

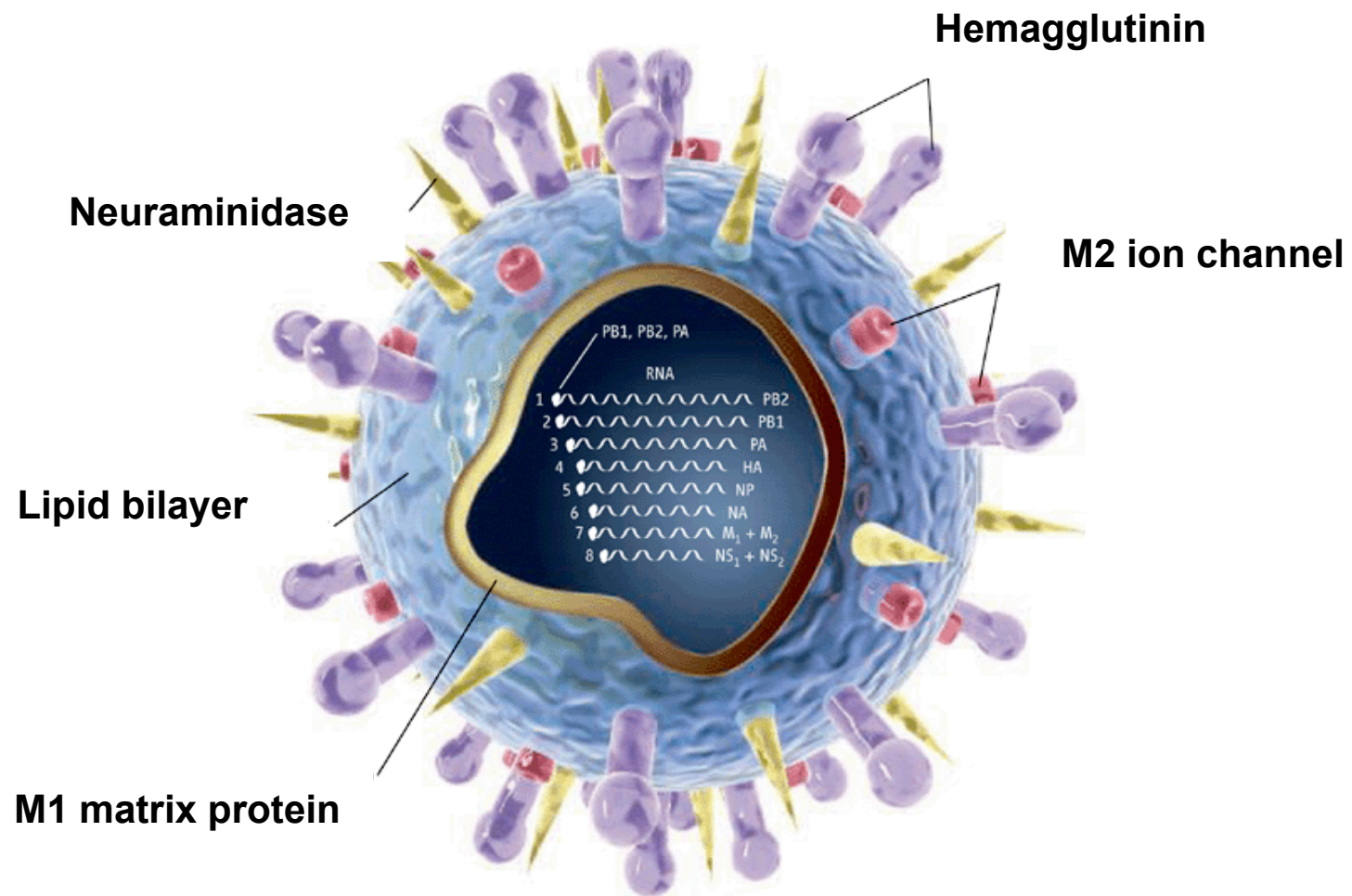
2009 Novel Influenza H1N1

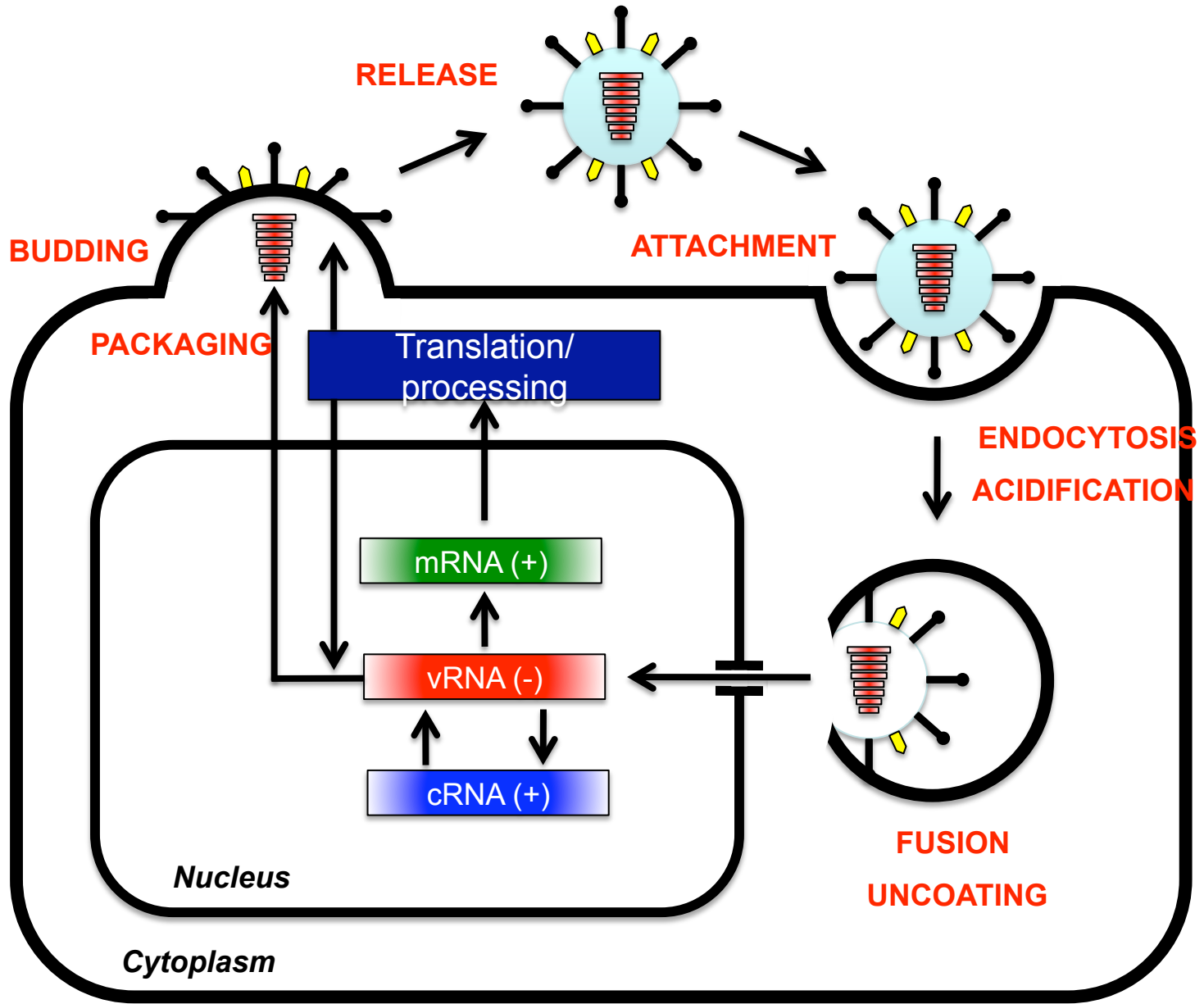
Gary S. Marshall, M.D.

Professor of Pediatrics

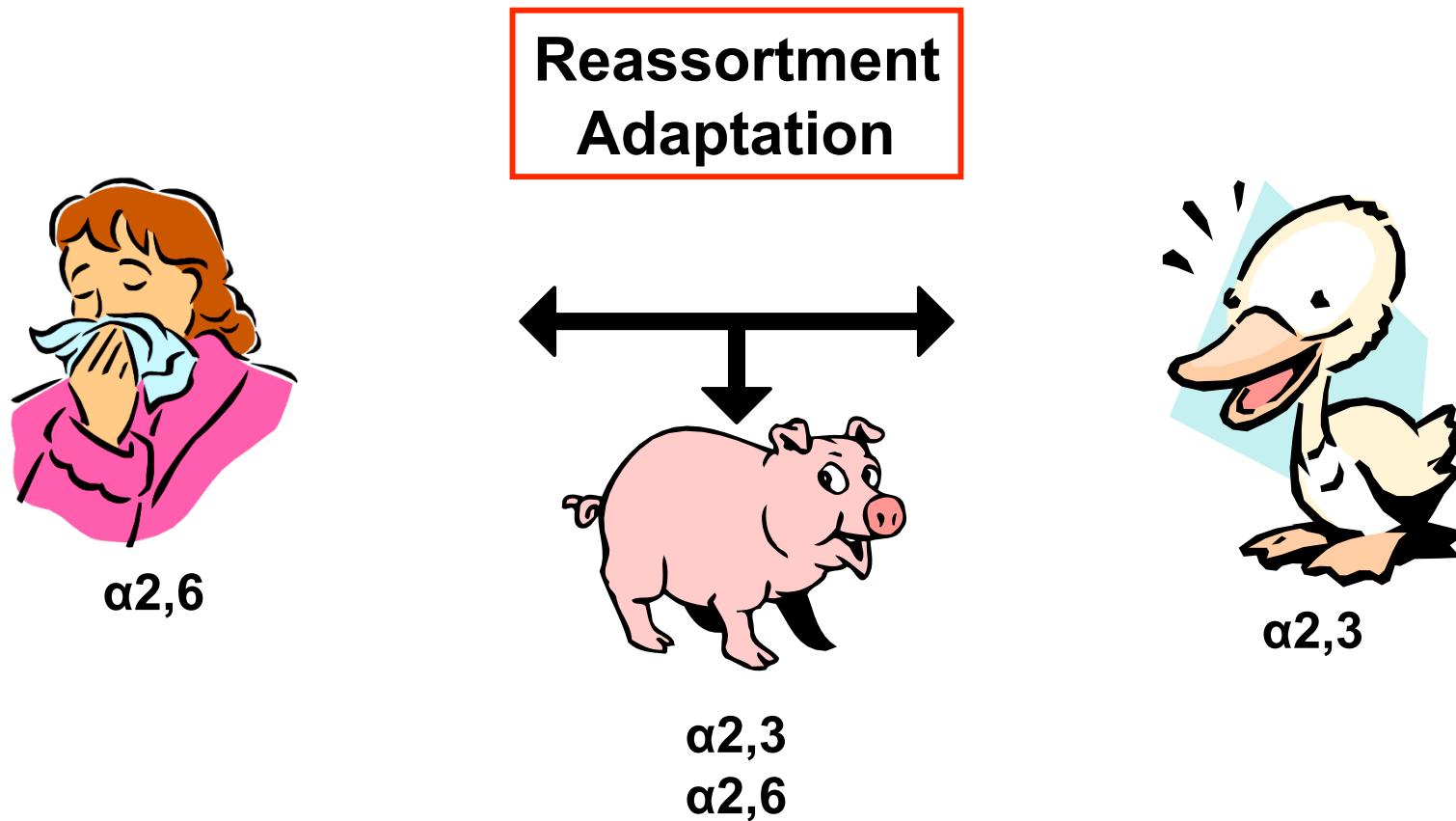
Chief, Division of Pediatric Infectious Diseases

Director, Pediatric Clinical Trials Unit





Host Range



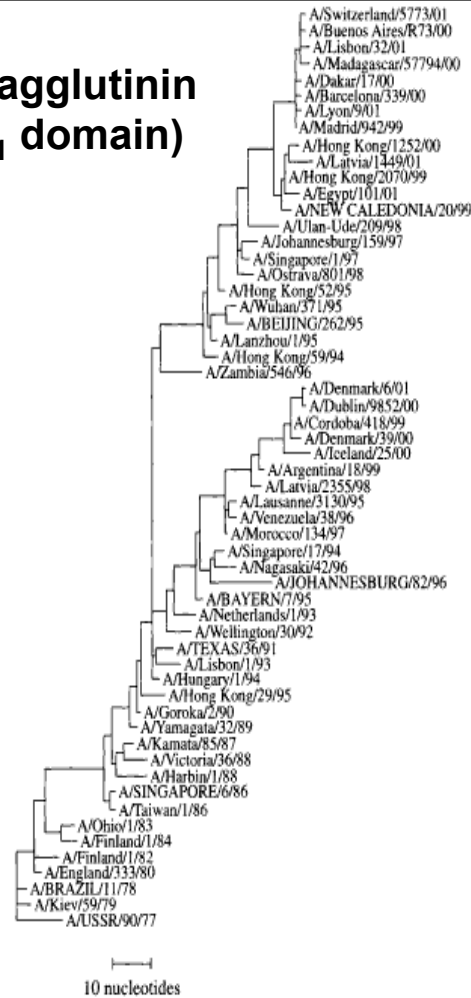
Antigenic Drift: Influenza A(H1N1) Viruses

Post-infection hemagglutination inhibition titers in ferrets

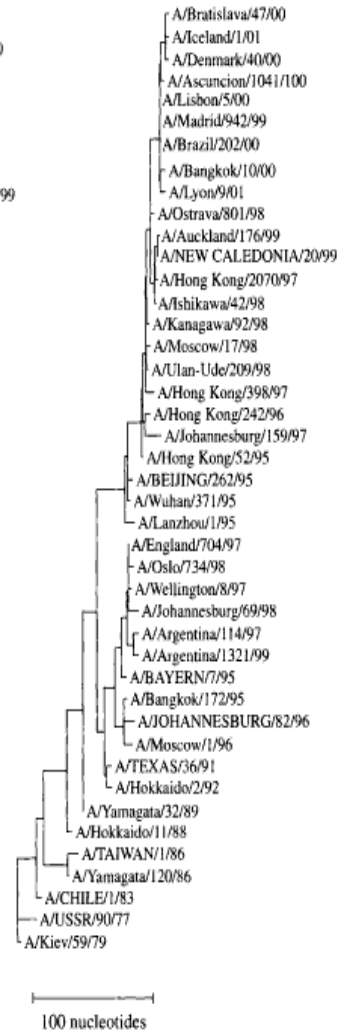
Virus strain	USSR 77	Brazil 78	Chile 83	Sing 86	Taiw 86	Texas 91	Bay 95	Beij 96	N Cal 99
USSR 77	1280	640	40	—	—	—	—	—	—
Brazil 78	320	1280	80	—	—	—	—	—	—
Chile 83	80	80	320	—	—	—	—	—	—
Sing 86	—	—	—	1280	320	1280	1280	—	—
Taiw 86	—	—	—	640	640	1280	1280	40	—
Texas 91	—	—	—	1280	640	2560	1280	40	40
Bay 95	—	—	—	640	640	2560	2560	80	40
Beij 96	—	—	—	—	—	40	40	640	320
N Cal 99	—	—	—	—	—	—	—	160	640

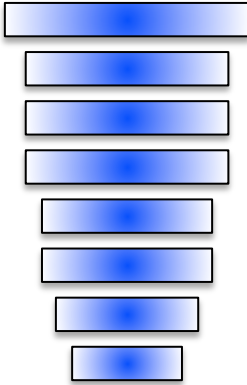
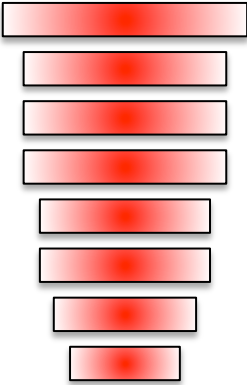
Influenza A(H1N1) Phylogeny

**Hemagglutinin
(HA₁ domain)**

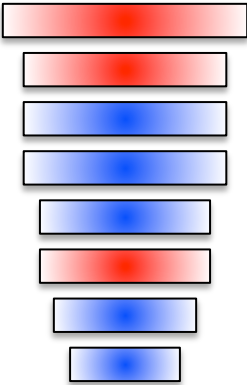
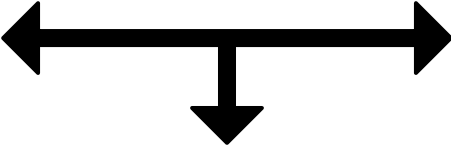


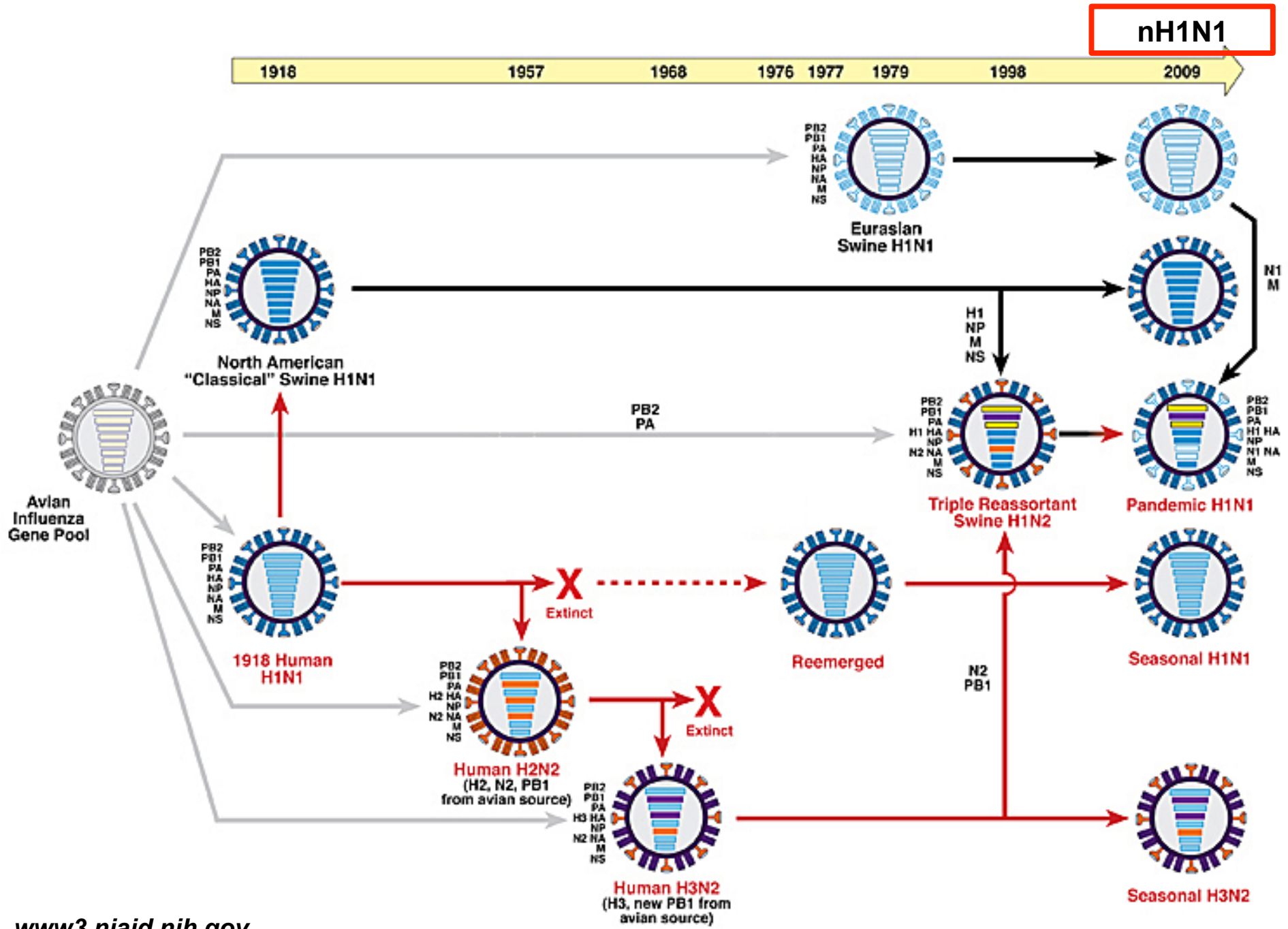
**Neuraminidase
(nuc 1-1384)**





Reassortment





Fort Dix: Influenza A/NJ/1976/H1N1

- **Outbreak of acute respiratory disease, Jan-Feb**
 - 13 hospitalizations, 1 death
 - 230 (of 19,000 personnel) infected
- **Virus known to be related to 1918 strain**
- **Mass immunization campaign**
 - Field trials in >7,000 volunteers
 - 45 million immunized in 10-week period
- **No cases identified outside of Fort Dix**

Swine Flu Vaccine: Guillain-Barré Syndrome

- **Background rate: 0.07-0.46 cases per 100,000 within 6 weeks of any vaccination**
- **Attributable risk: 0.49-1.17 per 100,000 (relative risk estimate 7.6)**
- **Approximately 500 cases and 25 deaths**
- **Possible mechanisms**
 - **Endotoxin (from *Salmonella* contamination) enhancement of vaccine-induced autoimmunity**
 - **Contamination with *Campylobacter jejuni***
 - **Low levels of NA leading to sialic acid-HA complexes that mimic GM1 ganglioside**

Swine Flu Vaccine: Guillain-Barré Syndrome

- **Fort Dix outbreak: a zoonotic anomaly**
 - Fully animal virus
 - Stressed, crowded population during a cold winter
- **Mass immunization campaign was premature**
- **Virus was different from 2009 nH1N1**

Seasonal Vaccine: Guillain-Barré Syndrome

- **Studies show no consistent association**
 - VAERS data, 1978-1981 season
 - 5.6 million US Army recipients, 1980-88
 - UK General Practice Research Database, 1990-05
- **Some studies demonstrate *decreased* risk**
- **Any risk of GBS offset by risk following natural infection**

Subjects Needed to Test for Increased Risk of Adverse Event Relative to Background Rates

Background rate in general population	Rate in vaccinated population		
	2-fold higher	10-fold higher	100-fold higher
1 in 10,000	141,000	5,500	500
1 in 100,000	1,238,000	53,500	2,500
1 in 1,000,000	12,951,500	532,500	23,500

Assumes 5% risk of Type I error and power of 90%

Genetic Lineage

Gene segment	2009 nH1N1	A/NJ/76/H1N1
PB2	Yellow	Blue
PB1	Green	Blue
PA	Yellow	Blue
HA	Blue	Blue
NP	Blue	Blue
NA	Pink	Blue
M	Pink	Blue
NS	Blue	Blue

Blue	Classical North American swine (1918 H1N1)
Yellow	Avian (1998)
Green	Avian (1968)
Pink	Eurasian swine (1979, derived from 1918 H1N1)

Notes on nH1N1 Vaccine Manufacture

- **Licensure of unadjuvanted, inactivated, egg-based vaccine through strain change supplement to seasonal BLA**
 - **Seed passage history**
 - **HAI analysis**
 - **Carton, label and PI**
 - **No new clinical data at time of licensure**
- **Government contracts with existing companies**
- **Anticipate 45 million doses by mid-October**
- **Most vaccine will be in multidose vials with preservative**

Emergency Use Authorization

- **Food, Drug, and Cosmetic Act, Section 564**
- **Emergency declaration by DHHS (April 25, 2009)**
- **Criteria**
 - **Serious or life-threatening**
 - **Product may be effective based on evidence**
 - **Benefits outweigh risks**
 - **No approved alternative**
- **Applicable to**
 - **Adjuvanted vaccines**
 - **Unapproved ages for approved vaccines**

US Government Vaccine Procurements

Product	Total acquisition
Bulk antigen, inactivated (15 mcg HA/dose)	181.8 million
Bulk virus, live, attenuated (10^7 pfu/dose)	12.8 million
Bulk adjuvant, oil-in-water	120.3 million

Vaccine Distribution

BARDA	CDC	STATE	LOCAL
Manufacture	Wholesale dist	Regional dist	Vaccination
CSL GSK MedImmune Novartis Sanofi	McKesson	Health departments Private providers	Priority individuals General public
5	4	30,000	300 million

BARDA, Biomedical Advanced Research and Development Authority (DHHS)

Unknowns

- **Growth in eggs adequate?**
- **Egg supply sufficient for both vaccines?**
- **Manufacturing capability sufficient for fill-finish?**
- **Traditional dose immunogenic?**
- **Adjuvant necessary?**
- **One or two doses?**

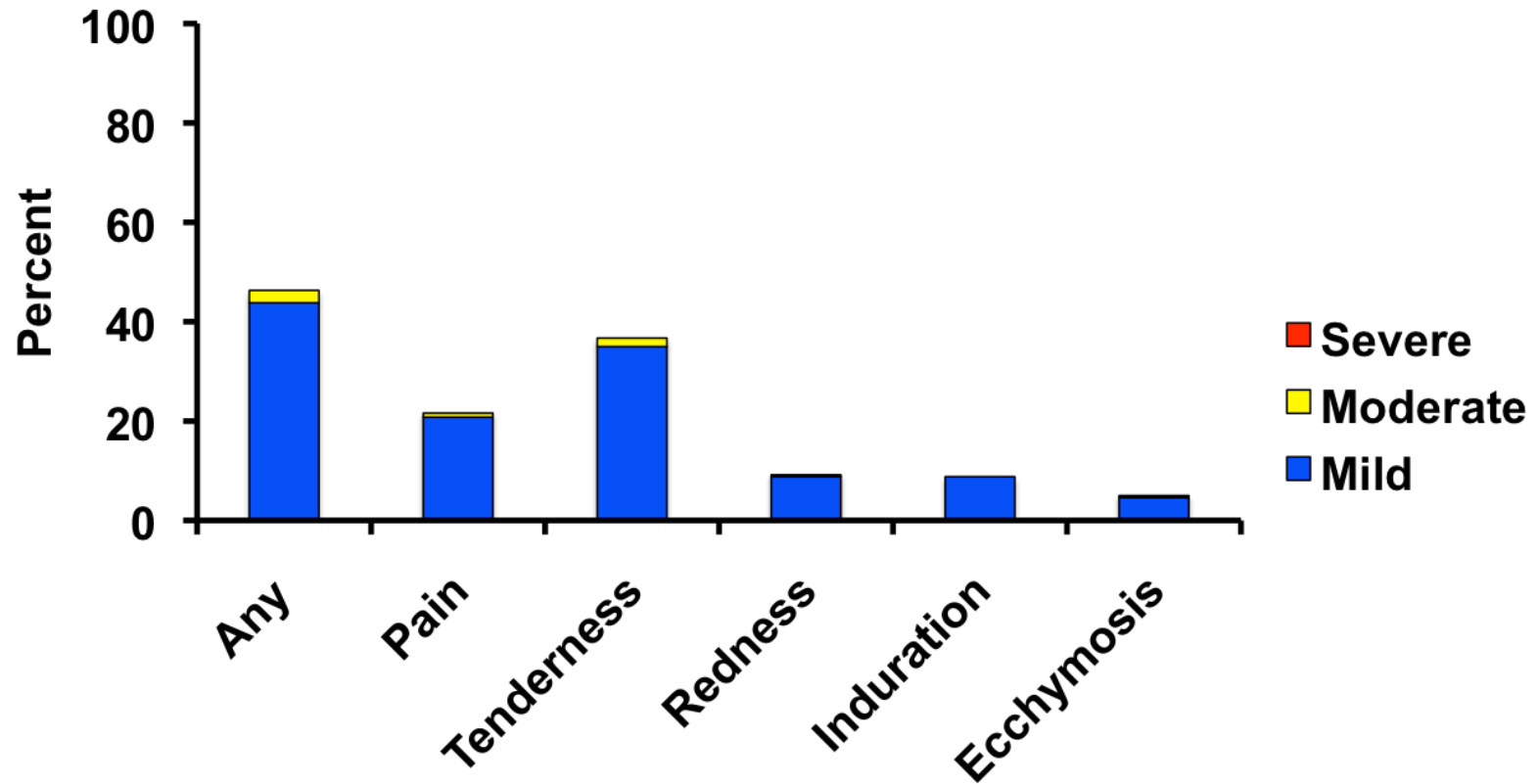
How Will We Know if the Vaccine is Safe?

- **Enhanced VAERS reporting**
 - Normal volume: 150 reports/day
 - Expected volume: 1,000 reports/day (400 serious)
 - Vaccination cards to facilitate reporting
- **Vaccine Safety Datalink**
 - 8 MCOs representing 3% of US population
 - Rapid cycle analysis (near real-time)
- **Vaccine Analytic Unit**
 - Defense Medical Surveillance System
 - 1.5 million active military personnel

How Will We Know if the Vaccine is Safe?

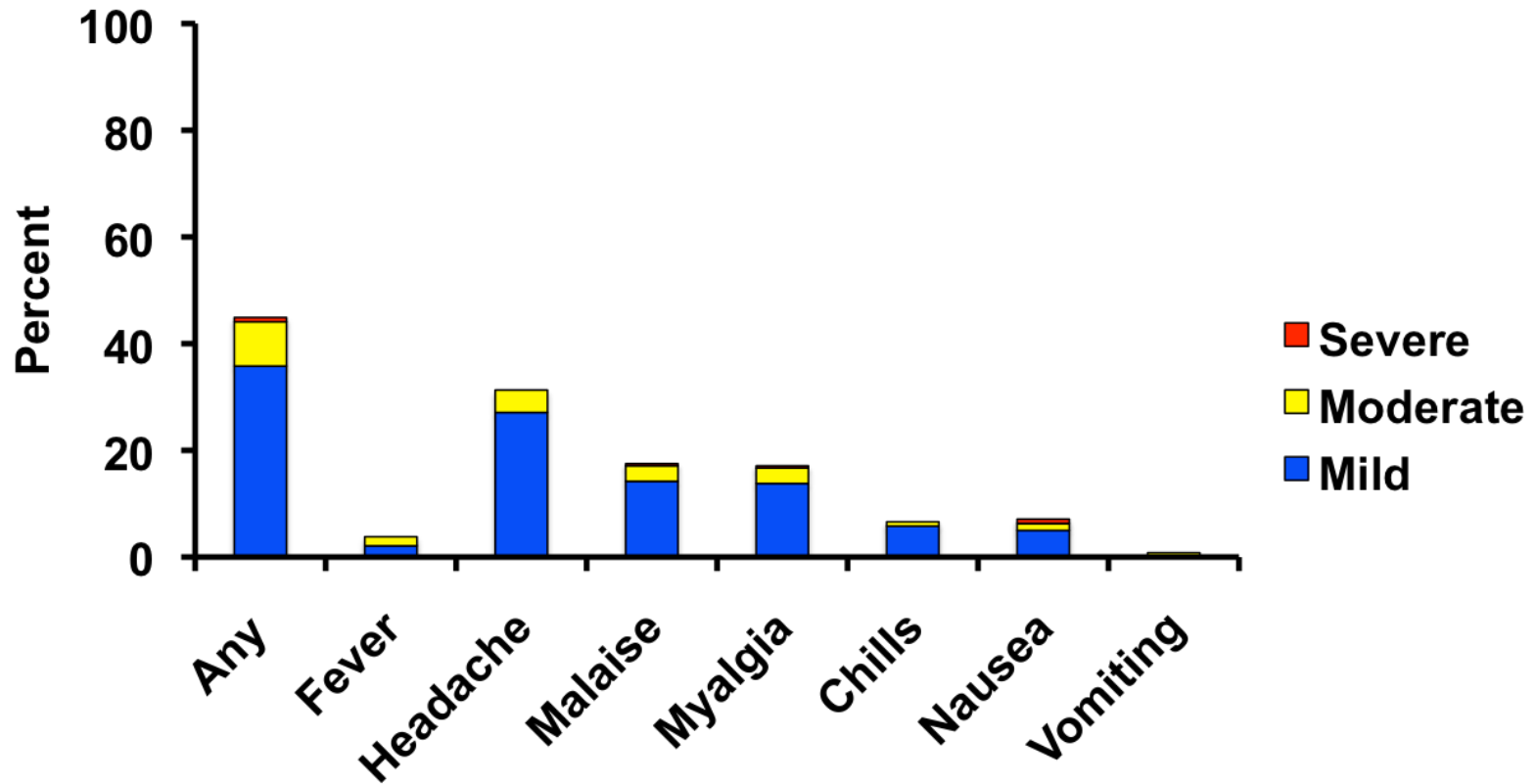
- **Case finding through Emerging Infections Program**
- **Enhanced VAERS reporting through collaboration with American Academy of Neurology**
- **Clinical Immunization Safety Assessment Centers**
 - **Collaboration with 6 academic centers**
 - **Evaluation of serious adverse events**

Solicited Local Adverse Events



Greenberg. *N Engl J Med* 2009;361:1 (N=240)

Solicited Systemic Adverse Events



Greenberg. *N Engl J Med* 2009;361:1 (N=240)