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Fourth Controlled Human Infection Model (CHIM) meeting, CHIM regulatory issues, May 24, 2023☆

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☆This manuscript is dedicated to Rodrigo Correa-Oliveira, who contributed enthusiastically to the meeting in May 2023 but sadly passed away on 27 October 2023.

[1]Co-first authorship.

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Declaration of competing interest

All authors declare no competing interests.

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Abstract

Many aspects of Controlled Human Infection Models (CHIMs, also known as human challenge studies and human infection studies) have been discussed extensively, including Good Manufacturing Practice (GMP) production of the challenge agent, CHIM ethics, environmental safety in CHIM, recruitment, community engagement, advertising and incentives, pre-existing immunity, and clinical, immunological, and microbiological endpoints. The fourth CHIM meeting focused on regulation of CHIM studies, bringing together scientists and regulators from high-, middle-, and low-income countries, to discuss barriers and hurdles in CHIM regulation. Valuable initiatives for regulation of CHIMs have already been undertaken but further capacity building remains essential. The Wellcome Considerations document is a good starting point for further discussions.

Keywords

Low- and middle-income countries; Infectious diseases; Human challenge; Deliberate infection; Vaccine

Abbreviations

CHIMs	Controlled Human Infection Models
CoP	Correlate of Protection
DSMB	Data Safety Monitoring Board
GMP	Good Manufacturing Practice
IABS-EU	International Alliance for Biological Standardization - Europe
LMIC	Low- and middle-income countries
LRTI	Lower respiratory tract infection
NTS	Non-Typhoidal *Salmonella*

RCT –	Randomized controlled trial
RSV	Respiratory Syncytial Virus
UNCST	Uganda National Council for Science and Technology
URTI	Upper respiratory tract infection
VRBPAC	Vaccines and Related Biological Products Advisory Committee

1 Introduction

This CHIM meeting was organised by EVI and IABS as a satellite meeting to the fourth CHIM meeting in Mombasa, Kenya, on May 24, 2023, to discuss the regulatory issues of CHIM studies. Inno4Vac (https://www.inno4vac.eu) is a public-private partnership, coordinated by the European Vaccine Initiative (EVI), and funded by the second programme of the Innovative Medicines Initiative (IMI2). Inno4Vc addresses scientific bottlenecks in vaccine development, including the use of controlled human infection models (CHIMs, also known as human challenge studies and human infection studies) to enable early evaluation of vaccine efficacy and prediction of immune protection. This subtopic is dedicated to the development of new and improved CHIMs for influenza, respiratory syncytial virus (RSV) and *Clostridioides difficile*. Another objective is to develop a strategy, including ethical and environmental considerations, for the integration of CHIMs into pharmaceutical development.

Wellcome Trust has a Human Infection Study Programme which was set up in 2017 and has funded to date 6 human infection studies to be established across Asia, Africa, and Brazil for diseases such as Pneumococcus, vivax malaria, hookworm, and schistosomiasis to name some. As well as supporting these studies to be established there has also been a focus to support the enabling environment and as such Wellcome have supported WHO to establish ethics frameworks for the conduct of human infection studies across high income and low-middle income countries. In 2020, the programme pivoted to support the production of a GMP Delta SARS-CoV-2 challenge agent and the subsequent characterisation study. A major goal of the programme moving forward is to drive the utility of these studies in the development and licensure pathway for products including vaccines and therapeutics.

The International Alliance for Biological Standardization Europe (IABS-EU, https://www.IABS.org) is an independent, non-profit scientific alliance set up to provide a forum where scientists can discuss data to improve the quality and the regulation of biological products from human and animal origin. Previous meetings and webinars laid the foundations for CHIMs, including Good Manufacturing Practice (GMP) production of the challenge agent, CHIM ethics, the performance of CHIM studies in children, environmental safety in CHIM recruitment; community engagement; advertising and incentives; pre-existing immunity; and clinical, immunological, and microbiological endpoints [1–6].

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2 Approval of CHIM trials

Round table discussion with discussion points raised by the panel members and the audience (panellists: Eric Boateng, Food and Drugs Authority, Ghana; Melissa Kapulu, KEMRI-Wellcome Trust Research Programme, Kenya; Ally Olutu, Ifakara Health Institute, Tanzania; Bridget Wills, Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam; and Rodrigo Oliveira, Fundação Oswaldo Cruz, Brazil).

2.1 How was the approval process in your country/region?

2.1.1 Vietnam—The dengue CHIM was set up in a non-endemic setting, with the intention to conduct studies in endemic settings in future. The process of transferring the CHIM to Vietnam started with close interaction with local regulatory stakeholders. The COVID-19 pandemic disrupted this process, but it also increased the awareness and appreciation among the stakeholders and the general public of how CHIM studies help understand and potentially treat or prevent infectious diseases.

2.1.2 Brazil—The hookworm CHIM is the first CHIM in Brazil. This CHIM regulatory submission met unexpected issues during review. However, once the first study is accepted, it is anticipated that the regulatory review of other CHIM studies may be more straightforward. One significant issue for human studies of hookworm vaccines is that the key target populations are children and pregnant women. Given the absence of ethical and regulatory frameworks for CHIM studies in these populations, such studies are unlikely to be conducted for the foreseeable future.

Until recently, first-in-human studies, including CHIM studies, were not allowed in many African countries. This has changed, and therefore, the time is right to discuss the regulation of these studies.

2.1.3 Tanzania—This country has been a pioneer in CHIM studies in Africa and has shared its experience with other local countries. Stakeholder engagement is essential to ensure that regulators are confident and comfortable with approving CHIM studies. Beyond regulators and ethics reviewers, engagement should also include health care professionals, potential participants, and members of the community from which participants are recruited.

2.1.4 Kenya—An intensive and lengthy engagement process was conducted with key stakeholders, which resulted in the first CHIM study in Kenya being conducted in a low-endemic setting to demonstrate feasibility. Further engagement was necessary to perform the CHIM study in an endemic setting. A recent guideline change requires regulatory approval to perform CHIM studies.

2.1.5 Malawi—For the new CHIM on *Streptococcus pneumoniae* in Malawi, regulators and ethicists were engaged early, even before protocol development, to discuss their views on how the studies should be regulated and performed. Regulators and scientists appreciated the early engagement, as it streamlined the downstream review process. Community members previously involved in discussions on CHIMs also participated in the interaction with regulatory bodies, to share their opinions and insights.

2.2 Does the availability of vaccine candidates speed up the process of regulatory approval of CHIMs, as these can look at the efficacy of such candidates?

In Brazil, the target population for a hookworm vaccine is large, vaccine candidates are available for clinical evaluation, and public sector vaccine manufacturing facilities are available, all of which contribute to the priority given to reviewing CHIM studies by regulators. The hesitance of regulators in some regions to approve CHIM studies is not based on general regulatory or ethical issues but rather caused by a lack of clarity on CHIM study designs and the rationale for conducting such studies from a regulator's perspective. Training and engagement appear crucial in addressing this hesitancy. Of note, Brazil is not yet inclined to approve CHIM studies without viable vaccine candidates in the pipeline.

Whenever CHIM studies can be conducted and are established, they tend to be an option included in the overall discussions on vaccine development. In this regard, it was reflected that CHIM studies can have an important role in downselection of vaccine candidates. In addition, CHIM studies also offer an early means to demonstrate proof-of-concept. Both use cases guide vaccine development, including selection of candidates for and de-risking investment in larger clinical trials. Despite the utility of CHIM studies in vaccine development, the rationale and the underlying science for performing a CHIM study need to be clear to justify any associated risks to participants. Nevertheless, the value of CHIM studies goes beyond development of specific vaccines or testing specific interventions. Their value in translational research may justify conducting CHIM studies even in the absence of vaccine candidates.

2.3 What is the biggest remaining hurdle in the regulatory process?

Panellists highlighted as a significant hurdle the lack of a regulatory framework for conducting CHIM studies in many countries. For instance, how is the challenge agent assessed and what are the requirements for approval of their use? Panellists highlighted the need for a clear framework and/or guidance as a critical gap.

To regulators, manufacturing control and consistency is critical, particularly before full GMP validation of manufacturing processes and product analytics required for market approval. Because the intent is not to seek market approval for challenge material and there is no definition of GMP-like manufacturing of the challenge material, uncertainty exists to the requirement for challenge material. Previous meetings have discussed the minimum criteria to produce challenge agents [3,7], which is still considered sufficiently comprehensive.

2.4 How does the route of administration impact the review of the protocol?

The route of administration may not mimic the route of infectivity; this aspect is not always clearly articulated by sponsors and may impact the translation of study results to real-world settings. The natural route of infection may not always be feasible in CHIM studies; however, it remains important to stay as close as possible to real-world infection conditions. The trade-offs of CHIM study feasibility versus translatability often will need to be discussed on a case-by-case basis and carefully considered to ensure relevance of the results from a CHIM study. Regardless, it is essential to justify the use of a specific route of challenge in a CHIM study. For example, for the tuberculosis respiratory challenge model,

while it may be ideal to directly inoculate lung alveoli to mimic natural infection, doing so can be challenging and measuring subsequent bacterial load in these distal sites is difficult.

2.5 How does the use of naïve versus non-naïve patients or primary versus booster (e.g., Pertussis, influenza, COVID-19, …) impact the review of the protocol? Especially in a changing context of the model, as was the case for SARS-CoV-2

Clearly, the choice of study population has a significant impact on endpoint outcomes, as non-naïve patients often do not respond in the same way as a naïve population. In a non-naïve population, transmission models may be more difficult to investigate. As such, selection of the study population is therefore a highly relevant issue. One workaround is to evaluate different doses of the challenge agent in subpopulations with different levels of immunity. Particularly given the limited sample size in CHIM studies, using the appropriate study population is essential to a successful and interpretable study. Engaging in early dialogues with regulators to come to a common understanding of the model and its purpose were key messages expressed.

3 Use of CHIM in children

Round table discussion (panellists: Kawsar Talaat, Johns Hopkins Bloomberg School of Public Health, U.S.A, Michelo Simuyandi, Centre for Infectious Disease Research, Zambia, Melba Katindi, Katindi & Company, Kenya)

The safety of a potential CHIM study in children is an even bigger issue than the safety of CHIM in adults. At present, studies with new challenge agents cannot be conducted in children, whereas studies with a licensed live-attenuated vaccine, such as the oral rotavirus vaccine, are permissible in children because both the benefit and safety in children have been established. Whether use of licensed live-attenuated vaccines should be categorized as CHIMs was debated.

There are different categories of acceptability, including ethical, religious, and cultural, among others. Acceptability across all these categories must be met before a CHIM in children can be performed. Views on acceptability can change over time. For example, vaccine studies in pregnant women were unacceptable 15 years ago but are now considered fully acceptable. Some participants raised the point that in phase 3 malaria randomised controlled trials (RCTs) including a large number of children, deaths will occur, and these deaths are considered acceptable as a consequence of being in equipoise - the participant may or may not benefit from being vaccinated with the test vaccine, yet all derive some benefit from being in the study (e.g., through more ready access to standard of care and/or receipt of a control comparator vaccine). In CHIM studies on malaria, these deaths are not expected to occur because of close observation and early treatment. On the other hand, any infection comes at a cost to the child, e.g., in growth rate or, even worse, in long-term sequelae, such as brain development. This makes CHIM studies difficult to perform in children, there is no equipoise. Finally, it is not just the risk and lack of benefit; the sampling during the study, blood draws, swabs, may be traumatic to the child, which should also be taken into account.

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The disease burden and mortality figures are sometimes higher in children than in adults, so scientific studies need to be performed in children. But as with clinical trials, studies should be started in adults and moved to children only if enough evidence of safety is available. Trials, whether clinical trials or CHIMs, cannot be done in children first.

Then there are ethical and legal hurdles. How are you going to explain a complex topic such as CHIM, e.g., to a child or teenager to obtain assent? From what age can assent be provided? Who will provide consent on the child's behalf, the parent, the custodian, the caregiver? Further discourse on these topics is necessary.

According to U.S. regulations, to conduct clinical investigations in children involving greater than minimal risk or greater than a minor increase over minimal risk, the study must present the prospect of direct benefit to individual subjects, the risk must be justified by the anticipated benefit to the subjects, the relation of the anticipated benefit to the risk is at least as favourable to the subjects as that presented by available alternative approaches, and adequate provisions must be made for soliciting the assent of the children and permission of their parents or guardians. The requirement to present the prospect of direct benefit argues against CHIM studies in children, where the benefit is not toward the participant but toward society in the form of generalizable knowledge. Especially for regulators who are new to CHIMs, as is the case in many endemic countries, conducting CHIM studies in children is currently a step too far.

In summary, the time is not right for CHIM studies using pathogens in children. At the same time, the discourse should continue to explore options in the future.

4 What is the regulatory value of data from CHIM?

Wilbur Chen, Center for Vaccine Development and Global Health, University of Maryland School of Medicine, discussed the example of Vaxchora® licensure. The Vaccines and Related Biological Products Advisory Committee (VRBPAC) agreed that CHIM studies would be acceptable to license this vaccine, based on an engineered parental *Vibrio cholerae* O1 Classical Inaba strain 569B, named strain CVD 103-HgR. However, both the standardisation of the challenge agent, *Vibrio cholerae* O1 El Tor Inaba strain N16961, and validation of the CHIM attack rates and severity of illness had to be undertaken. This was done in a study at three sites, showing consistency and reproducibility [8]. Next, an efficacy study was done, showing that the efficacy against moderate to severe cholera diarrhoea was 91% and against any diarrhoea was 80% [9]. Due to manufacturer circumstances, licensure was not pursued until 2012 when a new Investigational New Drug application was registered by a new manufacturer. In 2013-2014, a phase 3 pivotal efficacy study was done [10], showing vaccine efficacy of 90.3% at ten days and 79.5% at three months post-vaccination. This study also showed that a four-fold increase in vibriocidal titre ten days after vaccination is a correlate of protection. Using this correlate, an immunobridging study could be done to extend the approval of the vaccine to 2-17-year-old children.

In early, non-placebo-controlled studies, participants were invited back after three years and rechallenged, showing that they were still protected against disease. No ongoing post-

marketing studies are looking into the real-world effectiveness of the vaccine to compare these to the efficacy found in the CHIM studies.

To be able to use CHIM data for pivotal efficacy to support U.S. FDA licensure, the model preferably should be validated. This encompasses both the analytical and the clinical validation. To ensure analytical validity, the model must be reproducible in different settings and over time. A major step toward this is standardisation of the challenge agent to make sure that participants are challenged with exactly the same dose. But it also entails using an established set of disease endpoints. This should lead to a consistent attack rate. Clinical validation focuses more on the experimental challenge resembling the natural infection, leading to similar symptoms and outcomes. While this was achievable for cholera, with clear disease symptoms in participants closely matching those that occur in infected people in endemic areas, it may be more difficult for other challenge agents, which leads to less specific symptoms.

Although the CHIM studies for cholera worked well for the licensure of the vaccine for travellers from high-income countries, for use in endemic areas, CHIMs performed in healthy U.S. adults will not provide the answer of efficacy in target populations of LMICs.

Malick Gibani, Imperial College London, United Kingdom, discussed the invasive Non-Typhoidal *Salmonella* (NTS) experience. The *S.* Typhi challenge model showed consistent attack rates between studies, showing that the model is reliable and reproducible. Yet, challenge studies have consistently underestimated vaccine efficacy compared with field studies, most likely because vaccine efficacy assessment is sensitive to the endpoint definition. This leads to the questions, should a CHIM for NTS be developed? If so, can a CHIM for NTS be developed? And if yes, could this be applied to accelerate vaccine development? Although an NTS CHIM would increase the understanding of the biology of NTS infection and host response, it is unclear who would be the target for vaccination. Although the CHIM comes with common and less common risks, these can be minimised through participant selection and close observation in an inpatient setting. With several NTS candidate vaccines now in development and phase 3 efficacy field trials being difficult for these vaccines, a CHIM might be critical for demonstrating efficacy. There are several important unknowns that can only be addressed by running the experiment. Obviously, the experiment has to be run safely and ethically.

Although the S. Typhi CHIM did not lead to licensure of the vaccine, as did the cholera CHIM, the CHIM provided an extra level of evidence that led to the World Health Organization Strategic Advisory Group of Experts on Immunization (SAGE) recommendation of the vaccine, which in tum reassured Gavi to provide financial support for the introduction of the vaccine in endemic areas.

The NTS CHIM, on the other hand, cannot be used in the key target population, as CHIM studies cannot be done in children or immunosuppressed people. But an NTS CHIM could provide further insights into the biology of the infection, and may lead to a model of asymptomatic bacteraemia, which could be used to test vaccines or therapeutics.

Even in a validated CHIM, it is essential to use placebo controls, as these will show that the attack rate is still consistent between studies. Historical controls will be of lower value in such cases. Similarly, when testing several vaccines in one CHIM study, only one placebo group would be needed.

While CHIMs may often be insufficient to provide evidence for licensure, they can provide CoPs that can be used in pivotal studies to infer efficacy, potentially reducing the number of participants that need to be included in those studies. However, a vaccine CoP in a naïve population may not be relevant as a vaccine CoP for populations in endemic areas, where baseline immunity may be higher.

A recent paper was highlighted that reviewed how human challenge trials contributed to the development of vaccines for 19 different pathogens [11]. The paper also discusses opportunities for efforts to broaden the scope and boost the effects of human challenge trials, to accelerate all vaccine development.

5 CHIM models are disease specific, can we learn lessons from one disease for another?

Anna Durbin explained that instead of one dengue CHIM, there are four dengue CHIMs, one for each serotype. For optimal use of these CHIMs for dengue virus, as well as other flaviviruses and potentially even other mosquito-borne viruses, the protocols and endpoints need to be harmonised to improve consistent sample and data collection, and interpretation of study results when testing different vaccines or therapeutics. Moreover, standardised CHIMs can be more easily transferred to other groups, including those in endemic countries. Finally, this study-to-study consistency will also help regulators when reviewing applications. Setting up a new CHIM takes time, so being able to rely on previously well-designed study protocols can allow for accelerated model development.

Robert Choy discussed enteric CHIMs, where different diarrheal diseases can be reported using the same measurements, such as stool volume or frequency, although the effects may be different depending on the particular pathogen. A composite score, as used in *Shigella*, might be useful for other enteric disease models as well.

Charlie Weller noted that RCTs are not always feasible and alternative approaches to licensure are needed to prevent candidates from stalling in development. Development can stall if the disease incidence is low, e.g., for Nipah virus, or if large efficacy trials are required, e.g., for a Group B *Streptococcus* vaccine for maternal immunisation, where a clinical endpoint efficacy study has been estimated to require enrolment of 80,000 pregnant women. Finally, outbreaks of emerging infectious diseases are unpredictable in size and location, e.g., Ebola or Marburg.

A better understanding of CoPs can de-risk clinical development by better informing Go/No-Go decisions, de-risking investments in phase 3 studies, and providing a pathway for development when efficacy studies are infeasible. CoPs can be derived from multiple sources to build data packages thought likely to predict clinical benefit, including natural

history of infection data, analysis of immune responses in early phase clinical trials, breakthrough infections post-vaccination (where vaccines are available), passive transfer studies, extrapolation from animal models, and finally, CHIMs. However, a framework is needed to objectively evaluate the strength of the evidence supporting the use of a biomarker as a CoP.

CHIMs can be used for a range of goals, but when CHIMs are used as the primary basis of vaccine effectiveness for licensure, the model must be robust. Even when used for licensure, there is a difference between novel vaccines and follow-on vaccines, as for the latter, other evidence is available that can contribute to the totality of the evidence considered in a regulatory action.

How can the predictive value of the CHIM be optimised? The model can be too stringent, potentially leading to downgrading a good vaccine, which does not protect against infection but does protect against severe disease (which cannot be investigated in CHIMs but would be valuable in the target population). Even with an optimised CHIM, there will be residual uncertainty on how predictive a model is. The residual uncertainty is caused by inference of effectiveness and extrapolation of effectiveness. In a situation where you infer effectiveness and are extrapolating to another target population, this will increase the residual uncertainty. CHIMs have a high level of internal validity, while external validity may be uncertain. One of the advantages of CHIM studies is that they can be done in small (homogeneous) populations. However, this is also a disadvantage, as this may limit the extrapolation to a wider target population. Another aspect can be the presence of multiple serotypes or genotypes of an organism. Regulators are pragmatic about this aspect, provided it is clear what has been achieved and/or demonstrated with the CHIM and what has not. Extrapolation to other sero/genotypes can be done by looking at biomarkers such as neutralizing antibodies. However, this can also be done in post-licensure studies, where real-world data are used to look at the real value of a vaccine in the actual target population. In short, not all questions can be answered with CHIMs.

In terms of CoPs, it is expected that in most cases antibodies will be the most likely option. But if we want to go beyond short periods of time after immunisation, e.g., few weeks, antibodies may not be the most relevant biomarkers. Memory B and T cells may be more valuable but also much more difficult to study in a more standardised way, as well as much more expensive to study. Regulators would also welcome a further focus on T-cell biomarkers but realise that humoral markers are much easier to study in a more standardised way. Furthermore, there is the compartment issue, where are the T cells, where do you need to take a sample? Secondly, what is the appropriate time to take the sample? Finally, T-cell responses are diverse across individuals, which makes them more difficult to study. However, CHIMs may be a good way to find and optimise markers of cellular immunity.

And while regulators are open to new pathways, including CHIMs, policymakers may be less easily convinced. They want hard evidence, which could be provided only in part by well-optimised CHIMs.

When developing a CoP, how large should your study population be? Do you need to test it in multiple geographical regions? Scientists and regulators struggle to define a threshold and the level of evidence that is needed. Sometimes it is difficult to separate the antibody levels in protected individuals from the non-protected ones, whereas in other cases, like chikungunya [12], there seems to be a very clear separation, even if based on relatively small studies.

Although it adds value, no guiding principles for data sharing exist. Models can and will be shared for vaccine/drug development purposes as well as part of capacity building.

6 Challenges/opportunities of CHIMs for tropical diseases conducted in an endemic setting

Moses Egesa, MRC/UVRI and LSHTM Uganda Research Unit, Uganda talked about establishing the single-sex *Schistosoma mansoni* CHIM in Uganda (using only male cercariae). To build local capacity in the regulation of CHIMs, representatives of the regulatory stakeholders visited the laboratory in Leiden, the Netherlands, that established the first *S. mansoni* CHIM. During this visit, they also met with members of the local regulatory bodies to exchange experiences.

Back in Uganda, a joint review meeting was held in June 2019 bringing together research ethic committees, Uganda National Council for Science and Technology (UNCST), National Environment Management Authority, and the National Drug Authority. This meeting provided recommendations about the scientific validity, the ethics and regulatory process and the administrative conduct of the study. After the implementation of these recommendations, the protocol was reviewed and approved by institutional research ethics committee and the UNCST. Next, the local infrastructure was approved by the Institutional Biosafety Committee and the National Biosafety Committee of the UNCST. Audits and inspections of the site, including a site qualification visit (June 2019) and a site assessment visit (June 2023) have been conducted. Finally, initial oversight meetings have been held with the Data Safety Monitoring Board (DSMB) and the Trial Steering Committee. Alongside these activities, there were close interactions with the communities in which the CHIMs will be conducted.

Pongphaya Pongsuwan, Mahidol Oxford Tropical Medicine Research Unit, Bangkok, Thailand, shared the challenges, opportunities, and community benefits of executing malaria CHIM studies in Thailand, an endemic setting. One challenge is that the vector, the mosquito, is in the natural environment, at least in rural areas. Another challenge may be pre-existing immunity. This can be overcome by exclusion criteria based on blood tests. Eventually, a vaccine will be used in an unselected population, so people with pre-existing immunity may be part of the target population. The ethical and regulatory bodies were involved early, including the Thai FDA.

Conducting the CHIM provides the opportunity to expand knowledge through international collaboration, technology and knowledge transfer, and facility development. But there are also opportunities for the wider community in disease awareness.

When transferring a CHIM from a non-endemic country to an endemic country, regulators often request that the dose-finding is done again to the maximum dose provided in non-endemic countries. Indeed, the potential pre-existing immunity in endemic countries may require higher doses to reach the same level of symptoms. Given the limited resources in endemic countries, could the successful dose in non-endemic countries be used as starting point in endemic countries and further increased if necessary? Safety is the priority, so only if no further adverse events are seen, the DSMB may suggest increasing the dose in an endemic setting.

7 Hurdles for CHIM for RSV, influenza & *C. difficile*

Bruno Speder, hVivo, UK, discussed a few examples of CHIM studies that helped in the licensure pathway. The first example was a drug intended for the treatment of mild to moderate influenza disease. As clinical field trials with this drug were done in outpatients, and the study occurred in a weak influenza season, the enrolment was unsuccessful. In a scientific advice meeting with the European Medicines Agency, it was decided to perform a phase 2b CHIM study, leading to the selection of the dose to be used in the phase 3 field trial, while also preliminary data on efficacy were obtained.

The second example was an RSV vaccine, where the use of a phase 2 RSV CHIM study provided preliminary clinical evidence, which led to a breakthrough therapy designation being awarded by the FDA.

The third and final example was an investigational product for the treatment of influenza. As this concerned an inherently unstable molecule, a traditional phase 1 dose range finding studies in humans was impossible, as there is no measurable product in the bloodstream. In a Scientific Advice meeting with the Medicines and Healthcare products Regulatory Agency (United Kingdom), the decision was to follow the ‘Oncology approach’, testing the drug directly in patients. A phase 1 influenza CHIM study was done to create ‘artificial patients’ that can then be treated with the product. Safety, viral load, and respiratory symptoms were used as endpoints for this study. Theoretically, this could have been done as a phase 1 clinical trial in hospitalised influenza patients, but because of ethical limitations (lack of potential direct benefit) and the unknown timing of the infection in such patients, the CHIM study was a better option.

Upper respiratory tract infection (URTI) CHIMs may not be the best possible model for organisms where you want to prevent lower respiratory tract infections (LRTI). In some populations, e.g., for RSV infection in older adults, LRTI is what you want to prevent. Potentially, using the URTI model, vaccines that might protect against LRTI may be downselected.

Christopher Chiu, Imperial College London, UK, presented the Inno4Vac consortium and its objectives. Inno4Vac will develop three new CHIMs on influenza, RSV, and *C. difficile*. In addition, positioning of newly developed CHIMs in the regulatory framework is also part of the Inno4Vac consortium. Four topics stand out in need of further discussion,

1. The need for GMP

2. Positioning of resulting data for vaccine licensure
3. Containment
4. Role of pre-selection/treatment to enhance models

C. difficile, as a spore-forming organism, is very persistent, making GMP production difficult and limiting the manufacturers willing to undertake this work. For RSV and influenza, GMP is already the standard for production. However, for all pathogens, the requirement for GMP makes production of challenge agents expensive and slow, which can limit the impact of the challenge strain in the light of ongoing strain variation. While in some jurisdictions, such as the United Kingdom, challenge agents *per se* do not need approval by the regulatory authority, details are always required to be submitted as part of the full package once they are used to test vaccines or therapeutics. Therefore, to reduce the risk of a rejection at that stage, GMP manufacturing is often the standard. This also results in restriction of the variety of strains that are available, which can hamper research, for example, into universal flu vaccines. To speed up the process and reduce cost, would relaxation of certain GMP requirements during challenge agent production be acceptable?

7.1 When developing a challenge agent, the bulk of the cost is in adventitious agent testing. Could the classical tests be replaced by next generation sequencing (NGS)?

NGS testing would cost a lot less and speed up the process considerably. If a signal were found in NGS testing, the classical batch of tests could then be done, especially for respiratory pathogens that are commonly used as challenge agents. It was pointed out that these are delivered to the nose, where inhaled air may be filled with various other microorganisms that are never tested for and which generally do not lead to serious consequences in young, healthy, low-risk participants. So, could the range of organisms tested for be reduced in these cases? Currently, there is no consensus among the regulatory community as to whether NGS would be acceptable to replace classical tests but there is a gradual move in this direction.

7.2 Which standards should be used for assessing the quality and consistency of challenge agent lots if GMP were not to be followed?

There is no definition for “GMP-like”, but it was agreed that GMP adherence in manufacturing that could be signed off by a Qualified Person for release should be employed, even if the full GMP regulations and paperwork were not employed. This would reduce restrictions on where the work is done, so academic institutions have more capacity to undertake it, and with less paperwork, which would substantially reduce the workload. In the end, challenge agent production should follow a fit-for-purpose process. The Wellcome Considerations document is a good starting point and will be used for further discussions [13].

7.3 How do regulators view the position of CHIM data within the vaccine development pathway?

The discussion revealed a number of unresolved questions about how these data could be used. While CHIM data have contributed substantially to approval of some vaccines (such

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as Vaxchora), field efficacy trials in the target high-risk population are still preferred. There remains a risk that a vaccine candidate that does not prevent mild/asymptomatic infection (such as in the upper respiratory tract) might still be effective at preventing severe disease (e.g., in the lower respiratory tract). However, there may be a role for CHIMs in establishing such characteristics as lowering viral shedding and reducing transmission that could not be realistically established in field trials.

7.4 Given that *C. difficile* colonization is very common and can be controlled by simple hygienic measures, is containment necessary? Similarly, given that RSV is ubiquilous and usually mild in healthy adults, and simple measures can be used to mitigate risk (avoidance of high-risk individuals, self-isolation, face masks, etc.), would quarantine be needed?

It was generally agreed that pragmatic approaches should be taken based on pathogen and disease characteristics, with outpatient studies being possible once safety and consistency had been established.

7.5 Would it be acceptable to select or pre-treat the participants to increase the infection rate of a model?

Different opinions were expressed indicating that it is not possible to provide definitive answers at this stage. The value of pretreatment to increase colonization needs to be carefully discussed, to make sure the studies would still provide data that can be translated to real life conditions. Nevertheless, it was generally agreed that a *C. difficile* CHIM would be most useful in advancing vaccine candidates more rapidly than the conventional clinical development pathway.

8 Conclusion

Regulation of CHIMs is especially difficult in regions without previous experience with these studies, due to concerns about safety of the participants and the community. Valuable initiatives for harmonisation and regulation of CHIMs both in LMICs and HICs have been undertaken which will help to reassure regulators. When all precautionary steps have been undertaken, the regulators need to be open to consider approval for local CHIM studies.

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