# Clinical Development of Universal Influenza Vaccines: A Current Perspective

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1 What is a universal vaccine?

2 Pathway to licensure

3 Risk reduction via CHIVIM

4 Demonstrating clinical benefit

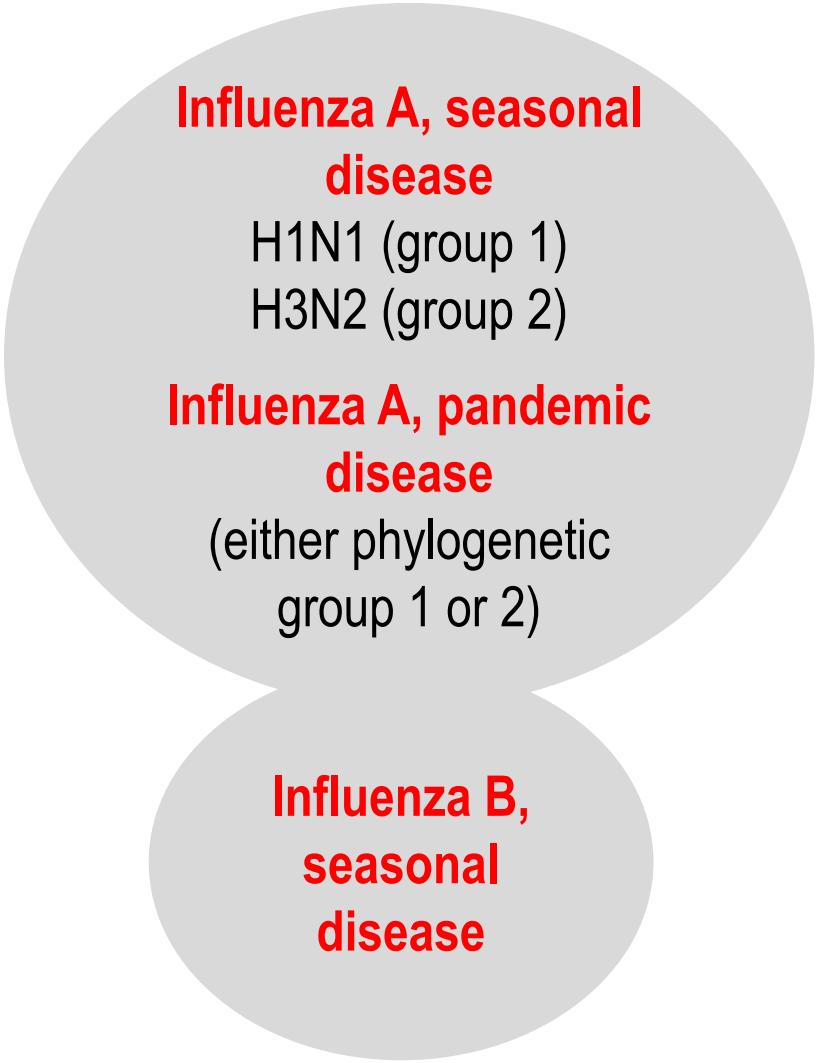
# “U-FLU” Target Product Profile

**WHO Preferred Product Chracteristics**

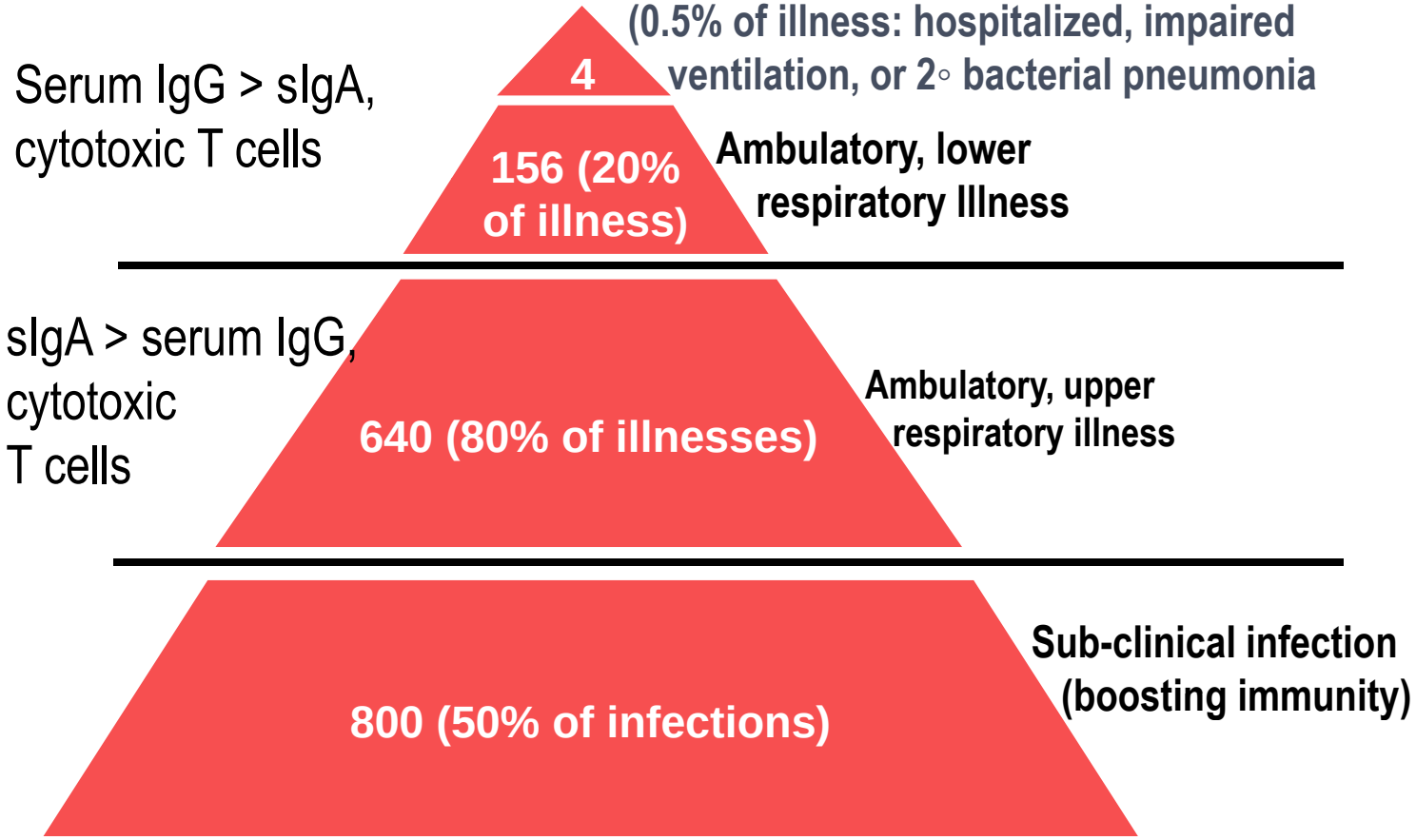
By 2027, influenza vaccines that have the potential to provide protection against severe influenza A virus illness for at least five years, and are suitable for high-risk groups in low and middle income countries, will be in advanced clinical development

**NIAID Criteria - Universal Influenza Vaccine**

- ≥ 75% effective against illness
- Protect against Grp I & 2 influenza A ± influenza B
- Duration of protection: minimum 1y, desirable multiple years
- Suitable for all ages



# Translating the Target into a Candidate Vaccine




Ideal Candidate induces or boosts:

Mucosal immunity
Systemic immunity
CD4 and CD8 T cells

Targeting conserved epitopes:
HA, NA, M2e
internal proteins (e.g. NP)

**Outcomes in 1600 children & young adults with influenza infection**



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# Some Candidate Vaccines in Active Clinical Development

Adjuvanted IIV w/ chimeric HA to focus immune response on conserved HA stalk

Prime: LAIV w/ chimeric HA

Boost: IIV w/ adjuvanted chimeric HA

M-001; a recombinant protein containing 9 conserved epitopes from Influenza A and B

Flu-v, 4-peptide vaccine targeting M1, M2, NP-A, NP-B.

**Uncertain whether any of these candidates targets a sufficient number of epitopes and elicits a profile of immunity capable of satisfying the Target Product Profile**

**Broadly protective for A+B disease, Multi-yr efficacy, For all ages, Affordable for LMICs**

# Risk Reduction Via CHIVIM (during early Phase 2)

Demonstrate vaccine protects young adults against virus shedding (and mild illness) after intra-nasal infection of the upper respiratory tract with H1, H3, and B viruses

Extend data to protection against i.n. challenge with antigenically diverse H1 and H3 viruses

**Define markers of immunity that are correlated with reduction of virus shedding & illness symptoms**

Based on immune markers, confirm immunization in young children, adults, elderly adults achieves "effective immunization" that persists for multiple years

Explore whether community exposure to influenza virus elicits boosting in the absence of overt illness



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# CHIVIM – Present State

## H1N1pdm09 challenge outcomes (90 days post vaccination)

**Largest recent study in US, N=3,116 persons screened, 179 enrolled (data shown is per-protocol set)**

| Treatment | Infected* (n/N) | % (95% CI) | Posterior P |
|---|---|---|---|
| Saline im + placebo tablet | 22/31 | 71 (55-85) | - |
| IIV4 im + placebo tablet | 24/54 | 44 (32-58) | 0.009 |
| Saline im + VXA-A1.1 tablet | 21/57 | 37 (25-49) | 0.001 |

* Any detectable virus (RT-PCR or culture) >36h post-inoculation

| Treatment | Influenza illness** (n/N) | % (95% CI) |
|---|---|---|
| Saline im + placebo tablet | 15/31 | 48 (30-67) |
| IIV4 im + placebo tablet | 19/54 | 35 (23-49) |
| Saline im + VXA-A1.1 tablet | 17/57 | 29 (18-42) |

** ≥ 1 self reported symptom (Flu-Pro questionnaire) + detectable virus (≥ 2 events)

Subjects screened for HI anti-H1 ≤10 (excluded 75%)
Randomization 1:2:2, licensed IIV4 as comparator, H1N1 HA Ad-vector (oral tablet vaccine) as test vaccine

Vaccine effect apparent w/ shedding endpoint, not with illness endpoint

IgA ASC count correlated with VXA-A1.1 protection against shedding

NCT02918006
Courtesy of S Tucker, Vaxart Inc; study funded by HHS/BARDA



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# Demonstrating Clinical Benefit per TPP

| | |
|---|---|
| **Vaccine efficacy ≥75%** | Large cohort randomized to U-FLU, licensed IIV, and control. Endpoint: RT-PCR confirmed influenza illness |
| **Against Influenza A (circulating subtypes with drift) and B (drifted strains)** | Generate robust efficacy estimates against A/H1, A/H3, and B lineages, despite drift |
| **Protection over multiple years** | Active surveillance for illness for ≥3years<br>Additional f/u under blind during licensure review |
| **Suitable for all ages** | First trial in children 6m – 17y of age and adults 18-50y (2 separate cohorts in same sites)<br>If Go after 1y interim analysis, enroll an older adult cohort (age >50y) and pregnant women cohort |



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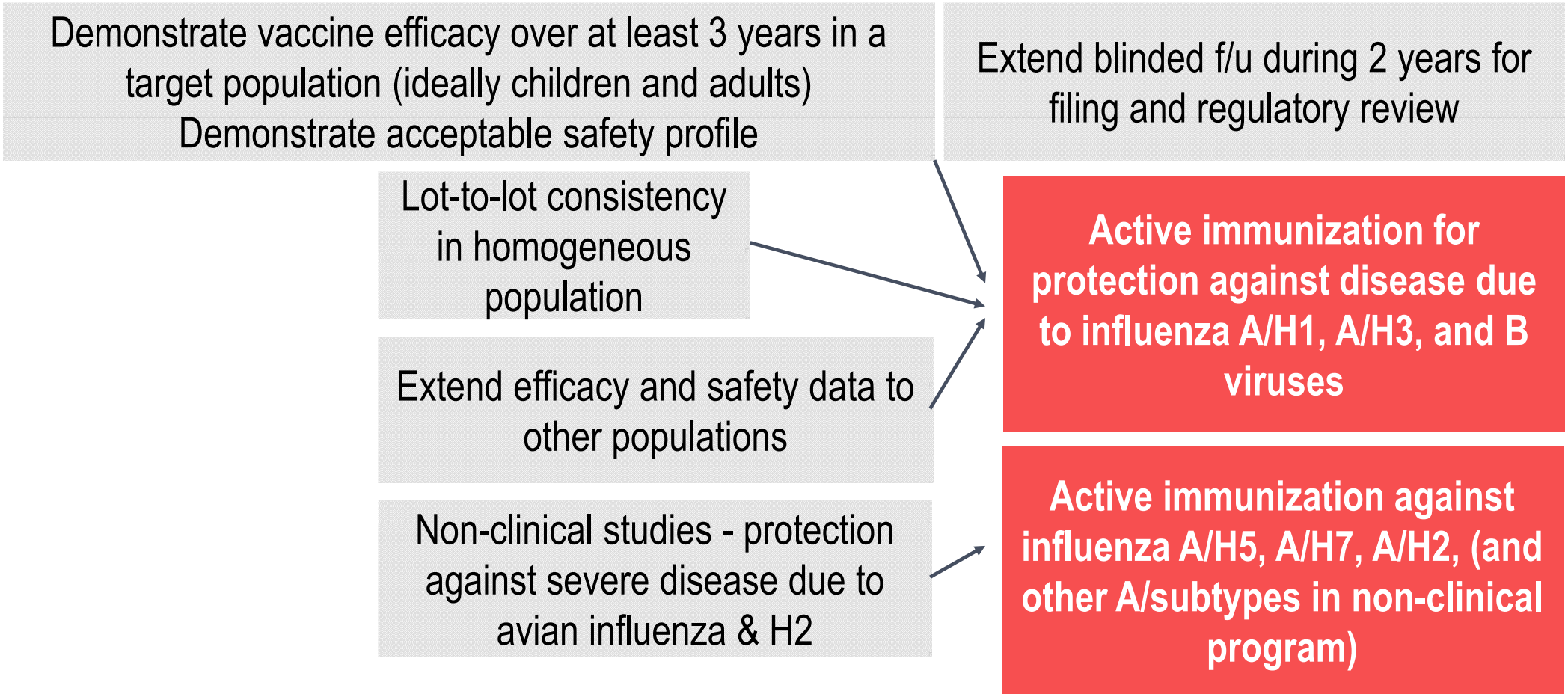
# Pathway to Licensure (Phase 3 development program)



# Main Points

Target: a better influenza vaccine: 1) broad protection against influenza A and B disease, 2) multi-yearr effect, 3) suitable for all ages including pregnant women, 4) affordability for LMICs

Pathway for licensure - 2 indications:
- For protection against seasonal influenza (A/H1, A/H3, B)
- Active immunization against pandemic threat subtypes

CHIVIM can de-risk a development program by qualifying candidates for field studies and identifying immune markers predictive of protection → need new challenge viruses

Demonstration of efficacy and safety will require large, multi-yr studies to assess absolute and relative efficacy. Must be done in countries where placebo controls are ethical due to absence of national influenza vaccine programs for targeted age groups

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