ARVAC
ALUMNI REFRESHER VACCINOLOGY COURSE

Written answers to questions not answered verbally

Week 2 - Day 3

Questions for Panel 2:

Questions	Answers from Alex Adjagba
What are the disadvantages to intergration?	I really dont know of disadvantages of being more efficient -)
Can you envisage that laboratories would be willing to fund at least some vaccines in the present situation?	i think it will help only if it is not vertical/earmarked and targeting the diseases they produce medicines for....

Questions for Georgios Stathopoulos:

Questions	Answers from Georgios Stathopoulos
Could WHO have mechanisms to incentivize development of vaccines for neglected diseases?	WHO is working along with partners to incentivize development for neglected diseases. The bottleneck there is the appetite for scaling up production, given that the market is not really profitable. Alternative models to the current ones should be considered in this framework to secure access.
The complexity of the supply chain circuits leads to a he storage of certain vaccines being altered . Does Africa not have the skills for local production ?	The first part looks to me like a statement. On the second, some countries already do, and others work towards this direction with regulatory strengthening, trainings, and more generally, assistance with local production. WHO leads on several fronts those initiatives, along with other partners
What is your opinion regarding those countries in which a vaccine clinical trial has been conducted? Should they have a special price once it has been approved?	Countries where clinical trials are conducted should be favored in some way (could be lower pices, faster access (Malaria vaccines were first piloted in countries that participated in trials) etc.) Access clauses should be worked out already in this early phase.
I understand that one of the main reasons why public funding is needed in early development is because of the high attrition rate in this phase of development, making private funding highly risky. What alternative could we consider with such limitation to better fund early development?	One could think of models that exist in the corporate sector, where early investors claim percentage of the profits that a startup they funded made. What if we had an R&D fund that is contributed to by Pharmas' profits that benefitted from the successful launch of a vaccine whose initial stages were de-risked by means of taxpayers' money? There are plenty of alternatives out there.

Given the various "defects" of the current vaccine market landscape you have so well described, what is your view of what does an ideal global vaccine market	Access to life-saving vaccines that HICs enjoy for everyone, at the same time, and at affordable prices! Sounds good? :)
How can we minimize vaccine waste. In covid 1/6 of the vial was wasted. That is also seen for other vaccines. Could this not help in reducing prices	I think wastage is a secondary issue when you are facing a lethal pandemic. All we need are vaccines, even if many are wasted. More generally though, there are efforts made to decrease wastage (UNICEF colleagues would be better placed to describe those). Generally, lowest wastage occurs with single-vial presentations (versus multi-vials), which are also the most expensive.
Previously I think WHO listed anti-vaxx and hesitancy as as one of the top 10 threats to global health how do we deal this this in vaccine use and supply	Hesitancy is definitely a major factor preventing us from getting to this last mile of coverage. Many efforts made to understand and tackle from a behavioral standpoint, a high priority for WHO.

Questions for Malick Gibani:

Questions	Answers from Malick
Can you envisage using a controlled human infection model in a pandemic due to an aggressive pathogen?	Highly unlikely due to ethics and safety -although SARS-CoV-2 CHIMs were conducted during the pandemic, and more recently ziKA
In jurisdictions like Brazil, where participant payment is prohibited, what ethical and operational strategies do you recommend to recruit and retain volunteers for CHIM?	You're right that country-to-country variation in regulatory standards can make moving challenge models to endemic countries difficult. There has been a lot of work in Brazil around the establishment of a hookworm challenge model. If I direct you to the following paper, it will give you an idea about some of the regulatory and logistical issues: https://pubmed.ncbi.nlm.nih.gov/34328562/
Typical cost of CHIM for efficacy? Much cheaper thna a typical phase 3	Cheaper but not cheap - est cost $1.5 to $3million for vaccine CHIM if a strain needs manufacturing
Since Nepal was also included how important is consent from the volunteer in minor/ major groups	At the time of writing, controlled human infection studies haven't been conducted in Nepal, instead a phase 3 typhoid vaccine study was conducted that helped to validate some of the findings from the challenge models. Country-to-country variations in regulations require engagement with the specific regulators. There are an increasing number of guidance documents that help to address these issues. Within South Asia, a paratyphoid challenge model is due to be set up in Pakistan. https://wellcomeopenresearch.org/articles/2-70
How's your work funded Gibani?..I'm thinking about this in relation to the first presentation.	Wellcome trust. Others (CEPI, Gates, MRC) also fund

Are there in-silico methods that are adding or even replacing some aspects of CHIS, su as systems pharmacology or organ-on-a-chip?	We would view these challenge models as being complementary to additional in vitro and/or in silico models. It is very difficult to fully model the complexity of the human host environment even within small animal or non-human primate models, particularly when accounting for variations such as diet, microbiome, genetics, etc. Additional systems like organoids or organ-on-a-chip models allow specific mechanistic insights that will be difficult to ascertain within a human host.
Which model is fit with the African context ?	Existing studies for schisto in Uganda, Malaria in Kenya, Tanzania, Pneumoccus in Malawi
How about the study of the impact of co-infections in CHIM in adults	Great question - flu-pneumococcus, rsv-pneumoccus in progress
Are the CHIMs more costly?	Cheper thanphase 3 but not super cheap
what do you mean by human challenge models?	Synonymous with CHIM
Any adverse events encountered in the human challenges you've handled, and how were they addressed?	Yes - as with most first in human studies. Need to provide back up healthcare if any complications
Are there any examples of CHIM evaluating secondary transmission of pathogens?	Yes, for flu - but practically challenging
How to handle limitations of external validity of CHISM given the strict elegibility criteria?	Absolutely - get us some of the way there but not perfect. Supporting data mostly
My question regards the use of placebos in possible future Human Challenge Trials (CHIMs). Given the ethical and methodological complexities involved, particularly the intentional infection of participants with pathogens, what is your view on the justification for using placebo control groups in such studies? Under what conditions, if any, do you believe this design remains acceptable from an ethical and scientific standpoint? Thank you.	This is a very important question and as always, there is no single right answer when we're discussing ethics. In my personal view, when testing a novel vaccine of unknown efficacy (outside of a pandemic), then it appears reasonable to include a placebo group - particularly if there are opportunities to offer vaccination at the end of challenge. In many bacterial challenge models, we offer the opportunity of rescue therapy, so all patients are appropriately treated. A deeper analysis of the ethical principles around challenge studies is available in WHO and other guidance documents. Please see the attached document for further assessment. https://ukpandemicethics.org/wp-content/uploads/2023/03/The-ethics-of-controlled-human-infection-model-studies-for-mitigating-pandemic-risks-Report.pdf
How well do findings from CHIM translate from carefully selected trial volunteers to broader, more diverse populations? In other words, can CHIM data truly speak for the real world, or do we need to combine with RWE data, biomarkers, epigenetic signatures? Thanks a lot for the great lectures	You're absolutely right. For many studies, we have seen high translatability between data from challenge study efficacy estimates to eventual efficacy estimates that have been observed in the field. This is particularly true for Salmonella Typhi, Cholera, and to a certain extent Shigella. For other vaccines, this has been less clear.

	Clearly, CHIM are not the be-all and end-all. In my view, these provide relevant supporting data at a very specific time point in the vaccine development timeline. It might be able to provide valuable supporting data to take a candidate from phase I through to phase II or from phase II through to an efficacy trial. It's not a be-all and end-all. Up until the point where we can accurately define correlates of protection, we still need to follow a traditional regulatory and testing pathway, but we would always need to combine it with real-world data.