tuberculosis antigens Ag85A, Ag85B, and TB10.4 (AERAS-402) and human adenovirus serotype 5 expressing Ag85A (Ad5Ag85A). Even though preexisting anti-vector immunity in the trial populations did not dampen the strength of the booster response, Ad-platform-induced CD8 T cells either failed to recognize M. tuberculosisinfected human targets or failed to provide significant protection over and above BCG in NHPs. Consequently, the Ad35 candidate is no longer being perused, but the Ad5 candidate is still in clinical development.

Another recombinant virus-vectored candidate in clinical development, TB/FLU-04L, employs a liveattenuated influenza A virus vector to express M. tuberculosis antigens Ag85A and ESAT-6. Similar to the FluMist vaccine, TB/FLU-04L is delivered by the intranasal route. This delivery platform was found to be safe and immunogenic in healthy BCG-vaccinated, QFT-

negative adults in a phase 1 trial in Kazakhstan. An additional phase 2a POD trial of TB/FLU-04L is currently planned for QFT-positive adults**.**

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VI. CONCLUSION:

After decades of research,the available regimens are characterized by variable efficacy, safety, long duration and tolerability. These new regimens are ideally able to treat tuberculosis sustained by both drug-susceptible and drug resistance strains without interfering with antiretroviral drugs, those allowing a more effective approach against HIV infected cases. The efficacy of a 4-months rifapentine-based regimen containing moxifloxacin was noninferior to the standard 6-months regimen in the treatment of tuberculosisand the clinical development of a TB vaccine is now at a pivotal juncture, with exciting efficacy signals to improve on. Observations from recent TB vaccine clinical trials with efficacy have raised expectations for identifying correlates of protection against TB. The use of animal and human challenge models, harmonization of preclinical and clinical vaccine studies, and evaluation of vaccine candidates in innovative experimental-medicine trials will advance TB vaccine devilment. e advancing TB vaccine candidates, it will be important to manage expectations and maintain the momentum to yield licensed products.

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