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Convening on the influenza human viral challenge model for universal influenza vaccines, Part 2: Methodologic considerations

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ABSTRACT

In response to global interest in the development of a universal influenza vaccine, the Bill & Melinda Gates Foundation, PATH, and the Global Funders Consortium for Universal Influenza Vaccine Development convened a meeting of experts (London, UK, May 2018) to assess the role of a standardized controlled human influenza virus infection model (CHIVIM) towards the development of novel influenza vaccine candidates. This report (in two parts) summarizes those discussions and offers consensus recommendations. Part 1 covers challenge virus selection, regulatory and ethical considerations, and issues concerning standardization, access, and capacity. This article (Part 2) summarizes the discussion and recommendations concerning CHIVIM methods.

The panelists identified an overall need for increased standardization of CHIVIM trials, in order to produce comparable results that can support universal vaccine licensure. Areas of discussion included study participant selection and screening, route of exposure and dose, devices for administering challenge, rescue therapy, protection of participants and institutions, clinical outcome measures, and other considerations. The panelists agreed upon specific recommendations to improve the standardization and usefulness of the model for vaccine development.

Experts agreed that a research network of institutions working with a standardized CHIVIM could contribute important data to support more rapid development and licensure of novel vaccines capable of providing long-lasting protection against seasonal and pandemic influenza strains.

1. Introduction

The Bill & Melinda Gates Foundation, PATH and the Global Funders Consortium for Universal Influenza Vaccine Development convened a meeting of approximately 60 experts in London, UK (May 31–June 1, 2018) to collect perspectives and identify best practices on how to improve the utility of a standardized controlled human influenza virus infection model (CHIVIM) as a tool for development and evaluation of novel universal vaccines. Participants included vaccine researchers, public health officials, regulatory experts, and representatives from the pharmaceutical industry. The meeting focused on five topics, each with a set of critical pragmatic questions. Leaders in the field chaired each session and moderated discussion panels to address the questions in depth with audience input. This report (in two parts) summarizes those discussions and offers recommendations to improve CHIVIM as a necessary tool for universal influenza vaccine development.

This article (Part 2) summarizes discussion and recommendations related to CHIVIM methods, including study participant selection and screening, route of exposure and dose, devices for administering challenge, rescue therapy, protection of participants and institutions, and other methodologic considerations. The authors would like to thank the following panelists who shared their experience and best practices in CHIVIM Methods: Rebecca Jane Cox PhD, University of Bergen Influenza Centre; John Oxford, PhD, Queen Mary College; Gene Saxon, MEng, MME, PATH; Mark Papania MD, CDC; Frederick Hayden, MD, University of Virginia

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School of Medicine; Adrian Wildfire, MSc, SGS Life Sciences; and Donald Milton, MD, DrPH, University of Maryland School of Public Health. Recommendations reflect a "majority report" with panelists' recommendations, as reflected in their slides and comments from the dais, and comments from the audience being reported. All panelists and participants had the opportunity to review and comment on a late draft of the meeting report. The companion article "Meeting Report: Convening on the Influenza Human Viral Challenge Model for Universal Influenza Vaccine, Part 1" covers the other topics discussed at the meeting, including realizing the full value of CHIVIM, selection of challenge virus strains, industry and regulatory perspectives, ethical considerations, standardization, and increasing capacity and access, as well as the complete list of meeting participants.

2. CHIVIM methods

2.1. Study participant selection and screening

When selecting participants for human challenge trials (HCTs), screening for healthy young adults reduces the risk of complications related to severe disease. However, a young healthy cohort does not well represent the immune compromise associated with high-risk groups such as infants, pregnant women, and elderly adults. Rather than screening out participants who have pre-existing immunity to influenza (high hemagglutination inhibition (HI) titers), it may be preferable to do extensive baseline testing for multiple indicators of pre-existing immunity. This information could help identify correlates of protection (CoPs) [1] (markers of immune function that statistically correlate with protection after vaccination) which could then predict whether immune responses attained in at-risk groups were likely to offer clinical benefit.

HI is the most widely used screening assay, though screening participants for low HI titers to increase attack rates was highlighted at the meeting as a possible bias, as this practice might enrich the challenge group with generally poor responders to influenza. There are many other potential immune markers (Table 1), and CHIVIM studies provide the opportunity to further explore these correlations. Careful characterization of pre-challenge immunity is essential for comprehensive explanation of challenge outcomes, leading to better predictions about the efficacy of vaccine candidates in at-risk populations.

Table 1
Influenza immunologic markers.

Immune Marker	Correlation	Reference
Hemagglutinin stalk-specific antibodies	Reduced influenza viral shedding; not predictive of reduced disease or reduced disease severity	Park et al. [28]
Anti-neuraminidase antibody	Resistance to infection and reduced disease	Memoli et al. [29]
Nasal IgA response	Protection against disease in challenge trial (study participants screened for low hemagglutination inhibition titers)	Gould et al. [30]
Cytotoxic CD8 T cells	Protection against influenza A infection; inverse correlation between virus shedding and CD8 + T cell counts in seronegative adults	McMichael et al. [31]
Pre-existing T-cells specific to conserved CD8 epitopes	Associated with milder symptomatic illness during the 2009 influenza pandemic	Sridhar et al. [32]
Preexisting influenza-specific CD4 + T cells	Less symptomatic influenza A infection in challenge trials	Wilkinson et al. [33]
Measured cell-mediated immunity ($\geq$100 IFN-γ spot-forming cells/10^6 peripheral blood mononuclear cells) in children after vaccination	Protection against community-acquired clinical influenza in a large controlled trial	Forrest et al. [34]

To fully characterize pre-existing immunity of CHIVIM study participants, useful assays include HI, microneutralization, neuraminidase (NA) inhibition, single-radial-hemolysis, stalk-specific antibodies, nasal IgA, IFNgamma ELISpot, T cell flow cytometry, and functional assays. Important participant screening information includes age, influenza illness and vaccine history. Screening could be tailored to the mode of action of the vaccine being studied in a particular trial. Screening for baseline pulmonary function and airway hyperactivity may be useful for reducing participant risk (see Rescue Therapy).

A more inclusive screening strategy reduces the need for extensive participant recruitment and expense and helps prevent selection of a skewed cohort. However, including participants with pre-existing immunity can result in lower attack rates, leading to compromised efficacy evaluations. High-dose challenge was discussed as a means of increasing attack rate, but the immunologic response to such a challenge may not be as physiologically meaningful and high-dose challenges can overwhelm the immune response.

2.2. Route of exposure and dose

When discussing route of exposure for challenge virus, the central focus of debate centered around the tension between assessing vaccine efficacy against severe disease and safety concerns associated with aerosol challenge delivery. Current influenza challenge models use the intranasal route. As discussed in Part 1 [2], aerosol delivery produces disease that better represents natural infection, but increases the risk of severe disease complications in study participants [3–7]. Another concern regarding aerosol delivery is that the virus may bypass immune defenses in the upper respiratory tract that are important to vaccine efficacy. Intranasal droplet challenge has a demonstrated history of safety and shows less dose variability but elicits milder clinical symptoms. HCTs that expose a participant to influenza virus via the intranasal route are able to assess protection against upper respiratory illness, but less so against lower respiratory illness, which is an infrequent outcome of current challenge models [6–9]. In field trials of influenza vaccines, efficacy is generally higher against moderate to severe disease and lower against mild disease. Thus, if a vaccine can prevent mild disease in a challenge setting, it could be argued to have potential to prevent more severe disease in a field trial.

The Common Cold Unit (Salisbury UK) conducted influenza challenge trials for over forty years using intranasal delivery with an excellent safety record [10]. In lieu of pre-screening for pre-immunity, healthy participants were stratified into categories according to baseline HI titers. After optimized intranasal delivery of diluted virus solution droplets, technetium-enabled studies showed widespread exposure to challenge throughout the respiratory tract [11].

A 1966 aerosol inhalational challenge trial with a low-dose of an H2 strain (3-$TCID_{50}$ (50% Tissue Culture Infectious Dose)) induced typical influenza disease in a small number of non-immune participants. Infections occurred only in participants with low or absent neutralizing antibody titers [12]. Another trial using intranasal challenge required 50–100 times that dose of H3N2 to achieve the same effect [13].

Modeling lower respiratory infection via aerosolized challenge may be useful for universal vaccine development, though panelists noted that most cases of community-acquired influenza are limited to the upper respiratory tract. Before aerosol challenge can be proposed, a delivery device that controls release of virus into the environment must be developed and validated, and clinical

experts should endorse a protocol for prompt initiation of rescue therapy in trial participants attaining a defined clinical endpoint (see below). Whereas aerosol delivery may better simulate severe lower respiratory infections, the risks should be carefully evaluated and should not outweigh the potential benefits.

2.3. Devices for administering challenge

Several devices have been developed for delivering viral challenge to the respiratory tract. The ideal device would reliably deliver a consistent dose to desired target areas, with low risk of environmental escape (Table 2).

Nasal delivery is simple and low risk, but the administered dose can be highly variable. Intranasal liquid challenge results in a short residence time, and the target delivery area is relatively small (150 cm^2) compared to aerosol delivery (estimated total lung surface area is between 50 and 75 square meters) [14]. For pulmonary challenge, dry powder inhalers can deliver small (<5 μm) particles to alveoli with one or two breaths. These inhalers are widely used for asthma medication, and the dosing is simpler but less precise than with nasal powders.

Liquid aerosol devices can deliver small particles (<5 μm) to the alveoli but require time to administer with significant risk of virus escaping to the lab environment. Vibrating mesh nebulizer systems can dose more efficiently with desired particle size, don't require air flow, and are currently licensed for asthma medication. Mesh nebulizers have been used to deliver live attenuated influenza vaccine in ferrets and are being studied as part of the World Health Organization Measles Aerosol Project [15].

2.4. Rescue therapy

Reducing the risk of severe illness during influenza challenge trials is a multi-approach strategy that includes pre-screening, careful monitoring, and appropriate use of rescue therapy. Screening for healthy adult study participants (<45 years) and excluding all at-risk groups listed by the CDC as well as current/recent cigarette smokers is recommended. Baseline screening tests for safety should include tests of pulmonary function, oxygen saturation, chest X-rays/CT, and testing for concurrent respiratory viral infections. Genetic susceptibility, upper respiratory tract bacterial pathogens, and low influenza cellular immunity are other possible screening criteria. Subclinical cardiac abnormalities have been associated with influenza, so baseline electrocardiography (EKG) or echocardiogram may be warranted [16].

Participants should be closely monitored for signs of severe illness such as shortness of breath, wheezing, and severe cough. Other recommended monitoring methods include frequent checks of vital signs, viral shedding (using rapid diagnostic tests), biomarkers for bacterial infection, peak expiratory flow rate measurements, spirometry, EKG, echocardiogram, cardiac enzymes, and chest X-ray/CT as needed.

Current influenza therapies include adamantanes (e.g. rimantadine), NA inhibitors (e.g. oseltamivir), and recently approved cap-dependent endonuclease inhibitor baloxavir marboxil [17], as well as combinations of these. Favipiravir and pimodivir are investigational polymerase inhibitors [18]. Pimodivir has been shown to be effective in combination with oseltamivir [19]. NA inhibitor treatment reduces hospitalization and mortality from severe H1N1 influenza if given within 4–5 days of illness onset [20–22]. Antibody-based therapies are in development as well. Intravenous anti-influenza immune plasma combined with oseltamivir tended to shorten respiratory function recovery time and reduce mortality from severe influenza A infection compared to oseltamivir alone [23]. However, one recent randomized controlled trial (RCT) testing high doses of the anti-HA stem antibody MHAA4549A combined with oseltamivir (NCT02293863) and another RCT testing hyperimmune globulin combined with a NA

Table 2
Challenge virus delivery devices.

Route of Delivery	Device	Dose	Target Delivery Area	Residence Time	Droplet Size (μm)	Risk of Virus Escape	Other
Nasal			150 cm^2			Low	
	Droppers	High variability	Limited and variable; depends on positioning	Limited, variable			Simple to use
	Spray	Varies with angle/depth of spray	Increased		50–100		Can agglomerate into drops
	Gel			Increased			Requires additional formulation steps
	Aerosol	Varies depending on coverage/ retention	Increased compared to spray	Variable	15–25		Dose delivered over time
	Dry powder	Less variable	Increased compared to liquid	Increased	25		Ongoing comparative delivery studies in ferrets
Pulmonary			50–75 m^2 [14]			High	
	Liquid aerosol (including jet and pool-type) nebulizers		Large (alveolar)		<5		Requires time to administer; Can target upper or lower respiratory tract or both; may damage virus
	Vibrating mesh liquid aerosol nebulizer	More precise	Large (alveolar)		Specific droplet sizes possible		Licensed for asthma medications; used to deliver LAIV in ferrets and are being studied as part of the WHO Measles Aerosol Project.[15] Less damage to virus
	Dry powder inhaler	Less precise than nasal powders	Large (alveolar)		<5		Widely used for asthma medications

LAIV, live attenuated influenza vaccine; WHO, World Health Organization.

inhibitor (NCT02287467) did not show superiority over oseltamivir alone in hospitalized influenza A patients.

Careful screening and monitoring of participants, selecting (or developing) challenge viruses that are sensitive to antiviral therapy, and early rescue therapy intervention (as soon as endpoints are reached) with a combination of two agents (using different modes of action) can reduce the risk of severe complications in CHIVIM trials.

2.5. Protection of study participants and institutions

Influenza challenge trials performed with virus inoculation by the intranasal route in the past 50 years have had good safety records with few unexpected serious adverse events (SAEs). Although the potential of influenza challenge trials to accelerate development of broadly protective influenza vaccines was acknowledged at this meeting, the participants agreed that safety was a paramount concern. Changes to the challenge model to increase the frequency or intensity of illness (e.g., virus strain or method of administration) should be done incrementally, with caution, and only if essential.

Careful risk evaluation should include consideration of both known and unforeseen risks. Known risks associated with challenge trials include SAEs, onward transmission from study participants [24], uncontrolled release, as well as more general risk associated with clinical trials such as failure in duty of care, negligence, procedural/equipment failure, or sabotage. Tools such as the National Institute for Health Research Clinical Trials Toolkit [25] can be used to define specific risks associated with a trial and determine how they can be mitigated.

The "8P's of Protection" screening tool [26] is used to assess risk for adverse events after a patient is discharged from the hospital. A similar list could be developed with methods for protecting against risks related to challenge trials, such as reviewing study design (following known guidelines and seeking independent expert advice), careful risk/benefit analysis, prescreening, proper documentation (informed consent and qualifications of investigators), rigorous trial monitoring, insurance protection, and periodic reappraisal of the safety plan. An example of planning for unforeseen risk might include limiting study size to ensure adequate duty of care is available in the event of multiple SAEs. CHIVIM sponsors should ensure that their insurance policy covers both negligent harm to trial participants and non-negligent harm (no-fault compensation) and should be aware of their coverage limits.

Designing safe challenge viruses (discussed above) is an important step for mitigating risk. Animal studies and dose-escalation first-in-human trials can provide important safety data and evidence of virulence/attack rate. Good manufacturing process (GMP) can increase safety, although currently there is no guidance available that is specific to the production of challenge viruses.

The panel discussion included possible protective measures for the staff conducting the study. It was noted that reverse barrier (protective isolation) infectious disease controls are effective. Personal protective equipment for clinical staff is recommended. Vaccination, antiviral prophylaxis, medical monitoring and diagnostic testing are other possible protective measures. Staff should also be screened when entering and leaving wards to prevent introduction of outside infectious agents.

2.6. Clinical outcome measures in experimentally induced influenza

One potential use for influenza challenge trials is for modeling disease transmission to evaluate the effect of potential vaccines on transmission rates. The Centers for Disease Control EMIT (Evaluating Modes of Influenza Transmission) [24] studies, which were designed to evaluate the contribution of aerosols to influenza transmission, provide some insight into how challenge models can be used to elicit better understanding of the transmission factors associated with influenza.

These studies placed experimentally infected donors in a sealed room with recipients to measure aerosol transmission. One study in the United Kingdom achieved a 25% attack rate with two days of exposure in a room with recirculating air. A similar study performed in the United States increased the number of donors and days of exposure, but there was no aerosol transmission observed, which may have been due to the presence of ventilation. There was one transmission by droplet nuclei in the US study, and no evidence of transmission by direct contact or large droplet spray.

A dynamic breath catcher was used to catch and measure aerosol viral particles from donor participants who had received intranasal viral challenge (H3N2 A/Wisconsin/67/2005). These participants had lower levels of viral shedding (one log lower than average measurements from community-acquired infection), and less variability in particle size compared to naturally infected participants. Sequencing of specimens collected from participants by nasopharyngeal swab and aerosol particle collection revealed 59 single nucleotide polymorphism differences between samples from the nose and from the lung. The results suggest that route of infection may play a significant role in influenza disease.

The Influenza Patient-recorded Outcome diary (Flu-Pro) [27] is another tool that can be used to measure clinical outcomes after influenza challenge.

2.7. Other methodologic considerations

Panelists discussed the lack of proxy measures for severe disease with experimentally induced influenza. Naturally infected adults often remain afebrile, but fever correlates with disease severity in children. Immunocompromised or elderly adults can have no fever but still go on to experience severe complications of influenza virus infection.

The issue of study size was addressed. The average size for respiratory challenge trials requiring containment is about fifty participants. Specimen sampling and safety constraints can limit the feasibility of managing larger numbers. Larger studies may be necessary to attain adequate power, so the enrollment of sequential cohorts may be necessary. Flexibility with timing of administering vaccine and challenge can help prevent participant dropout.

The panel also discussed the optimal timing for conducting challenge trials in relation to seasonal influenza patterns. The potential for possible exposure to naturally circulating virus during the period of time between vaccination and challenge must be carefully considered. The advantages of conducting HCTs outside of influenza season were weighed against practical concerns, such as the problem of having to interrupt longer duration trials and the fact that recruitment is often easier during student holidays. With careful isolation/containment procedures, it is possible to conduct HCTs during influenza season.

3. Conclusions

Several gaps were identified that should be addressed in order to make CHIVIM a more effective tool for influenza vaccine research:

- Need to determine appropriate ranges for screening criteria
- Need standardization of delivery devices and standard operating procedures for optimal delivery

- Need for agreement on standard rescue protocols
- Challenge trials can only evaluate reduction in virus shedding and (mild to moderate) symptom intensity; severe disease cannot be modeled

The panel agreed on the following recommendations for improving and standardizing the methodology of CHIVIM:

- Screen for healthy adult study participants and exclude those who are at-risk for severe illness, smokers, and participants with respiratory virus infections
- To balance ease of enrollment versus minimizing variability between subjects, it was suggested not to screen out all participants with pre-existing immunity (high HI titers) but instead perform thorough baseline characterization of immunity (CoPs) and balance immunity profiles of each trial's treatment groups by stratification
- Empirically establish effective dose for each new challenge strain in a dose escalation trial
- Nasal atomizer is recommended for delivery of challenge, based on safety, variable particle size, larger surface area delivery, and participant comfort
- Rescue therapy intervention should be available for participants to minimize risk
- Rescue therapy should combine two treatment agents with different modes of action
- A careful risk evaluation should be performed before any challenge trial, including consideration of both known and unforeseen risks
- The risks of using aerosol challenge are significant; such studies should be deferred until an appropriate delivery device is developed and validated, a rescue therapy protocol is available, and there is assurance of significant public health benefits that would justify risk.

All authors attest they meet the ICMJE criteria for authorship

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Declaration of Competing Interest

The authors declare that they have no competing interests.

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