Hot Topics – Vaccine Solutions for Tropical Diseases

In 2017, Bill Gates warned that an emerging, airborne viral disease remained the biggest infectious disease threat to humankind: "Whether it occurs by a quirk of nature or at the hand of a terrorist, epidemiologists say a fast-moving airborne pathogen could kill more than 30 million people in less than a year. And they say there is a reasonable probability the world will experience such an outbreak in the next 10 to 15 years."[1]

Since that time, COVID-19, caused by the betacoronavirus SARS-CoV-2, has emerged from a bat reservoir in temperate China, causing a global pandemic that has resulted in over 1.5 million deaths and 68 million cases of infection within 11 months, giving us a portent of the impact an emerging, airborne virus with a higher R number and case-fatality ratio might have on mankind in a future pandemic. HIV, a less easily transmitted blood-borne pathogen, evolved from multiple animal-to-human simian immunodeficiency virus (SIV) transmission events, primarily in the Congo and South Eastern Cameroon, has resulted in the deaths of 32.7 million people from AIDS-related illnesses since the start of the HIV epidemic in 1981. These two examples offer contrasting epidemiological pathways for highly infectious diseases following pandemic initiation events.

Currently, the haemorrhagic arboviruses (Ebola and Marburg haemorrhagic fevers, Crimean-Congo haemorrhagic fever (CCHF), Rift Valley fever (RVF), Lassa fever, Hantavirus diseases, dengue and yellow fever) are primarily limited by climatic conditions and the geographic reach of their vectors (ticks and mosquitoes) and are unlikely to spread uncontrollably in the immediate future, even with the accelerative effects of global warming. However, to put the threat of emerging tropical diseases into perspective, the World Health Organization estimates that a staggering 2 billion people harbour parasitic worm infections. The majority of high-burden parasitic and novel, highly pathogenic emerging viral infections occur within the tropics and sub-tropics (-30 to +300) where animal reservoirs occur in greater numbers and diversity and access to effective, long-acting prophylactics and curative treatments to such diseases is limited. A troubling truth regarding many zoonotic diseases is that advances in drug and vaccine development for such pathogens has frequently been driven by veterinary needs; the requirement to treat or protect large numbers of commercially reared animals for sale or slaughter. Drugs such as praziquantel and the benzimidazoles, staples in the treatment of cattle and latterly human helminthic infections, originated from research at the SmithKline Corporation into drugs for livestock. Albendazole was introduced in 1977 as an anthelmintic for sheep in Australia and was not registered for human use until 1982.[2] However, as global economies have begun to 'level up' and centralised vaccination programmes have moderated or controlled the majority of childhood diseases, monies are being made available as 'trickle-down' to tackle the less frequent infectious disease threats. Rabies, one of the World Health Organization's twenty neglected tropical diseases (NTDs), predominantly affects poor and vulnerable populations living in remote rural locations. Only very recently has rabies become subject to a (WHO) sponsored United Against Rabies eradication programme (2018). This campaign is largely dependent on vaccinating zoonotic reservoirs, mostly wild dogs and other mammals, although every year, more than 29 million people worldwide receive post-bite vaccinations. The traditional developmental pathway for tropical diseases vaccines is both long (10–20 years) and expensive ($1–2B) although the current SARS-CoV-2 pandemic may have ushered in a new paradigm of accelerated development based upon markers of safety over efficacy.

Of the neglected tropical diseases prevalent in 149 countries (affecting more than 1.4 billion people including more than 500 million children), only six are identified as controllable by existing drugs or vaccines and were prioritised by WHO for elimination or eradication by 2020. However, in terms of Disability Adjusted Life Years (DALYs, or the sum of years of productive life lost due to premature mortality and/or disability), tuberculosis and malaria have a higher impact than all twenty NTDs combined. Indeed, despite a global focus on HIV, the pathogen that has proved the most intractable, both in terms of sheer numbers of annual infections and resistance to a wide-ranging spectrum of initiatives is Plasmodium spp., or malaria (Figure 1.).

Disease	DALYs (in thousands; 95% CI)
Malaria	82,685 (63,426–109,836)
HIV/AIDS	81,547 (75,003–88,367)
Tuberculosis	49,396 (40,065–56,071)
NTDs	26,060 (20,300–35,120)
Intestinal nematode infections	5,184 (2,979–8,811)
Ascariasis	1,315 (713–2,349)
Trichuriasis	638 (349–1,061)
Hookworm Disease	3,231 (1,695–5,732)
Leishmaniasis	3,317 (2,180–4,890)
Schistosomiasis	3,309 (1,705–6,260)
Lymphatic filariasis	2,775 (1,807–4,000)
Foodborne trematodiases	1,875 (708–4,837)
Rabies	1,462 (852–2,659)
Dengue	***712 (226–1,513)***
African trypanosomiasis	560 (76–1,766)
Chagas Disease	546 (271–1,054)
Cysticercosis	503 379–663)
Onchocerciasis	494 (360–656)
Echinococcosis	144 (69–286)
Trachoma	144 (104–189)
Yellow fever	<0.5 (0–0.5)
Other NTDs	4,724 (3,525–6,351)

DALYs = Disability-adjusted life years; NTDs = Neglected tropical diseases; CI = Confidence intervals [62].
Citation for Table 3:
Murray, CJ (2014), *Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010*. Lancet, 2014. 380(9859): p. 2197–223.

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Figure 1: DALYs for NTDs versus the top three global infectious diseases

In 2019, there were an estimated 229 million cases of malaria worldwide with 409,000 deaths. Children aged under five years remain the most vulnerable group. In contrast, in the same period, 1.7 million people became newly infected with HIV, with 690,000 people dying from AIDS-related illnesses. Nineteen countries (in sub-Saharan Africa and India) carry almost 85% of the global malaria burden and more than 90% of the sub-Saharan Africa population live in malaria-endemic areas with little access to drug or vaccine prophylaxis.[3] Whilst there is a relatively effective vaccine for preventing tuberculous diseases (BCG; 50–58% VE)[4], both HIV and malaria have proved resistant to traditional vaccine development platforms and pathways. Barriers to development of

a malaria vaccine are many and varied, including market pricing in LMIC countries (poor return on investment), complexity of life cycle, multiplicity of antigen targets and short duration of protection. The current front-runner, GlaxoSmithKline's RTS,S, completed initial Phase III clinical testing in 2015, but owing to a proportion of serious adverse events in the paediatric population (5–17m), RTS,S has not yet been authorised for use and, despite a positive review from the EMA, the WHO has recommended further trials in the target age group before granting pre-qualification. With vaccine effectiveness in malaria vaccines observed to be approximately 30% at best, there would still appear to be room for improvement regarding both safety and overall performance.

Augmenting the traditional vaccine development pathways, the use of challenge trial efficacy data has proved pivotal in the licensure of vaccines against specific pathogens including malaria, cholera and typhoid. Malaria drug development has been accelerated with the establishment of controlled human malaria infection models (CHMI) for transmission (mosquito bite challenge), blood stage (infected erythrocytes) and liver stage malaria (direct venous inoculation of sporozoites). It is to be hoped that new malarial vaccine candidates may be also be fast-tracked according to relative efficacy obtained from human challenge modelling. Indeed, where traditional pathways for vaccine development have proved wanting, e.g. rapid advancement of 'best in class' or dose ranging studies, such CHMI studies offer accelerated route to licensure with smaller cohorts for similar or higher statistical significance. CHMI models are now operational in Kenya, Tanzania, Mali, Columbia and Thailand amongst other LMIC sites and these offer vital data for estimating vaccine effectiveness in non-naïve populations.

As mankind encroaches further onto natural preserves and interactions with exotic species becomes ever more commonplace, the need for pandemic preparedness is enhanced. COVID-19 is a 'shot-across-the-bows'. Next time we need to have better tools at our disposal and faster roll-out of stockpiled solutions if we are not to suffer a catastrophe similar to Spanish Influenza in 1918.

Developing a Vaccine for Tropical Diseases

Licensing and decisions on public health use of a vaccine rely on a robust development programme that permits a risk-benefit assessment of the product in the target population. Studies undertaken early in clinical development, as well as well-designed pivotal trials, allow for this robust characterisation.

The development of a vaccine from a tropical disease is no different in that regard, with the need for solid non-clinical, clinical and CMC development.

Non-clinical Development

The non-clinical safety assessment and design of non-clinical studies for vaccines for tropical diseases should follow the WHO Guidelines on non-clinical evaluation of vaccines.[5]

The design of preclinical safety studies should reflect route and frequency of administration, as proposed in the protocol to support clinical trials.

Immunogenicity and protective activity should be tested in an animal model. This study should demonstrate that the vaccine can protect from some aspect of infection and will be used to estimate dose range for humans. Toxicity and safety studies should also be performed in animals and should study if the product risks are appropriate for the anticipated use. They should focus on unexpected consequences of the effect of the vaccine dose and direct effects due to vaccine virus replication and tissue tropisms. The evaluation includes scoring and statistical analysis for histopathogical lesions and clinical signs between treatment and control groups.

If there is a risk for neurovirulence, this should also be examined for in animal studies. This is particularly true for dengue vaccines.[6] At this time, the most well-established model for vaccine neurovirulence is the non-human primate, which has historically been used to evaluate new seeds of yellow fever vaccines and live polio vaccines. Novel rodent (hamster and mouse) models for yellow fever vaccine virulence are currently under development. A rodent model could eventually be considered in place of non-human primate testing.

Clinical Development

The first part of the clinical development is a Phase I safety trial, in which the vaccine is administered to a group of healthy volunteers to test the safety profile of the vaccine.

In a second stage, usually an immunogenicity study is performed. The objectives of such an immunogenicity trial include selection vaccine formulations and posologies (including primary and booster doses), comparison of immune responses documented in a specific population.

Although not required as part of the critical path for vaccine licensure, controlled human infection model (CHIM) trials can provide initial proof-of-concept that a vaccine is likely to have clinical benefit, and this may de-risk decisions to evaluate candidates in large Phase III efficacy trials. There is also the potential for dengue CHIM to assist in the identification of an immune correlate of risk or protection and potentially expand the indication for a vaccine. There are several controlled infection models available for tropical diseases like malaria,[7] typhus,[8] dengue[9] and cholera.[10]

Vaxchora, a cholera vaccine (although only for travellers to endemic regions), has been approved both by the Food and Drug Administration (FDA)[11] and the European Medicines Agency (EMA),[12] based on a CHIM efficacy study. This CHIM efficacy study was supported by large Phase III studies in different populations to build a sufficiently large safety database.

Pivotal trials for vaccines will need to be conducted based on a clinical endpoint, until a surrogate or correlate of protection is established. The pivotal efficacy trials should be designed and powered to provide statistically robust estimates of vaccine efficacy to support licensure. They may evaluate a single vaccination regimen, or more than one regimen, and may or may not include evaluations of efficacy before and after booster doses.[13]

In case the vaccine will be co-administered with another vaccine, comparative immunogenicity trials that are intended to support co-administration of a vaccine with one or more other vaccines are required. The trials should demonstrate non-inferiority for immune responses to each of the co-administered antigenic components in the group that receives co-administered vaccines, compared with the groups that receive each vaccine given alone.

CMC Considerations

At the time the step from animals to humans is made in drug development, the product should already be very well characterised.

The potency of bacterial or viral antigens in the vaccine should be given special attention as this is a crucial factor to mediate toxicity

and other adverse reactions. Therefore, specifications for potency should ideally be set sufficiently narrow. Specifications being too wide might project into false dose estimations, thus leaving room for uncertainty regarding the validity of dosing assumptions defining the starting dose. Assays measuring impurities, sterility and inactivation of biological agents have to be available at this early point in development.

If possible, components (e.g., reagents, adjuvant and excipients) should be referenced to the relevant regulatory standards where monographs are available.

When developing a vaccine for tropical regions, it is important to follow the correct stability testing, to ensure the product is compliant with harsher climate conditions in the tropical regions. Following ICH stability guidelines,[14] the world has been divided into five zones, with each country assigned to a certain zone. The different zones are highlighted in Table 1.

Zone	Type of climate
Zone I	Temperate zone
Zone II	Mediterrean / Subtropical zone
Zone III	Hot dry zone
Zone IVa	Hot humid / Tropical zone
Zone IVb	Hot Higher / Humidity

Table 1: ICH Stability Zones

Zone	Temperature	Humidity	Minimal duration
Zone I	21°C ± 2°C	45% RH ± 5% RH	12 Months
Zone II	25°C ± 2°C	60% RH ± 5% RH	12 Months
Zone III	30°C ± 2°C	35% RH ± 5% RH	12 Months
Zone IVa	30°C ± 2°C	65% RH ± 5% RH	12 Months
Zone IVb	30°C ± 2°C	75% RH ± 5% RH	12 Months

Table 2: Long-term Stability Testing Conditions

Interaction with Regulators

As with any development programme, it is strongly recommended to interact with the appropriate regulatory agencies, via a scientific advice meeting, at different timepoints in the development, to ensure that all aspects of the programme are in line with regulatory expectations and meet the requirements of the licensure dossier.

This is especially important in the following cases:

- The clinical programme proposes a novel approach to any aspect of development for which there is no precedent or guidance available.
- The proposed programme conflicts with existing guidance to which the NRAs involved would usually refer when considering programme suitability.
- Particular difficulties are foreseen in providing evidence to support an expectation of vaccine efficacy (i.e. there is no immunological correlate of protection and a vaccine efficacy study is not feasible).
- There are other special considerations for the total content of the pre-licensure programme (e.g. when different vaccine constructs are to be used for priming and boosting).

Several regulators have established incentives for manufacturers to develop vaccines for neglected tropical diseases.

The European Medicines Agency (EMA), in cooperation with the World Health Organization, can provide scientific opinions on vaccines that are intended exclusively for markets outside of the European Union (EU). This is the so-called article 58 procedure, introduced in 2004.[15]

The aim is to facilitate patient access to these vaccines in low- and middle-income countries, including new or improved therapies for unmet medical needs.

In this procedure, EMA's scientific review is combined with the local epidemiology and disease expertise of WHO and national regulators in the target countries. It is targeted both at new vaccines and for improved versions of already authorised medicines.

EMA's Committee for Medicinal Products for Human Use (CHMP) assesses medicines and vaccines under this procedure to the same rigorous standards as medicines intended for use in Europe.

Following the evaluation, EMA publishes its scientific opinion of the benefit-risk balance of the product, which aims to facilitate prequalification of the medicine by WHO and registration in the target countries.

The FDA has a programme in place called the `Neglected Tropical Disease Priority Review Voucher system`. [17] Under this system, a company that receives approval for a product to treat or prevent a neglected tropical disease receives a so-called `Priority Review Voucher`. With this voucher the company can, for a drug / vaccine of their choice, request a review under FDA's Priority Review Designation pathway.

This pathway allows FDA to review a drug in just six months instead of the standard 10.

For companies and patients alike, FDA's priority review process can be extremely beneficial. For patients with serious conditions, the expedited review means they have access to a potentially life-saving or -changing treatment. For companies, it means they can market their product more quickly and begin recouping their often considerable development costs. As the priority voucher can also be sold to a third party, this has created quite an extensive secondary market.

This system was first set up under the Food and Drug Administration Amendment Act (FDAAA) of 2007, which created the Neglected Tropical Disease Priority Review Voucher system. The aim was to stimulate the development of compounds for a number of neglected tropical diseases. In 2014, a number of diseases were added to the list by the US Congress.

The FDAAA also gave FDA the regulatory authority to add any other infectious disease for which there is no significant market in developed nations and that disproportionately affects poor and marginalised populations. The FDA used this prerogative to add a number of diseases on the list.

The current list with diseases is presented in Table 3.

Eligible diseases under the Tropical Disease Priority Voucher	
Malaria	Blinding trachoma
Buruli ulcer	Cholera
Dengue/Dengue haemorrhagic fever	Dracunculiasis (guinea-worm disease)
Fascioliasis	Human African trypanosomiasis
Leishmaniasis	Leprosy
Lymphatic filariasis	Onchocerciasis
Schistosomiasis	Soil transmitted helminthiasis
Yaws	Tuberculosis
Added by Congress	
Cueva virus	Ebola virus
Marburg virus	Zika virus
Added by FDA order	
Chagas	Neurocysticercosis
Chikungunya virus disease	Lassa fever

Table 3: Eligible diseases under the Tropical Disease Priority Voucher

Conclusion

Tropical diseases are an emerging threat, not only in their original endemic regions, but also outside of those. This threat is

only expected to rise in the coming years. Developing a vaccine for tropical diseases broadly follows the same principles as the development of a regular vaccine, with some major attention points – like stability – that need to be kept in mind.

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