

Universal Influenza Vaccine Is it feasible?

**World Health Organization
Global Vaccine Research Forum
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Bamako, Mali**



Public health impact of influenza

- Influenza viruses cause significant morbidity and mortality annually
 - Annually, 3 to 5 million severe illnesses and 0.25 to 0.5 million deaths worldwide
- Groups at high risk of severe disease include:
 - Very young and very old
 - Chronic underlying cardio-pulmonary disease
 - Pregnant women
 - Immunocompromised
- Vaccination is the cornerstone of influenza prevention
 - Seasonal vaccines only 30% to 50% efficacy in older adults
 - Candidate pandemic vaccines are poorly immunogenic



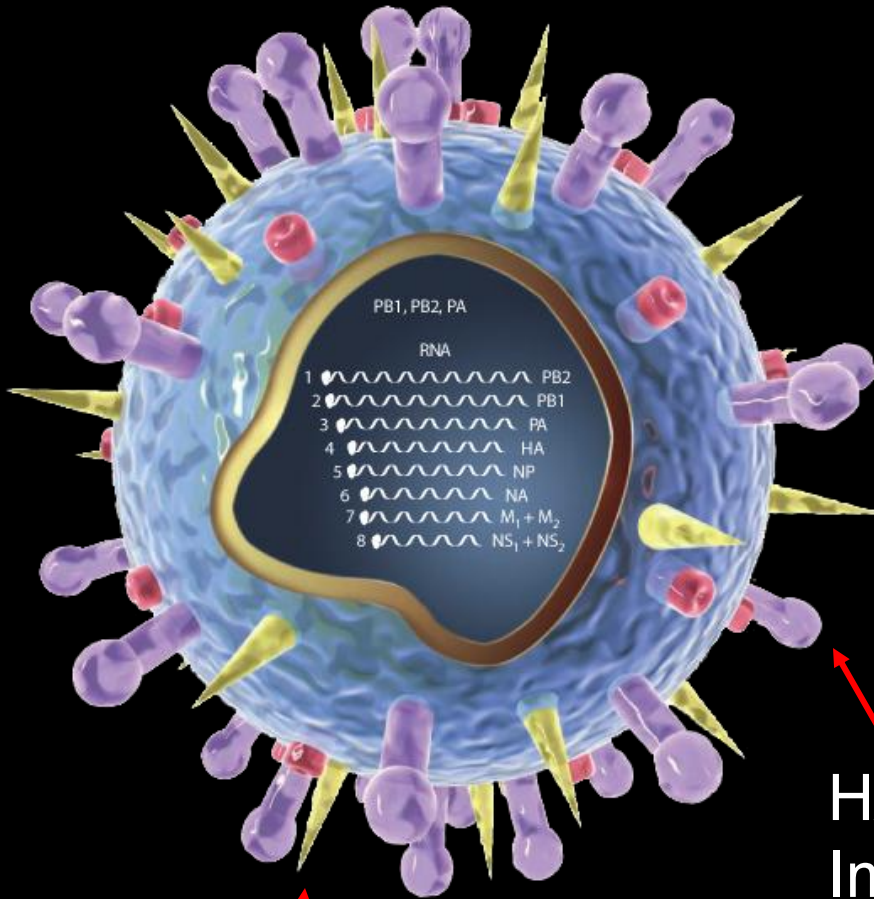
Influenza virion

Enveloped;
segmented, negative strand
RNA virus

Categorized into serotypes
based upon surface
hemagglutinin (HA) and
neuraminidase (NA)
glycoproteins

HA: 16 types, surface
Immunogenic, highly variable
Drift. Shift.

NA: 9 types, surface
Immunogenic, variable
Drift. Shift.



Current influenza vaccines

- Safe and efficacious
- Vulnerable to drift/shift of HA and NA
 - Antibodies target highly variable HA and NA regions
 - Protection following infection/vaccination is limited to specific strains
 - Emergence of strains not covered in vaccine
 - 1 or 2 AA changes can threaten efficacy
- Little to no cross-protection against drifted strains within subtypes or to other subtypes



Current influenza vaccines

- Formulated and standardized based on HA content to induce neutralizing antibodies
- Require constant reformulation due to antigenic drift
 - Costly, time-consuming, year-round process
 - Surveillance, vaccine seed production, optimization of growth, reagent production, potency testing, stability, formulation
 - Repeated for northern and southern hemispheres
- Predominantly produced in embryonated eggs
- Poorly responsive to surge capacity for a pandemic outbreak



Universal influenza vaccine

- “Heterotypic” “Heterosubtypic”
- A single influenza vaccine that would provide “protection” against any given subtype of influenza A.
- Could be used for several influenza seasons before reformulation.
 - Remove annual “guesswork” for strain selection
 - Reduce production costs (thus vaccine costs)
 - Eliminate vaccine “mismatches”
 - Reduce the potential for vaccine shortages
 - Increase the global supply of vaccine
- Could be stockpiled for epidemics/pandemics
- Surge capacity
 - Rapid scale-up, reduce production bottlenecks



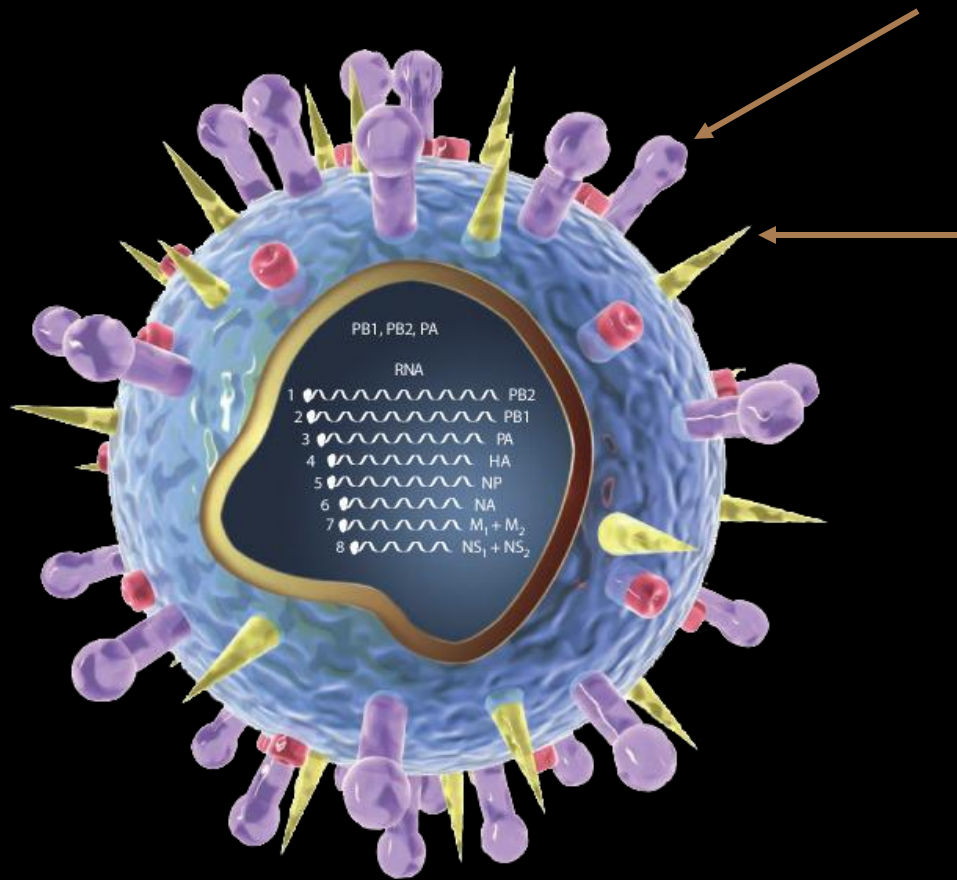
Universal influenza vaccine

- Target conserved proteins or cross-reactive epitopes
 - Less sensitive to antigenic drift
 - Current vaccines do not induce antibodies against these conserved regions
- Identify less immunodominant, but more cross-reactive B and T cell epitopes on HA, NA and conserved proteins to “engineer” sequences that would direct the immune response to:
 - Induce humoral and / or cellular immunity
- Utilize recombinant technologies to optimize expression and delivery/uptake of the antigen
 - Best delivery would be through a live virus vector to trigger broad immune response



What are the targets?



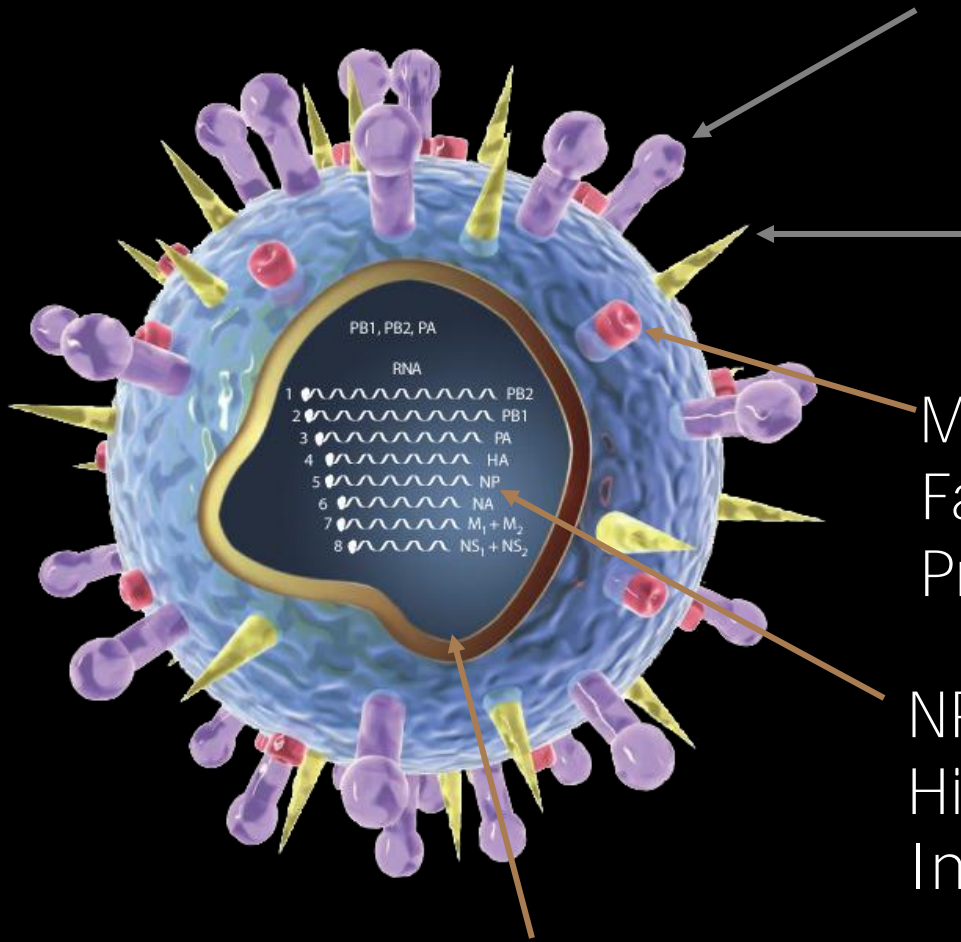


HA: surface, immunogenic
Highly variable. Drift. Shift.

NA: surface, immunogenic
Variable. Drift. Shift.

Is it possible to:

- Identify less dominant, yet more broadly reactive epitopes
- Engineer HA and/or NA genes to direct immune response
- Incorporate into vectored vaccine along with conserved Ags



PB1, PB2, PA

RNA

1	~~~~~	PB2
2	~~~~~	PB1
3	~~~~~	PA
4	~~~~~	HA
5	~~~~~	NP
6	~~~~~	NA
7	~~~~~	M ₁ + M ₂
8	~~~~~	NS ₁ + NS ₂

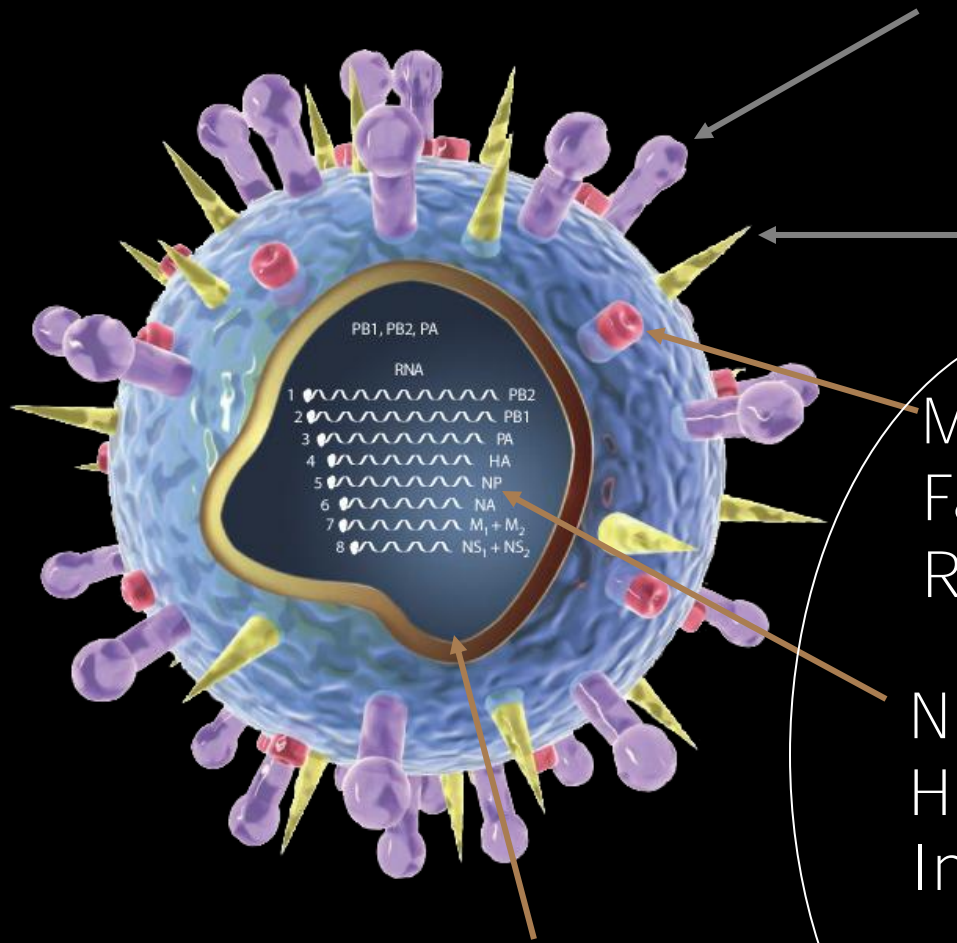
HA: surface, immunogenic
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NA: surface, immunogenic
Variable. Drift. Shift.

M2e: surface, immunogenic??
Fairly conserved. Ab-mediated.
Protective? Reduce severity.

NP (nucleoprotein): internal
Highly conserved.
Induces CMI. Reduce severity?

Matrix: internal
Highly conserved.
Induces CMI.



HA: surface, immunogenic
Highly variable. Drift. Shift.

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Variable. Drift. Shift.

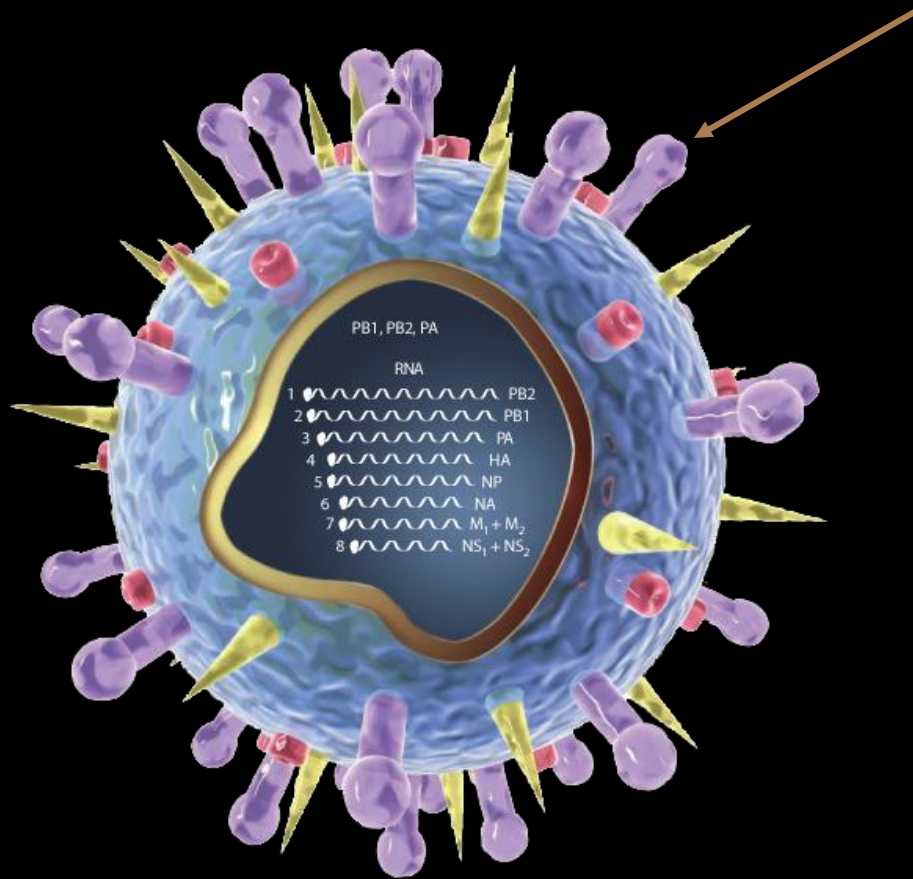
M2e: surface, immunogenic??
Fairly conserved. Ab-mediated.
Reduce severity of infection.

NP (nucleoprotein): internal
Highly conserved.
Induces CMI. Reduce severity?

Matrix: internal
Highly conserved.
Induces CMI.

Combination?

HA: Fusion Peptide
Highly conserved.
Transiently accessible on
infected cell surface.



Is M2e the holy (Universal) grail?

- **DNA vaccine**
 - M2, M2+NP, M2+NP+HA
- **Recombinant protein**
 - Alone or fused to other proteins (flagellin)
- **Virus-like particles**
 - Alone and in combination with other proteins and immunostimulants
- **Peptides**
- **Conjugated to viral cores**
 - HBc
- **Encapsulated in spheres, emulsions, crystals, liposomes**
 - Mixed with immunostimulants
- **Strung together like party lights**
 - 1x2x3x4x5x6



Is M2e the holy (Universal) grail?

- **Vaccine approaches raise antibodies.**
 - Are ELISA antibodies of X titer sufficient?
- **What correlate of protection would we use?**
- **Is there a cellular correlate?**
 - Which cellular marker would we use?
 - Which assay would we use to measure cmi?
- **Do we need to conduct large efficacy trials?**
 - Since we are not expecting neutralizing antibodies that provide protection from infection, how would we design a trial for “clinical protection” or reduce disease severity?



	PRECLINICAL	PHASE I	PHASE II	PHASE III	MARKET APPROVED	
Egg-based Inactivated		 		 	 	
Cell-culture Inactivated		 	 	 	 	
Live	 	 	 		 	
Recombinant Protein & VLP	 		 			
Universal Protein	 		 			
Viral Vector	 	 	 			

Technology Landscape – August 2009

SEASONAL	PANDEMIC	SEASONAL & PANDEMIC
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Research in progress

- Live-attenuated influenza viruses (LAIV)
- DNA
 - Plasmid-based, single or multiple gene combinations
- Recombinant subunit expression systems
 - Baculovirus, yeast, tobacco plants, fungi
- Virus-like particles (VLP)
 - Lentivirus, baculovirus, fungi, tobacco plants
- Live-virus vectors
 - Adenovirus, MVA, alphavirus
- Peptides
 - Synthesized multigenic (conserved CTL epitopes, variable regions)



Challenges

- **Safety**
 - New carriers, vectors, fusion proteins, substrates, adjuvants
- **Correlates of protection**
 - How do we measure immunity without standardized assays?
 - What is the role of cellular immunity?
 - Clinical protection vs. “sterilizing” immunity?
 - Size and cost of human clinical trials?



Challenges

- Formulation and potency determination
 - How do we standardize and stabilize target antigen?
 - Will each target require new, specialized release assays?
- Genetic stability
 - Will they drift under pressure?
- **Expect complicated regulatory pathways**



Summary

- Current influenza vaccines based primarily on HA are safe and immunogenic but highly vulnerable to antigenic drift/shift
 - Quickly compromises efficacy requiring bi-annual reformulation and annual immunization.
- Broadened and longer lasting immunity can be achieved by incorporating highly conserved proteins that elicit cellular and humoral immunity.
 - New vaccine candidates early clinical development.



Summary

- Significant challenges are yet to be overcome
 - Establishing correlates of protection
 - Demonstration of safety
 - Regulatory scrutiny
- Licensure of a universal influenza vaccine would make a significant contribution to epidemic and pandemic preparedness.
- Continued research in this area should be encouraged, accelerated and funded.



Is a Universal Influenza Vaccine Feasible?

- Yes
- However, it will require:
 - more than a single native protein
 - rational design of specific B and T cell epitopes
 - delivery systems to induce B and T cell immunity
 - parallel work on specialized release assays
 - large efficacy trials to identify correlates of protection
 - a novel regulatory strategy for licensure
 - lots of money



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