An update on newer vaccines in development phase for malaria, tuberculosis, and human immunodeficiency virus/acquired immune deficiency syndrome

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ABSTRACT
Malaria, tuberculosis (TB), and human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) are the three major public health problems globally and especially affecting many in low-income countries, particularly in Sub-Saharan Africa and Southeast Asian region. For many years, these three most devastating diseases have received most of the world’s attention. The effective public health interventions in managing and controlling these diseases are able to reduce the burden to some extent but are not able to effectively prevent the occurrence of these diseases. Hence, lot of research is simultaneously going on in developing safe and effective vaccines against these diseases. Despite the continuous efforts to produce the effective vaccines against these diseases, there has not been much success, except recently for malaria, where anti-sporozoite subunit vaccine, RTS, S/AS01, has completed Phase III vaccine trials and got the positive regulatory assessment from the WHO. This review updates on the newer vaccines in the development phase for malaria, TB, and HIV/AIDS.

Keywords: Acquired immune deficiency syndrome, human immunodeficiency virus, malaria, tuberculosis, vaccine

Introduction
Malaria, tuberculosis (TB), and infection with human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS) collectively cause more than five million deaths per year but have nonetheless eluded conventional vaccine development; for this reason, they represent one of the major global public health challenges, as we reach toward the end of the 2nd decade of the 21st century.[1] Recent vaccine trials have provided evidence that it is possible to develop vaccines that can prevent infection by HIV and malaria and modify the response to existing TB vaccines. Advances in vaccinology, including novel adjuvants, prime-boost regimens, and strategies for intracellular antigen presentation, have led to progress in developing a vaccine against TB. In this review, we have summarized the vaccine research done so far and updated on the status of the newer vaccines in the developmental phase for these diseases.

Malaria Vaccine
Malaria is the most devastating parasitic disease afflicting humankind. About 43,800 people died due to malaria in 2015, and most of these deaths were reported from Sub-Saharan Africa and Southeast Asia and South America.[2] The disease results from infection with protozoan parasites of the genus, Plasmodium, and is transmitted by female Anopheles mosquitoes. A long-lasting, broadly efficacious malaria vaccine would be the most sustainable approach...
to control and eventually eradicate malaria. A malaria vaccine that may be feasible is strongly supported by the fact that people living in malaria-endemic areas develop protective immunity against malaria symptoms during childhood. There are more than thirty *Plasmodium falciparum* malarial vaccine candidates, which are being evaluated worldwide in different stages of clinical trials, including two indigenous vaccines from India. These are presented in Table 1.

After more than 50 years of intensive research and development, only one malaria vaccine candidate, i.e., anti-sporeozoite subunit vaccine, RTS, S/AS01, has completed the Phase III evaluation and got the positive WHO regulatory assessment. Despite only partial efficacy, this candidate is now forecasted to become the first licensed malaria vaccine. This vaccine is based on the recombinant virus-like particles of hepatitis B surface antigen displaying repeats from the *P. falciparum* circumsporozoite protein. It is preerythrocytic-stage hybrid recombinant protein vaccine. Results of a large multicenter Phase III trial of RTS, S/AS01, involving more than 15,000 children over 11 sites in Sub-Saharan Africa, have shown vaccine efficacy (VE) against clinical malaria of 51.3% (severe disease of 44.5%) after 12 months, 45.7% (severe disease of 37.7%) after 18 months, and 26% (severe disease of 2.2%) for whole period of 48 months after administering three doses in children aged 5–17 months at 1st vaccination and of 27% (severe disease of 15%) in infants aged 6–12 weeks at 1st vaccination. VE after administering four doses was 39% against clinical malaria and 31.5% against severe malaria for the whole period (48 months). The RTS, S/AS01 Clinical Trials Partnership reported the safety and VE of the RTS, S/AS01 vaccine during 18 months following vaccination at 11 African sites with varying malaria transmission. Despite this positive outlook, it is cautioned that this vaccine is only partially protective against disease and wanes over time. The WHO recommends pilot implementation of this vaccine with four dosage schedules in 3–5 distinct epidemiological settings, to examine the extent to which this vaccine impacts all-cause mortality including gender-specific mortality, and excess cases of meningitis and cerebral malaria need to be investigated for their causal association.

**Tuberculosis Vaccine**

TB is the ninth leading cause of death worldwide and the leading cause from a single infectious agent, ranking above HIV/AIDS. In 2016, there were an estimated 1.3 million TB deaths among HIV-negative people (down from 1.7 million in 2000) and an additional 374,000 deaths among HIV-positive people. The only licensed vaccine against TB, Bacillus Calmette–Guérin (BCG), protects against severe extrapulmonary forms of TB but is virtually ineffective against the most prevalent form of the disease, i.e., pulmonary TB. Currently, about 16 types of TB vaccines are being tested in different phases as shown in Table 2. The aim of the development of new TB vaccine is the generation of long-lasting protection against the most prevalent form of pulmonary TB in all age groups and focus on either replacement of BCG or as a booster following vaccination with prime BCG. A double-blind, randomized, placebo-controlled trial is considered the optimum design for a Phase III efficacy trial. For a disease where no current vaccine is available (such as for HIV or malaria), the ethics of trial design is focused on appropriate sample size and selection of placebo. The rabies vaccine is considered a good placebo for malaria as this will offer some benefit to those participants not receiving the malaria vaccine. For a new TB vaccine, the scenario is different due to the currently available TB vaccine, BCG. BCG is one of the most widely administered vaccines in the world and despite varying efficacy does provide some protection against childhood forms of TB. To date, it has been the view of researchers, ethics committees, and regulatory agencies that in a country where TB is endemic, it would be unethical to withhold the BCG vaccine in a randomized control trial of a new TB vaccine. This view has driven the development of vaccines designed to work in combination with BCG and slowed the development of vaccines designed to replace BCG. For a vaccine designed to enhance previous BCG vaccination, a randomized placebo-controlled trial of the boosting vaccine is possible without withdrawing BCG vaccination.

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**Table 1: Malaria candidate vaccines being evaluated worldwide**

| Protein adjuvants tested in clinical trials | Recombinant antigen delivery platforms tested in clinical trials | Heterologous expression systems used for cGMP manufacture | Recombinant malaria antigens progressed to clinical testing |
|--------------------------------------------|---------------------------------------------------------------|--------------------------------------------------------|----------------------------------------------------------|
| ADJU-PHOS (aluminum phosphate); Alhydrogel (aluminum hydroxide/alum); Alhydrogel + CPG7909; AS01B; AS02A; Montanide ISA 720; Montanide ISA 51; GLA-SE | Soluble protein; LSP; fusion protein; HBsAg VLP; EPA conjugate; Alfalfa mosaic virus coat protein VLP; virosome | *Escherichia coli*; *Saccharomyces cerevisiae*; *Pichia pastoris*; *Lactococcus lactis*; *Nicotiana benthamiana*; *Pseudomonas fluorescens*; *Drosophila S2* cells | PICSP; PIIRAP; PIcULOS; PIAMA1; PIHSA1; PILSA3; PIMSP1; PIMSP2; PIMSP3; PIGLURP; PIRESA; PIZA7A; PI11.1; PIEBAT17; PISERA5; PI3230; PI525; PvCSP; Pvs25; (PIRH5; VAR2CSA; Pf48/45; PVDGP); PIMSP-119 |

VLP - Virus-like particle; EPA - Environmental Protection Agency, PICSP - Plasmodium falciparum circumsporozoite protein, LSP - Long synthetic peptides, HBsAg - Hepatitis B surface antigen
The new TB vaccine (VPM1002) is a recombinant BCG vaccine. VPM1002 is a formulated, lyophilized cake of live recombinant Mycobacterium bovis rBCG. VPM1002 is the active pharmaceutical ingredient. It is a genetically modified BCG vaccine derived from the M. bovis BCG subtype. The available preclinical and clinical data reveal that VPM1002 is immunogenic and may be better than BCG in terms of safety. VPM1002 could be a safe, well-tolerated, and efficacious alternative to the BCG vaccine in the future. With an annual capacity of 100 million doses, Serum Institute of India Private Limited can meet the global demand for a BCG vaccine and is well poised to supply the new vaccine if efficacy trials are successful. Serum Institute of India Private Limited is conducting Phase II/III trial with two groups of adults successfully cured of Category 1 pulmonary TB receiving either VPM1002 or placebo. Single dose of VPM1002/placebo will be administered to calculate efficacy of the vaccine against TB recurrence. This study is designed as a multicenter, double-blinded, randomized, placebo-controlled trial with two groups of Category 1 pulmonary TB patients who have successfully completed anti-TB treatment and declared cured by bacteriological confirmation in India.

**Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome**

More than 40 million adults and children are living with HIV/AIDS worldwide and close to 5 million people (including 800,000 children) become infected each year. HIV/AIDS is the leading cause of death in Sub-Saharan Africa and the fourth biggest killer worldwide. Asia currently experiences the world’s fastest growing HIV/AIDS epidemic. Highly active antiretroviral therapy has reduced progression to AIDS, deaths, and HIV transmission from mother to child in North America and Western Europe. However, success with treatment has not been matched by progress toward prevention, and evidence of rising HIV infection rates is emerging, particularly in marginalized communities.

Development of a safe, effective, and affordable HIV vaccine remains the scientific and public health challenge of this new century. It is hampered by the tremendous genetic variability of the virus and the paucity of knowledge on possible immune mechanisms of protection. The first clinical trial of an HIV vaccine was conducted in the United States in 1987. Since then, over 30 candidate vaccines have been tested in over 80 Phase I/II clinical trials, involving over 10,000 healthy volunteers. Most of these trials have been conducted in the United States and Europe. A few trials also have been conducted in developing countries (Brazil, China, Cuba, Haiti, Kenya, Thailand, Trinidad, and Uganda) as well. The effort to develop and evaluate HIV vaccines was strengthened by the African AIDS Vaccine Programme.

Traditional approaches of using live-attenuated or whole-inactivated viruses were considered unsafe for the development of HIV vaccines because of the risk of permanently integrating proviral DNA within host chromosomes. Advancements in vaccine development had to wait until the mid-1980s when recombinant DNA technologies were becoming available. There are three scientific paradigms that have attracted researchers including induction of neutralizing antibodies, induction of CD8 T-cell-mediated immunity, and combination approaches. The status of HIV vaccines under development under these three approaches is presented in Table 3.
Table 3: Human immunodeficiency virus vaccines under development

| Study          | Antigen                  | T-cell | Combination (antibody/T-cell) |
|----------------|--------------------------|--------|------------------------------|
| Timeline       |                          |        |                              |
| Site           |                          |        |                              |
| Immunogen      | Clade B/B-Env            |        |                              |
| Delivery vehicle| Protein                  |        |                              |
| Characteristics of participants| 5100 MSM/300 Women |        |                              |
| Result         | No VE                    |        |                              |

Ad5 - Adenovirus type 5 vectored; HIV - Human immunodeficiency virus; IDUs - Intravenous drug users; MSM - Men who have sex with men; VE - Vaccine efficacy HVTN - HIV vaccine Trial Network; RV - Recombinant vaccine

Two gp120 products emerged as potential candidates for an efficacy trial under induction of neutralizing antibodies approach including VAX003 and VAX004. The Phase III VaxGen AIDSVAX gp120 trial failed to produce protection among men having sex with men in North America and drug users in Thailand, and it showed no VE.[17,18] Disappointing results of VaxGen trial made HIV researchers to turn from B-cell-targeted vaccines designed to induce neutralizing antibodies to T-cell targeted approach.[19] In 1998, it was observed that live attenuated canarypox virus expressing HIV antigens were capable of inducing CD8 cytotoxic T-cells against Env- or Gag-expressing target cells in 64% of the volunteers. This study established the prime-boost concept for future HIV vaccine research. The cytotoxic T-lymphocyte vaccine approach was to develop a vaccine designed to lower viral set point and delay disease progression, rather than to prevent initial infection. Hence, STEP and Phambili HIV vaccine was tested in trials.[20] However, the results were not encouraging. Then, vaccines based on combination approaches were developed and tested. RV144 trial turned out to be the first trial of a vaccine against HIV-1 to show any degree of efficiency. RV144 was a randomized, multicenter, double-blind, placebo-controlled efficacy trial of recombinant canarypox vector vaccine done among 16,402 health participants in Thailand.[21] The 1st-year VE approached 60%; however, the efficacy waned over time to 31.2% (95% confidence interval, 1.1–52.1; P = 0.04) over 42 months suggesting early but nondurable vaccine effect.

Recently, Kang and Gao review on strategies employed for the development of HIV vaccines emphasized on the killed whole-virus vaccine approach.[22] SAV001-H was the first preventive HIV vaccine which was developed using a killed or "dead version" of HIV-1 virus by Kang et al., at Western University’s Schulich School of Medicine and Dentistry in Canada. The result of the US, FDA, Phase I clinical trial, which was completed in 2013, showed no serious adverse effects in 33 participants. Vaccination with SAV001, the genetically modified and killed whole-HIV-1 vaccine, could enhance humoral immune responses including broadly neutralizing antibody production in HIV-negative individuals.[23] Therefore, SAV001 represents a promising starting point for the development of a safe and effective prophylactic HIV-1 vaccine using the killed whole-virus approach. This approach could be easily adaptable to include different subtypes of HIV-1.

Conclusions

It is stated that malaria vaccine, RTS, S/AS01, has completed Phase III trial and obtained the WHO-positive regulatory assessment. However, the WHO does not recommend its use in younger age category as VE is low and recommends to further examine its impact on all-cause and gender-specific mortality and its efficacy in different epidemiological settings. For TB, there are about 16 candidate vaccines in different phases of development and their results are awaited. One of the candidate vaccines for TB is being tested in India as well (VPM1002). For HIV/AIDS, SAV001 represents a promising starting point for the development of a safe and effective prophylactic HIV-1 vaccine using the killed whole-virus approach. The quest to develop a successful HIV, TB, and malaria vaccine is long and winding. We are entering the modern era of HIV, malaria, and TB vaccinology due to a better understanding of the immune mechanisms and pathways and newer forms
of vaccine immunogens. Hopefully, we will have better malaria, TB, and HIV vaccines in the future.

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