Global development of universal pandemic influenza virus vaccines

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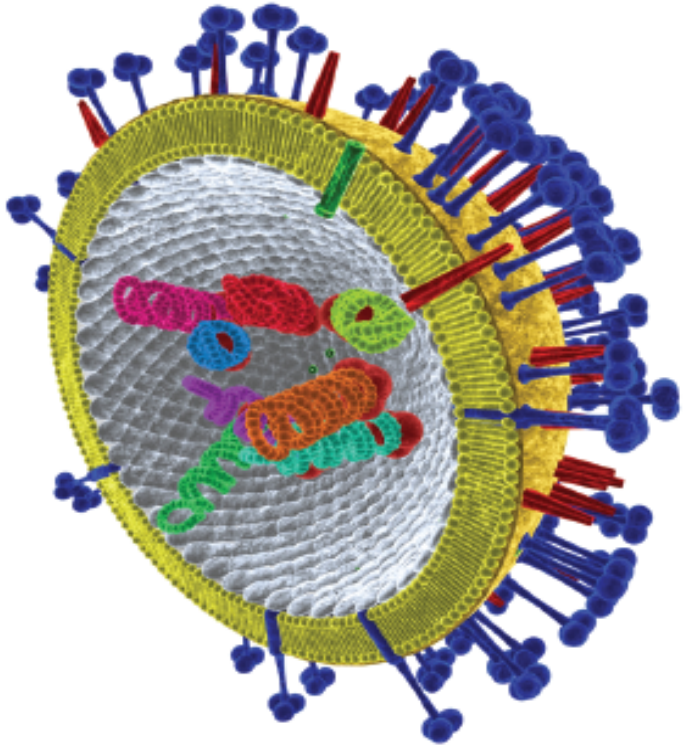
2018 World Influenza Conference

Beijing

September 8th, 2018

Mount Sinai

Influenza virus



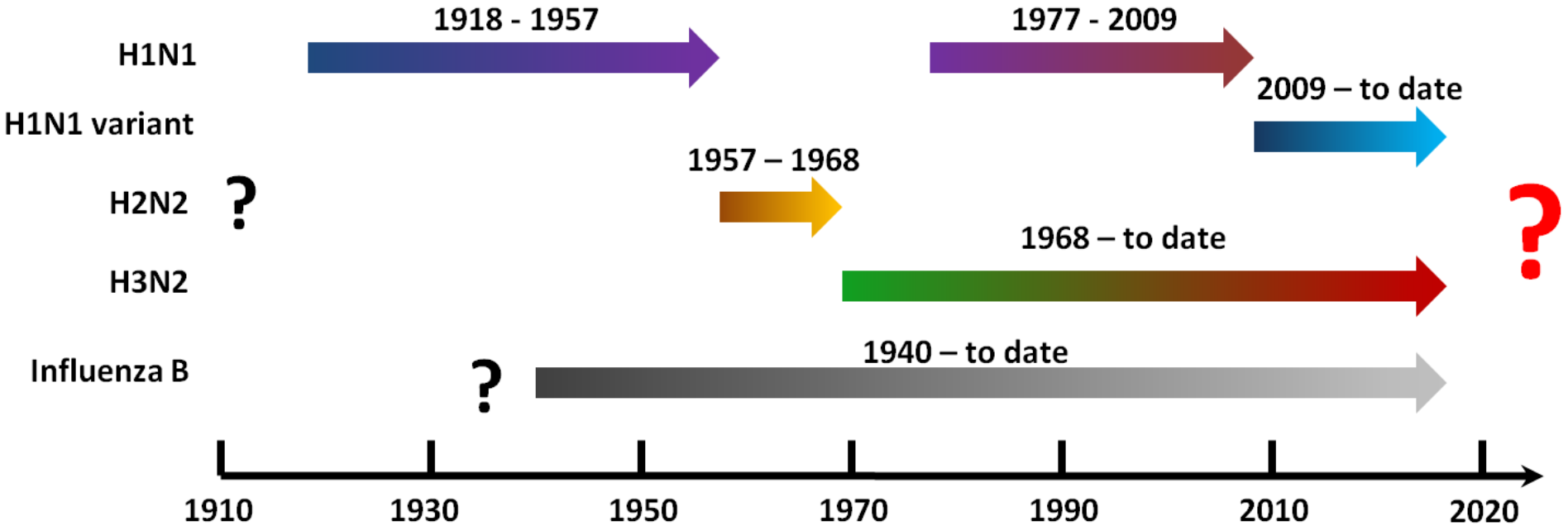
- *Orthomyxoviridae* family
  - Influenza A, B, C and D
- Lipid envelope
- RNA genome
- 8 genomic segments
  - **HA (H1-H18)**
  - NA (N1-N11)
  - M2
  - Conserved internal proteins

adapted from Krammer and Grabherr, Trends Mol Med 2010

Influenza in humans

- Causes a spectrum of mild to severe respiratory disease in human
- Causes epidemics (A and B) and pandemics (A)
- Epidemic/seasonal influenza:
  - Worldwide: 3-5 million severe cases; 290,000 to 650,000 deaths (WHO)
- Pandemic influenza: H1N1 pandemic in 1918 claimed approx. 40 million lives
  - Introduced from the animal reservoir (birds, mammals)

Dynamics of influenza virus circulation in humans



Antigenic Drift and Antigenic Shift

Influenza virus vaccine strains for the Northern Hemisphere from 1998 to 2019

NH winter season0	H1N1	H3N2	B-strain
1998–1999	A/Beijing/262/95	A/Sydney/5/97	B/Beijing/184/93
1999–2000	A/Beijing/262/95	A/Sydney/5/97	B/Beijing/184/93 or B/Shangdong/7/97
2000–2001	A/New Caledonia/20/99	A/Moscow/10/99	B/Beijing/184/93
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2002–2003	A/New Caledonia/20/99	A/Moscow/10/99	B/Hong Kong/330/2001
2003–2004	A/New Caledonia/20/99	A/Moscow/10/99	B/Hong Kong/330/2001
2004-2005	A/New Caledonia/20/99	A/Fujian/411/2002	B/Shanghai/361/2002
2005-2006	A/New Caledonia/20/99	A/California/7/2004	B/Shanghai/361/2002
2006-2007	A/New Caledonia/20/99	A/Wisconsin/67/2005	B/Malaysia/2506/2004
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2008-2009	A/Brisbane/59/2007	A/Brisbane/10/2007	B/Florida/4/2006
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2015-2016	A/California/7/2009	A/Switzerland/9715293/2013	B/Phuket/3073/2013
2016-2017	A/California/7/2009	A/Hong Kong/4801/2014	B/Brisbane/60/2008
2017-2018	A/Michigan/45/2015	A/Hong Kong/4801/2014	B/Brisbane/60/2008
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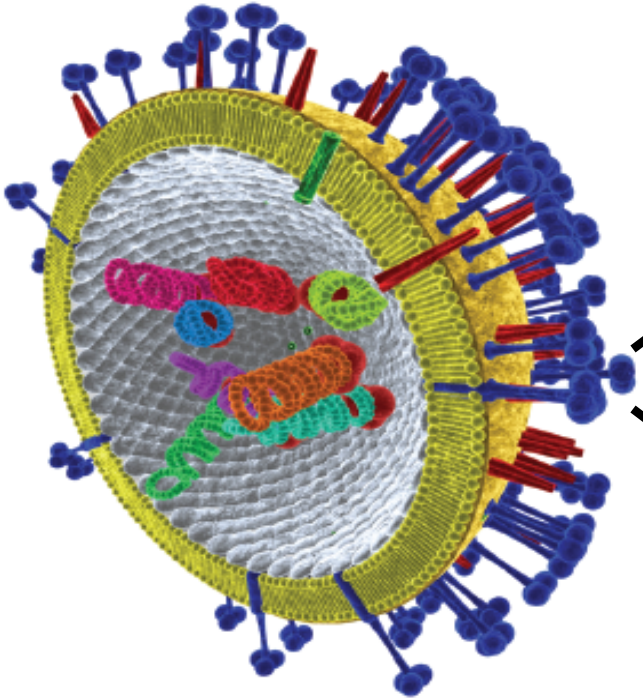
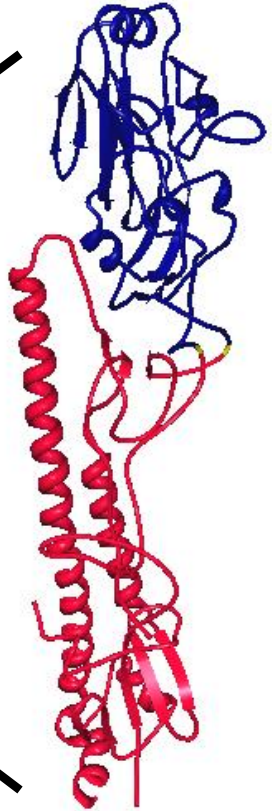
2017/18 vaccine effectiveness (VE) estimate: <u>About 25%</u> (H3N2, source: CDC)

What is the problem?



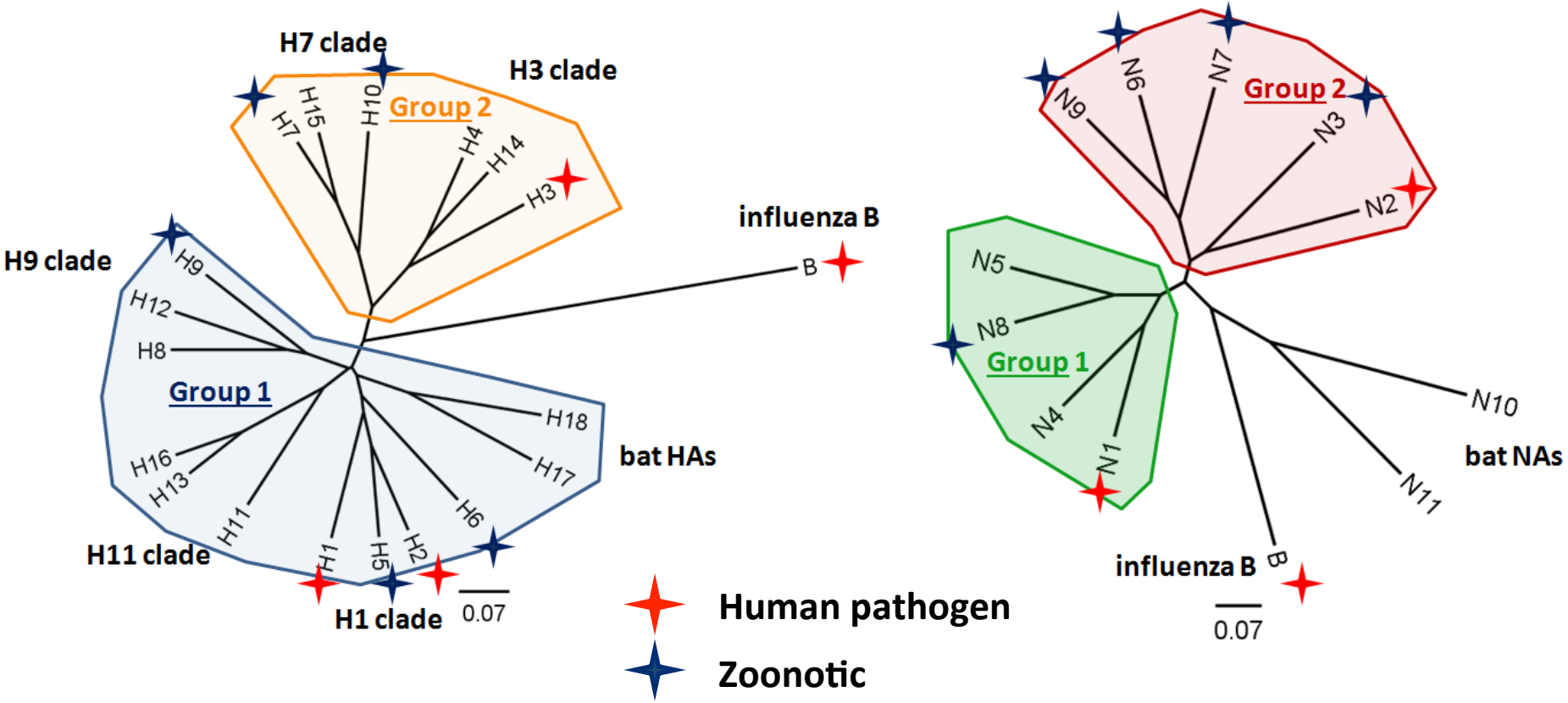


Globular head domain: mediates binding to host receptors

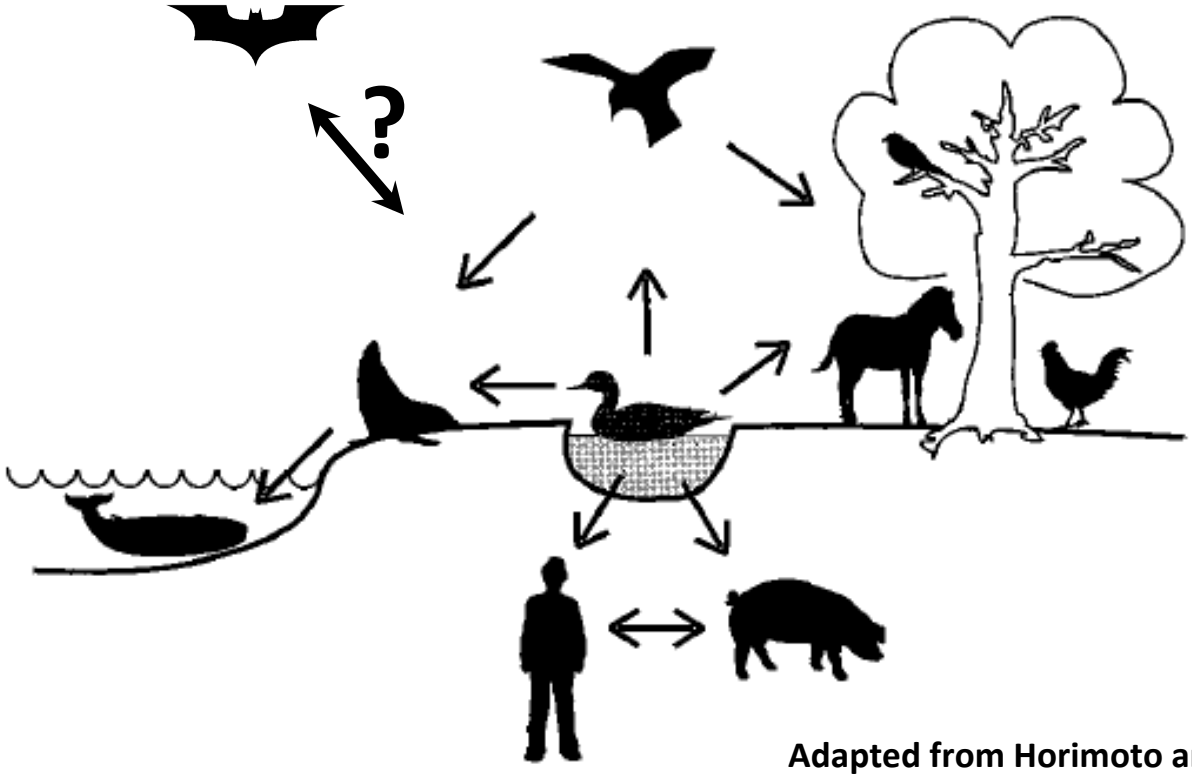
Stalk domain: mediates fusion of viral and endosomal membranes

adapted from Krammer and Grabherr, 2010, Trends Mol Med.

Influenza viruses come in many flavors…



…and infect many different host species

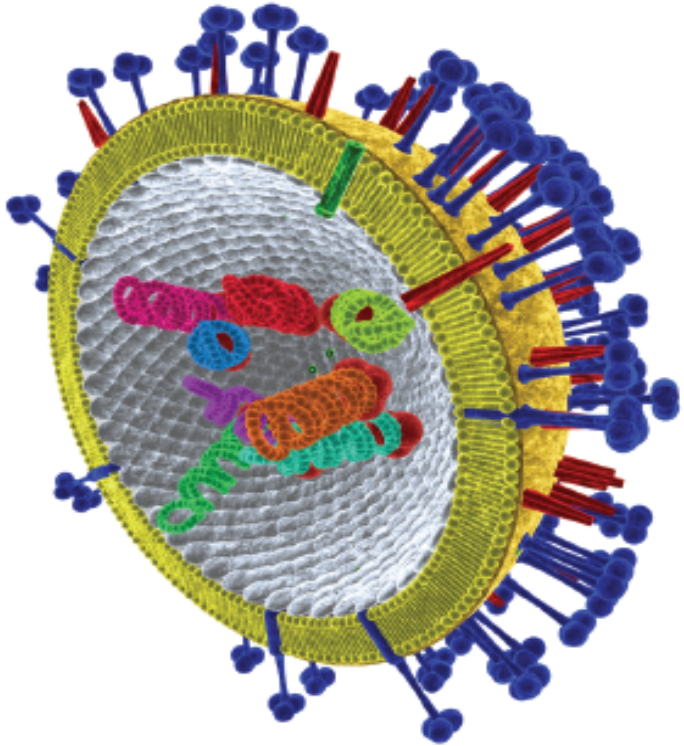


Adapted from Horimoto and Kawaoka, CMR, 2001

Which problems would a universal influenza virus vaccine address?

1. Annual re-formulation and re-administration
   - Cannot easily be implemented in LMICs
2. No specific formulation for tropical/sub-tropical countries available
3. Mismatches occur frequently for current vaccines
   - Egg adaptation of vaccine strains
4. Vaccine coverage
5. Can influenza B be eradicated?
6. Pandemic preparedness

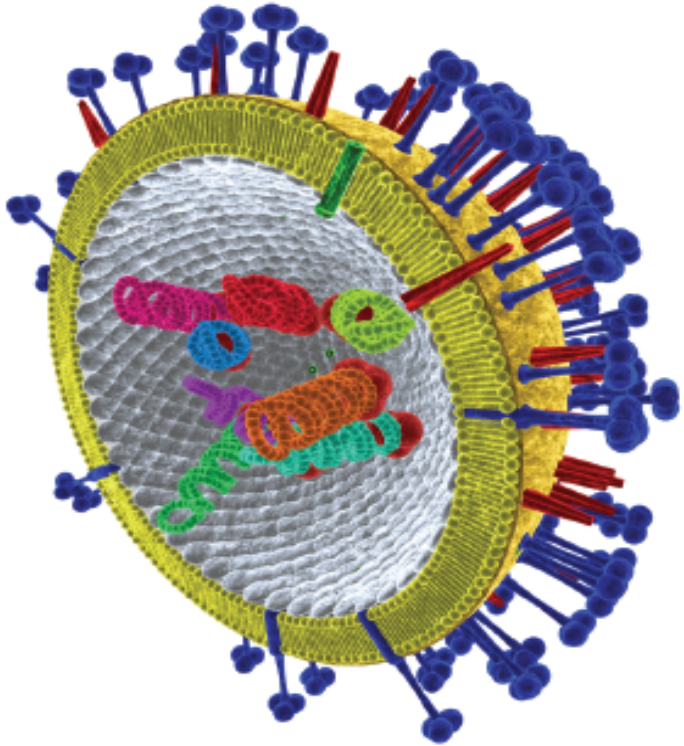
Target Overview for Universal Influenza Virus Vaccines



- Internal proteins
- M2e
- Neuraminidase (NA)
- Stalk domain of the hemagglutinin (HA)
- Conserved regions of the head domain of HA

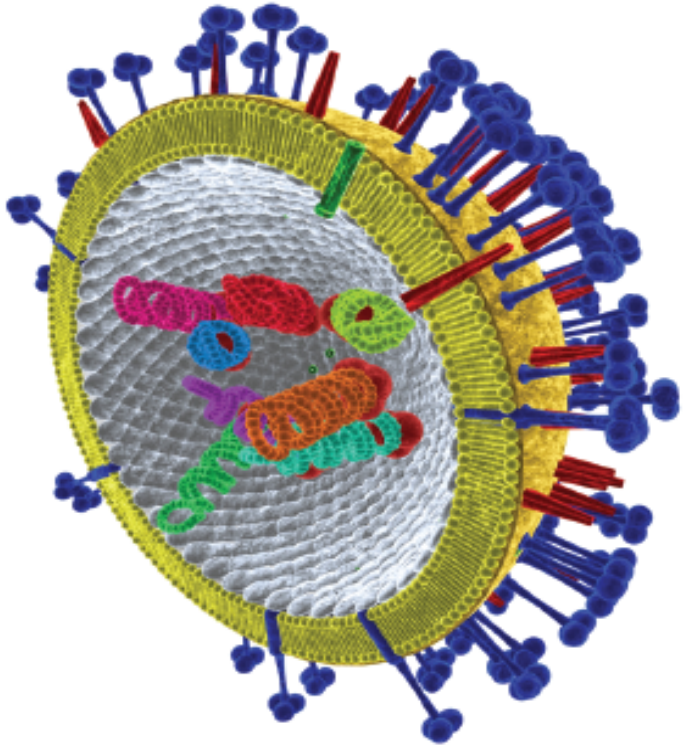
adapted from Krammer and Grabherr, Trends Mol Med 2010

Internal proteins



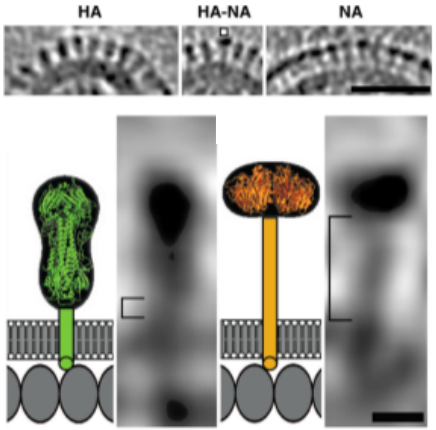
- **Nucleoprotein (NP), M1 and polymerase subunits**
  - **Conserved (e.g. about 90% amino acid identity for NP between human H1 and H3 isolates)**
  - **Strong T-cell epitopes**
  - **Not easily accessible for antibodies**
- **Various experimental T-cell based vaccines with NP and M1 in animal models and clinical trials**
- **<u>Vectored vaccines</u>**
  - **NP+M1 expressing MVA vaccine was able to induce strong CD8+ and CD4+ T-cell responses (Lillie et al., Clin Infect Dis, 2012)**
- **<u>Peptide vaccines</u>**
  - **Multimeric-001 (BiondVax) contains NP and M1 epitopes (Atsmon et al., 2012, J Clin Immunol)**

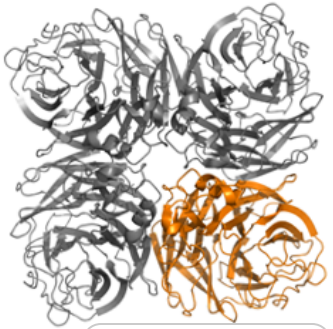
M2e



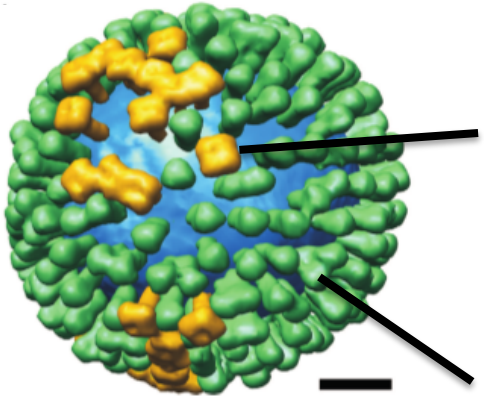
- 23 N-terminal amino acids which form the ectodomain of the tetrameric M2 ion channel
- Displayed on the cell surface, low copy number on the virus
- Conserved (~80% amino acid identity)
- Early development of particle-based M2e vaccines (Neirynck et al., Nat Med, 1999 and others)
- Vaccination induces infection-permissive (not sterilizing) immunity
  - morbidity, virus replication
- Mechanism
  - Mainly antibody dependent cell-mediated cytotoxicity (El Bakkouri et al., J Immunol, 2011 and others)
- Discussed as “additive” to regular influenza virus vaccine

Neuraminidase (NA)





N2, PDB ID: 2AEP

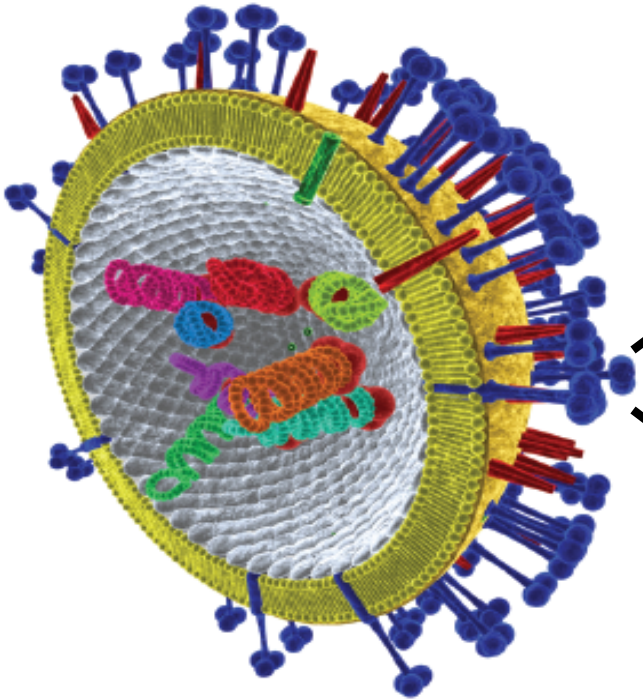


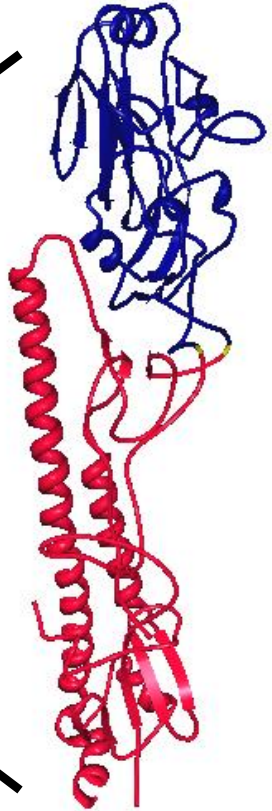
Harris *et al*, PNAS, 2006

Scale bar = 20 nm

- Is expressed on the virus and on infected cells
- Drifts slower than HA, well conserved within the subtype (e.g. within N1)
- NA content not standardized in commercial vaccines and there is barely any immune response to the NA that is present (Chen et al., Cell, 2018)
- Human anti-NA mAbs can be highly and broadly protective (Chen et al., Cell, 2018)
- Anti-NA antibody levels in humans correlate with protection
- Recombinant NA vaccines induce broad protection within the subtype (Wohlbold *et al.*, mBio, 2015)
- Mechanism of protection: Inhibition of enzymatic activity

Parts of the hemagglutinin (HA) are conserved as well





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Stalk domain: mediates fusion of viral and endosomal membranes

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PLoS one

Heterosubtypic Neutralizing Monoclonal Antibodies Cross-Protective against H5N1 and H1N1 Recovered from Human IgM$^+$ Memory B Cells

Mark Throsby[1¤a], Edward van den Brink[1¤b], Mandy Jongeneelen[1], Leo L. M. Poon[2], Philippe Alard[3], Lisette Cornelissen[4], Arjen Bakker[1¤c], Freek Cox[1¤a], Els van Deventer[1], Yi Guan[2], Jindrich Cinatl[5], Jan ter Meulen[1¤d], Ignace Lasters[3], Rita Carsetti[6], Malik Peiris[2], John de Kruif[1¤a], Jaap Goudsmit[1]*

1 Crucell Holland BV, Leiden, The Netherlands, **2** Department of Microbiology, The University of Hong Kong, Queen Mary Hospital, Hong Kong Special Administrative Region, People's Republic of China, **3** Algonomics NV, Gent-Zwijnaarde, Belgium, **4** Central Veterinary Institute, Wageningen University, Lelystad, The Netherlands, **5** Institute for Medical Virology, Johann Wolfgang Goethe University, Frankfurt am Main, Germany, **6** Laboratory of Cell Biology, Bambino Gesu Children's Research Hospital, Rome, Italy

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Antibody Recognition of a Highly Conserved Influenza Virus Epitope

Damian C. Ekiert,[1] Gira Bhabha,[1] Marc-André Elsliger,[1] Robert H. E. Friesen,[2] Mandy Jongeneelen,[2] Mark Throsby,[2] Jaap Goudsmit,[2] Ian A. Wilson[1,3]*

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PLoS one

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Mandy Jongeneelen

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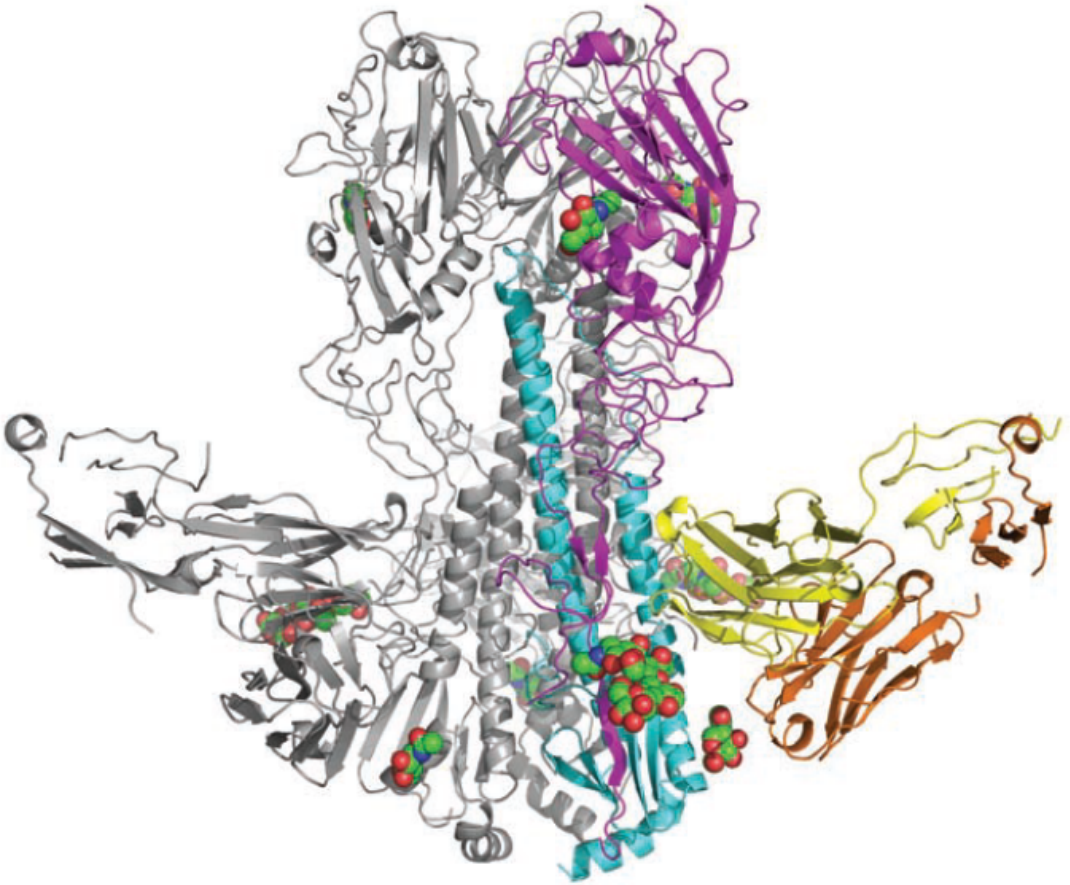
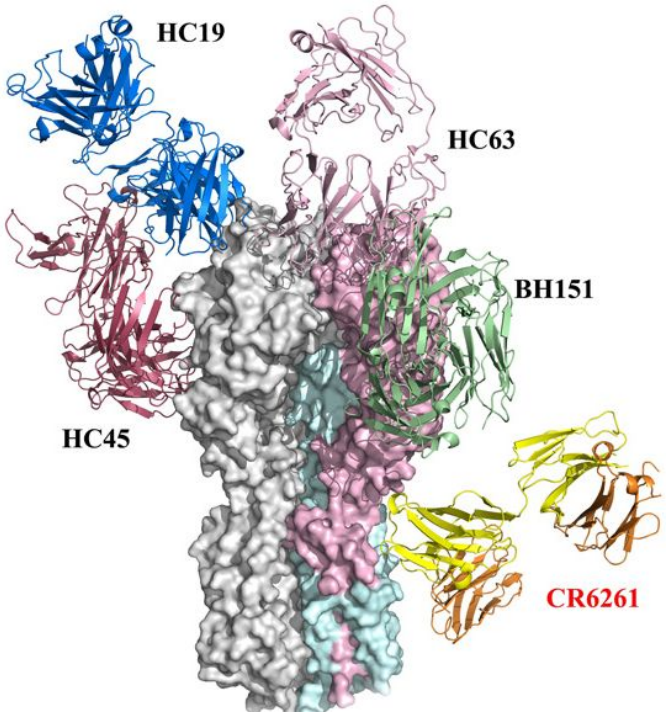


Antibodies against the influenza virus HA stalk domain

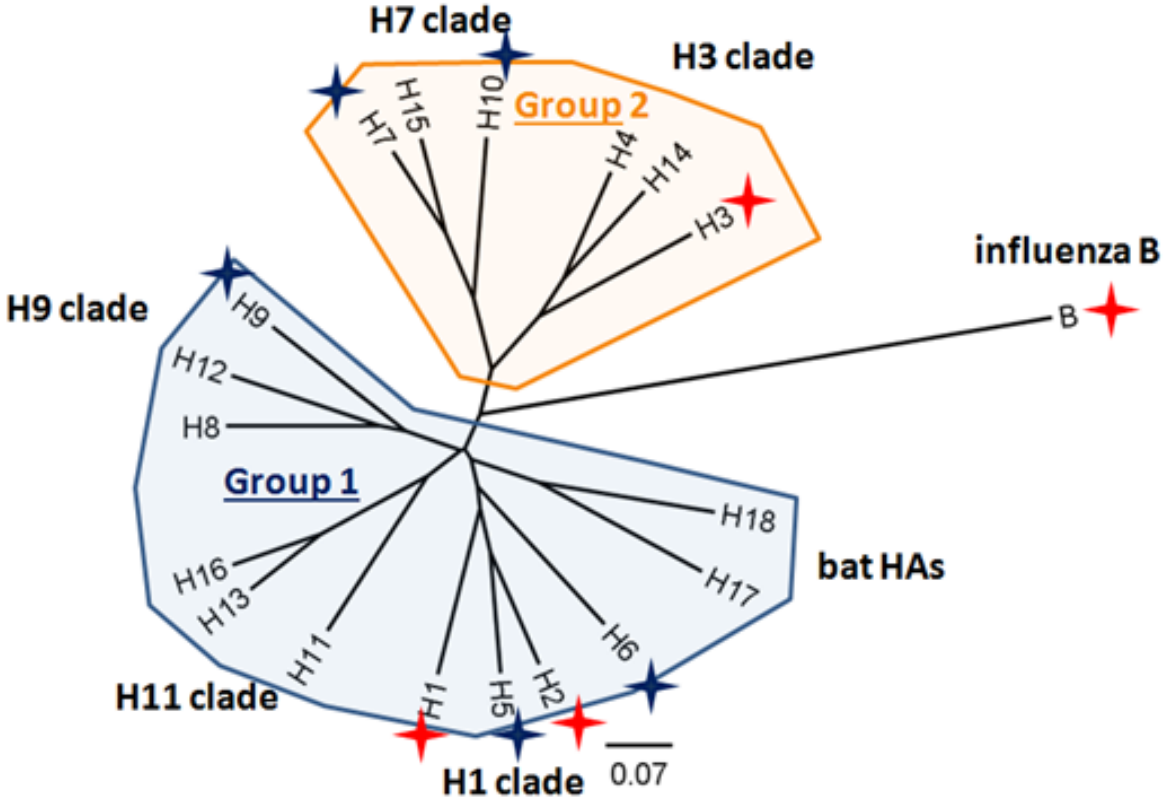
Immunodominant head domain

Stalk domain



- Rare and not induced/boosted upon regular seasonal vaccination
- Have been isolated from humans and mice
- Cross-reactive between HAs of different subtypes
- Broad neutralizing activity
- Conformational epitopes
- HI negative

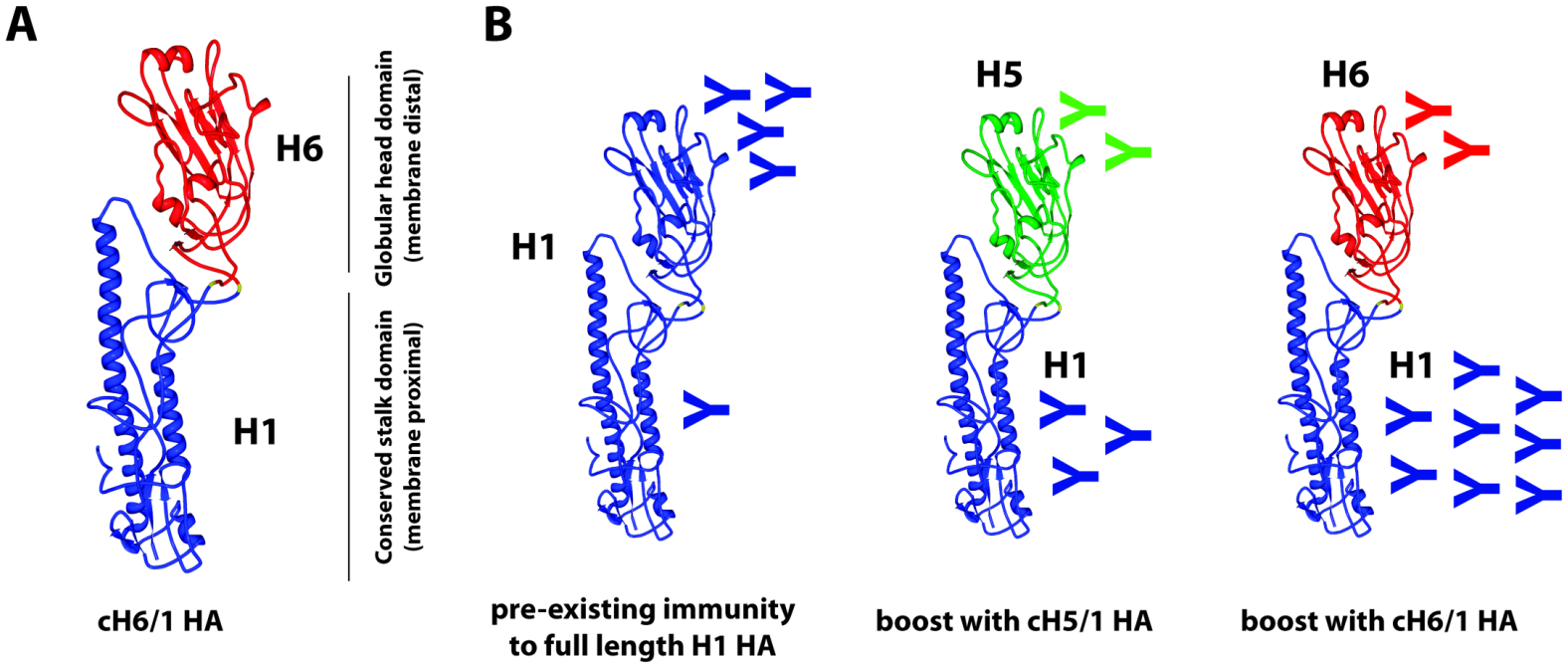
Influenza virus HA subtypes



Cross-neutralizing antibodies against the influenza virus HA

	C179	CR6261	F10	CR8043	CR8020	12D1	6F12	CR9114	FI6
H1	+	+	+	-	-	-	+	+	+
H2	+	+/-	+	-	-	-	-	+	+
H5	+	+	+	-	-	-	-	+	+
H6	+	+	+	-	-	-	-	+	+
H9	+	+	+	-	-	-	-	+	+
H3	-	-	-	+	+	+	-	+	+/-
H7	-	-	-	+/-	+/-	-	-	+	+/-
B	-	-	-	-	-	-	-	+/-	-

Chimeric HA technology



Krammer *et al.*, Nature Immunology, 2013 etc.

VIROLOGY 126, 106–116 (1983)

Preparation of Influenza Virus Subviral Particles Lacking the HA1 Subunit of Hemagglutinin: Unmasking of Cross-Reactive HA2 Determinants

P. N. GRAVES, J. L. SCHULMAN, J. F. YOUNG, AND P. PALESE[1]

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Received October 12, 1982; accepted November 29, 1982

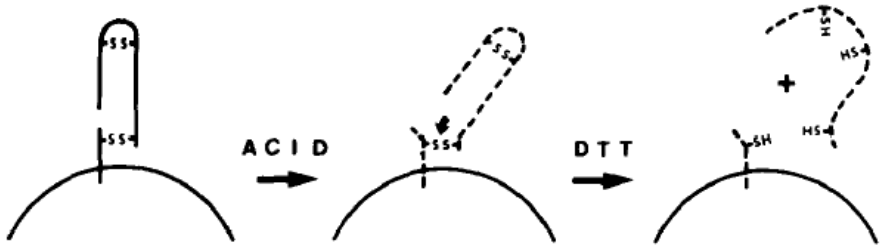
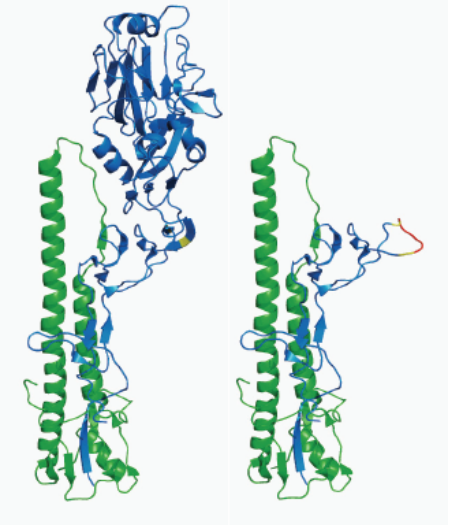
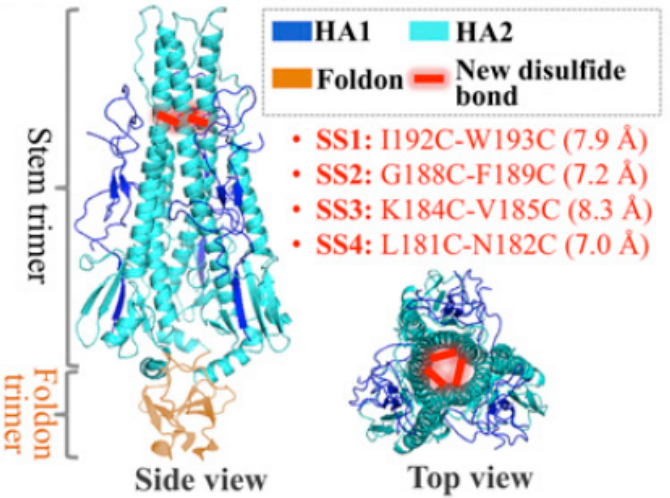


FIG. 5. Removal of the HA1 subunit of hemagglutinin by acid/DTT treatment of influenza virus. The model shows that acid treatment of virus alters the configuration of hemagglutinin. Subsequent neutralization, followed by DTT treatment, releases intact HA1 from the virus, resulting in the formation of subviral particles lacking the HA1 subunit.

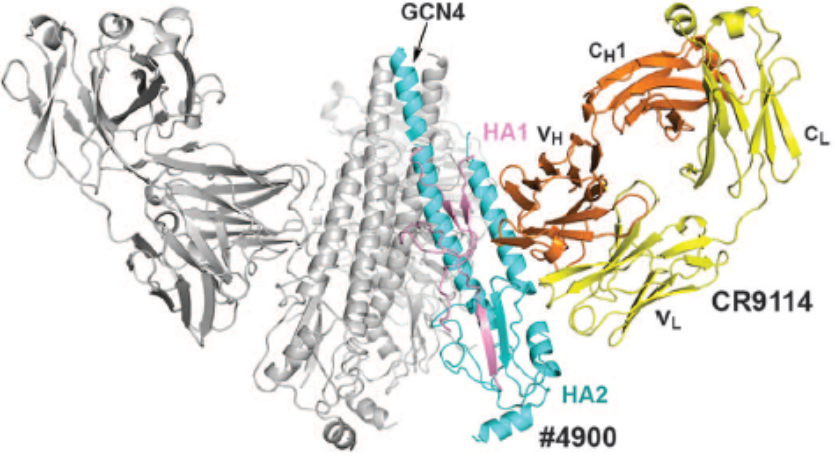
Headless HA



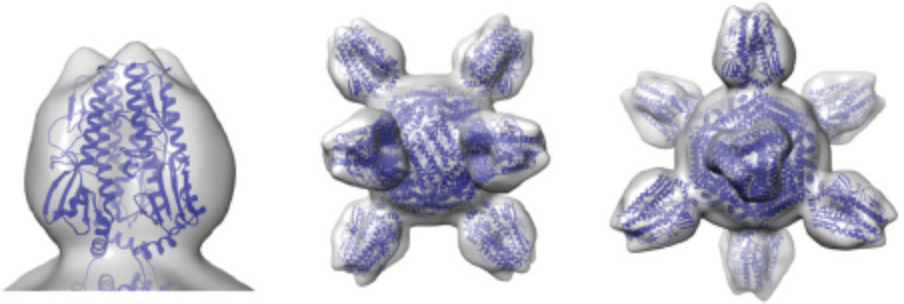
Steel *et al*., mBio, 2010



Lu *et al*., PNAS, 2014



Impagliazzo *et al*., Science, 2015



Yassine *et al*., Nat. Med., 2015

How far are we are we with developing those vaccines?

- HA stalk
  - cHA vaccines (Phase I/II trials)
  - Headless/mini HA (Johnson & Johnson, Vaccine Research Center/NIH)
  - …
- HA head
  - COBRA (UGA/Sanofi Pasteur)
  - VLP combinations (NIH)
  - DNA vaccine combinations (Inovio)
  - …
- Internal proteins
  - MVA/AdV NP-M1 (Jenner Institute)
  - Peptide-based approached (BiondVax etc.)
  - …
- M2e (multiple entities)
- NA???

Conclusions

- **Current vaccines provide limited breadth**
- **Universal influenza virus vaccines are in early clinical trials and could**
  - **Abolish the need for annual reformulation/ readministration**
  - **Make influenza virus vaccines globally available**
  - **Enhance pandemic preparedness**
- **Influenza B viruses can theoretically be eradicated**
- **We are getting there……but we need to move faster**

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