Spotlights on new publications

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New vaccine candidates IV

Malaria

Mosquirix® (RTS,S/AS01), a circumsporozoite protein-based vaccine, is the first WHO recommended malaria vaccine to be administered in children residents in moderate-to-high transmission African countries. Later, R21-Matrix-M was manufactured using R21, a virus-like particle comprising the central repeats of Asn-Ala-Asn-Pro (NANP), and C-terminal sequence of circumsporozoite protein fused to the hepatitis B surface antigen and a saponin adjuvant (Matrix-M). **Mehreen S Datoo** and her colleagues conducted a double-blind, randomized clinical trial (phase III) across four African countries with different malaria transmission intensities and seasonalities. The trial recruited 4844 children from Mali, Tanzania, Burkina Faso, and Kenya to evaluate the safety, immunogenicity, and protective efficacy of R21-Matrix-M. After vaccination, children [(5-36 months (m)] were followed up for 18 m at seasonal sites, and 12 m at standard sites. While 3103 children received 5 µg R21 plus 50 µg Matrix-M, the control group (1541 children) received licensed rabies vaccine (Abhayrab®). Both vaccines were administered in three doses (four weeks apart) followed by a booster administered 12 m after the last dose.

While side and serious adverse effects of special interest were recorded across 28 d after each dose, its protective efficacy was evaluated starting two weeks after the third dose up to 12 m. Clinical assessment, i.e., intensity of symptoms was recorded using standardized methods (temperature and parasite density), and all adverse events were monitored until resolution. Besides, its humoral immunogenicity was evaluated using measurement of IgG antibodies against the central NANP region sequence by ELISA before the first dose, at 28 d, and 12 m after third dose, as well as 28 d after the booster dose.

Results revealed that R21/Matrix-M vaccine was well tolerated with few adverse side effects; fever (46.7%), and pain at the injection site (18.6%) were the most frequent. However, there were 20 adverse events of special interest including 16 febrile convulsions, two cases of meningitis, and two cases of cerebral malaria. Vaccine protective efficacy evaluated after 12 m was 75%, and 68% at the seasonal and standard sites, respectively with no significant difference in efficacy between both sites. The younger age group had the highest 12 m protective efficacy of 79%, and 95% at both sites, respectively. Cross-sectional blood film results at 12 and 18 m showed significant reduction of parasite intensity in children who received R21/Matrix-M compared with those in the control group. Moreover, a significant rate of reduction was recorded at seasonal sites (86.8%) versus 29.6% at standard sites over 12 m follow up. The clinical trial also observed that R21/Matrix-M vaccine induced antibodies against NANP repeat sequence that was correlated with vaccine protective efficacy. The NANP-specific antibody production was higher in the younger age group (5-17 m) than those of 18–36 m age group. It was concluded that R21/Matrix-M was well tolerated and offered a high efficacy against clinical malaria in African children. Due to its safety, low-cost, and relatively high efficacy, the investigators recommended its large-scale supply aiming to reduce malaria' burden in sub-Saharan Africa. Compiled from **"Safety and efficacy of malaria vaccine candidate R21/Matrix-M in African children: A multicentre, double-blind, randomised, phase 3 trial." Lancet 2024 Feb, 403(10426):533-544.**

Echinococcosis

Since surgery is the main treatment for hydatid cyst, it is important to develop an efficient control strategy, e.g., vaccination to reduce the impact of cystic echinococcosis (CE) on human and animal. Research into vaccine development against CE is ongoing, but so far, no approved vaccines for use in human or animals. Previous studies showed that vaccinated animals have a higher level of immunity to infection than unvaccinated controls. On the other hand, vaccination of dogs (definitive host) against *Echinococcus* spp. is an important strategy to reduce eggs shedding into the environment, decreasing potential risk of human and animal infections. Several challenges address

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for vaccine protective efficacy including improved production process of recombinant antigens, ensured long-term stability, and using combinations of antigens.

In a systematic review, Iranian researchers (**Maryam Hataminejad, *et al.***) summarized the outcomes of 6 crude, and 35 recombinant antigens against *E. multicaulis*. Among the 6 crude or purified antigens or immunomodulators, protoscolex antigens were the most commonly used crude antigens. Recombinant vaccines included *Em*14-3-3 alone or in combination with other peptides or antigens, *Em*II/3 alone or in combination with BCG, *Em*Y162 with tetraspanins (TSP) genes, *Em*95, and antigen B. Besides, the most commonly used adjuvants were complete or incomplete Freund's, saponin, cytosine phosphoguanine oligodeoxynucleotides (CpG ODN), and alum. However, 13 studies utilized no adjuvants in their vaccination protocols. The route of administration also differed; subcutaneous (no.=19), intraperitoneal (no.=10), intranasal (no.=9), oral (no.= 4), and intramuscular (no.=3) with an optimal dosage of 50 µg. The majority of the reviewed studies utilized mice as an animal model, and few studies immunized other vertebrates, i.e., dogs, rabbits, pigs, and Rhesus monkeys. Challenge infection was performed either by intraperitoneal or oral injection of an infection dose ranging from 1000 to 2000 protoscoleces/animal. Of note, ~20% of these studies did not assess protective efficacy against challenge infection. To determine the immune response, studies used specific antibodies (total IgG, IgG1, IgG2a, IgG2b, IgG3, IgA, IgE, and IgM), as well as cytokine measurements (interferon-gamma, interleukins, and tumor necrosis factors). In addition, lymphocyte and splenocyte proliferation assays were performed in 27% of the reviewed studies.

Regarding vaccination outcomes, protection against *E. multilocularis* was achieved in both definitive and intermediate hosts. While vaccination of the definitive hosts significantly decreased worm burden and enhanced both mucosal and systemic immunity, it considerably reduced cyst width and weight. The best protective efficacy was obtained using recombinant vaccine of 14-3-3 antigen mixed with adjuvants either saponin (97%) or GERBU (84.47%). Using crude or purified excretory/secretory antigens combined with ribotan (an immunomodulator), a significant protection (91.70%) was achieved.

The reviewers discussed the results of these studies and concluded that recombinant vaccines containing *Em*Y162, *Em*95, and combined *Em*II/3-*Em*14-3-3 antigens as well as crude or purified excretory/secretory antigens formulated with ribotan exhibited the most efficient outcomes with sufficient immune responses against *E. multilocularis*. Compiled from **"Current status and future prospects of *Echinococcus multilocularis* vaccine candidates: A systematic review." Vet Anim Sci 2024 Mar 5:24:100345.**