VACCINES AT GROUND LEVEL

SAFETY

&

EFFICACY

Vaccine Safety

Conditions For Which Vaccines Have Been Implicated

- ADHD
- Arthritis
- Autism
- Cancer
- Diabetes
- Inflammatory bowel disease
- SIDS

Vaccine Safety
Sudden Infant Death Syndome (SIDS)

- 4 million US births each year
- Several vaccinations in 1st year starting at birth
- Multiple antigens
- SIDS occurs in ~1:1500 infants

➢ Therefore, ~50-100 SIDS deaths are predicted to occur in the US annually within two days of being vaccinated

Vaccine Safety
ICH Safety Guidelines Don't Apply To Vaccines*

- 1500 Exposed
- 300-600 Exposed for at least 6 months with anticipated commercial dose
- 100-200 Exposed for 1-2 years
- These number don't provide enough power to detect an effect of vaccination on SIDS

*** International Council of Harmonization Guidelines (ICH) For long term treatment of non-life threatening conditions**

Vaccine Safety & SIDS

How Big A Trial Would We Need to Detect A 2-fold Increase?

Power To Detect A Doubling In Event Rate

Sample Size	Event Rate 5-10%	Event Rate 1-2%	Event Rate 0.1-0.2%
1000	0.82	0.17	0.07
5000	0.99	0.80	0.07
10,000	0.99	0.98	0.17
50,000	0.99	0.99	0.79

From Susan Ellenberg, PhD / FDA / CBER / Nov 2000

Vaccine Safety & Trial Size

Size of Recent Vaccine Safety Databases

Secret For Large Trials: KISS*

Vaccine	Patients Exposed (Pre & Post Licensure)
Varicella	~ 70,000
Rotavirus	> 30,000 (suspected intussusception)
Pneumococcal Conjugate	> 100,000

* KISS = Keep It Simple, Stupid

- Only essential data collection
- Even informed consent must be highly efficient

Vaccine Safety
Other Considerations

- Must establish safety of
  - All vaccine components, including adjuvants
  - When given with concomitant use vaccines

- Personal opinion: We musn't compromise safety, but
  - Should consider creative approaches, such as
  - Staged vaccine introduction for high risk populations (e.g. populations at high risk of diarrheal death for rotavirus)
  - Existing data capture mechanisms
    - UK or Canadian health care databases
    - HMO databases such as Kaiser

Vaccine Benefit
Primary Efficacy Measure

- If prophylactic efficacy surrogate established by prior clinical efficacy studies (e.g., HBV, *Neisseria Meningitidis* A,C)
  - → immunogenicity

- If prophylactic efficacy surrogate not established (e.g., HCV, HIV, *H. pylori*)
  - → clinical efficacy in field studies (validation of surrogate)

- Special cases (e.g., bioterrorism vaccines)
  - → possibly animal challenge studies and human immunogenicity

Vaccine Efficacy
Immunogenicity as the Primary Measure

- Appropriate for assessing efficacy of
  - Improved existing vaccines (e.g., adjuvants, cell culture-derived flu vaccine)
  - Combinations of already approved vaccines

- Typically expressed as seroprotection / seroconversion rates
- Major issues
  - Choice of the protective level / allowable non-inferiority margin
  - Seroprotection levels vs GMTs
  - Assay selection (e.g., EIA vs SBA) and validation
  - Duration of protection
  - Impact of preexisting antibodies (e.g., in early months of life)
- Need prospectively defined measures and analyses

When There Is No Efficacy Surrogate
Options for Assessing Clinical Efficacy

- Field Efficacy
  - Nearly always necessary
- Human Challenge
  - Selected circumstances when ethically appropriate
- Animal challenge for bioterrorism vaccines

Vaccine *Case Studies*

- Menveo (Meningococcal ACWY)
  - Conjugate vaccine approved based on immunogenicity
- Meningococcal B
  - Antigens identified by ‘reverse vaccinology’
- Group B Strep
  - Investigational vaccine tackling tough issues (e.g. validation of a surrogate, vaccination during pregnancy)
- Seasonal & Pandemic influenza
  - H1N1 incorporated into yearly trivalent vaccine
- *H Pylori*
  - Where to test for efficacy

Neisseria Meningiditis

- Gram neg diplococcus best known for its role in meningitis
- Meningitis – young & adolescents most vulnerable
- Meningococcemia – death within hours *(Waterhouse-Friederichson)*
- 2500-3500 cases in US annually
- Multiple serotypes
- Geographic diversity (e.g. A in Sub-Saharan Africa)
- Evolving epidemiology (Y was previously uncommon in US)

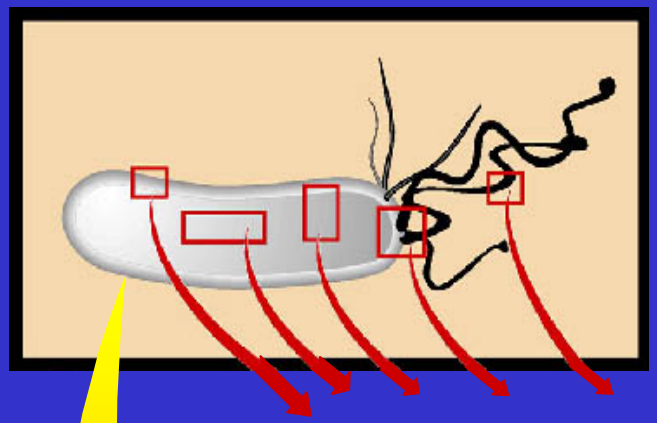
CDC Data From 2009

Incidence By Serogroup (Cases per 100,000)				
Age	B	C	Y	Other
<1	1.54	0.19	0.58	0.19
1	0.38	0.00	0.00	0.00
2-4	0.26	0.06	0.00	0.00
5-17	0.05	0.03	0.11	0.00
18-34	0.10	0.16	0.03	0.00
35-49	0.02	0.06	0.10	0.01
50-64	0.04	0.06	0.10	0.00
≥ 65	0.02	0.02	0.20	0.05
Total†	0.09	0.07	0.10	0.01

Menveo: Meningococcal (Groups A, C, Y, & W-135) Oligosaccharide Diphtheria Conjugate Vaccine

- Clinical development began ~2001
  - Built on meningococcal C monovalent (Menjugate)
- US approval for ages ≥ 2 (January 2011)
- ~9 safety / immunogenicity trials involving ~15,000 subjects
- Comparator: Menactra (Sanofi – Aventis)
- Efficacy measure: serum bacteriocidal antibody
  - Titer ≥ 1:8 or at least a 4x increase (dep on baseline)
- A ***'straightforward'*** vaccine, development of which....
  - Spanned a decade in clinical development
  - Spanned two companies
  - Is not yet done (ages <2 ongoing, most vulnerable)

Meningococcal B Vaccine & Reverse Vaccinology
Standard Antigen Discovery Did Not Work



Failed to Produce Candidates

Antigen selection

Test Convalescent sera

Test immunogenicity

Identify components

Purify components

Clone genes

5-15 Years

Immunogenicity testing in animal models

VACCINE DEVELOPMENT

Vaccine

MenB Vaccine: Genomic-Based Approach

Reverse Vaccinology

Immunogenicity testing in animal models

VACCINE DEVELOPMENT

Vaccine

1-2 years

Expression of recombinant proteins

In silico vaccine candidates

Computer Prediction

Start from the whole genomic sequence

Sequence Of Steps & Outcomes

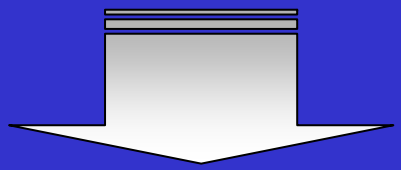
600 predicted surface-associated proteins

350 proteins expressed in *E. coli*

344 purified and used to immunize mice

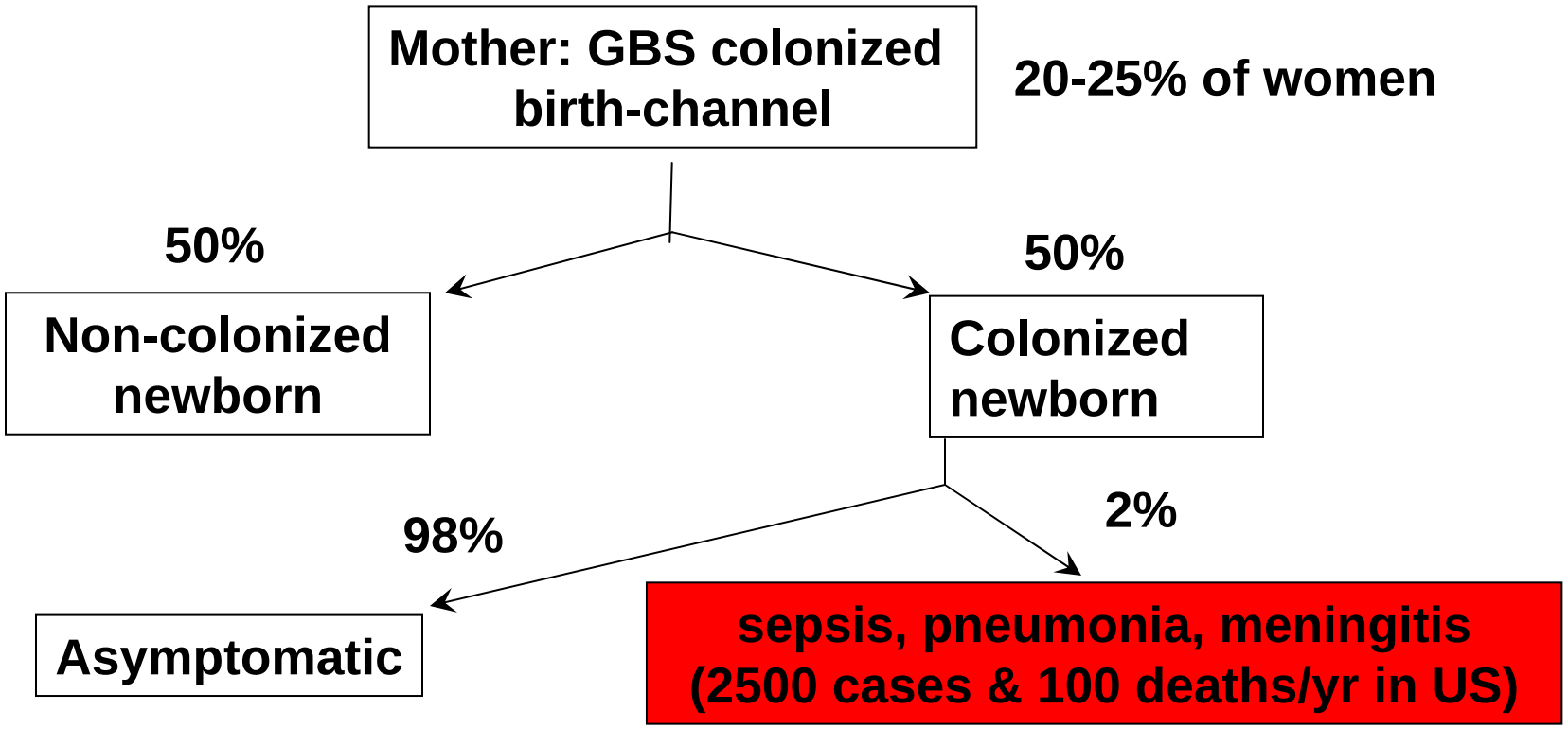
91 novel surface-exposed proteins identified

28 have bactericidal activity



7 best candidates selected: NOW SUBMITTED IN EU FOR APPROVAL; PHASE 2 TESTING FOR US MARKET

Group B Strep (GBS): Maternal to Infant Transmission (Leading Cause of US Neonatal Morbidity, Mortality)



CDC recommends routine prenatal culture and intra-partum administration of antibiotics (PCN, ampicillin) for women with positive cultures (Schrag, Schuchat 2001), *but a vaccine is needed to deal with* (a) emerging resistance and (b) unplanned pregnancies/no prenatal care

Evidence that Anti-Capsular Antibodies Protect Newborns

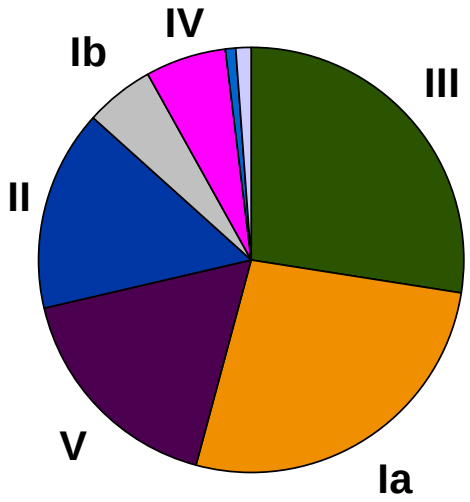
- Maternal Ab correlates with infection of newborns[1-3]
- Protective potential of anti-GBS Ab demonstrated in murine neonatal pup challenge model[4]

Therefore, antenatal vaccination to produce anti-GBS antibodies is likely to be protective, ***but***

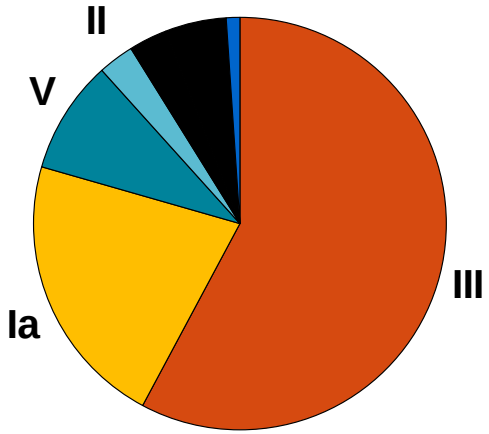
1. **Feng-Ying C. Lin,et al. J. Infect. Dis., 2001, 184:1082**
2. **Feng-Ying C. Lin, et al. J. Infect. Dis. 2004;190:928**
3. **Baker CJ, Kasper DL.. NEJM 294:753-756, 1976.**
4. **Rodewald AK et al. JID 166:635, 1992.**

Diversity: Good in the Workplace But a Challenge For Vaccine Development

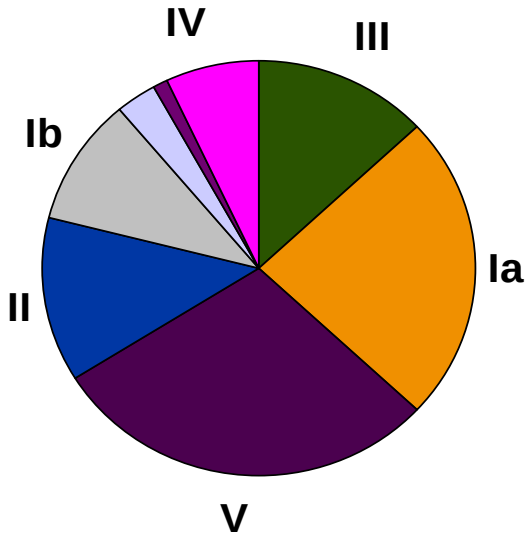
Early onset (n=98)



Late onset (n=111)



Adults > 65 years



9 GBS serotypes characterized (Ia, Ib, II, III, IV, V, VI, VII and VIII) and found to be antigenically unique

US serotype distribution in 2005; Active Bacterial Core (ABCs) surveillance unpublished data from 7 surveillance areas.

Active Bacterial Core surveillance

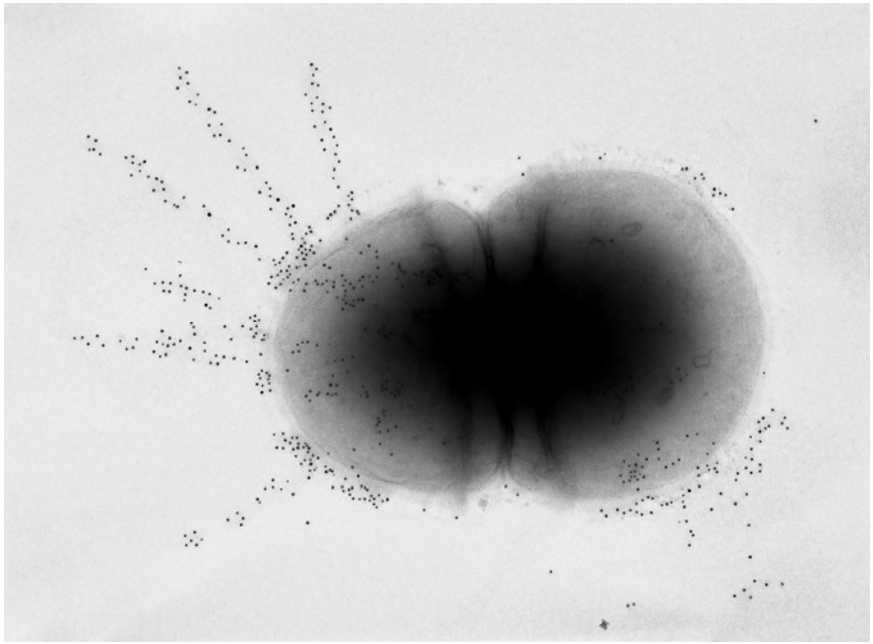
GBS Vaccine Design: Conquering Diversity

- Prepare combination of CPS-glycoconjugates
  - Combination of Ia, Ib, III and V may represent ~85% of isolates based on US & UK epidemiology

- Include conserved GBS proteins to increase breadth
  - Putative surface-associated and secreted proteins identified by genome analysis

- 8 GBS genomes sequenced -> 650 possible antigens (e.g. transmembrane)
  - 450 proteins expressed, purified & used for immunization
  - Cocktail of 4 highly preserved proteins identified
  - Function unknown – so localized using immunostaining
  - ***Led to a scientific breakthrough***

Serendipity And a New Paragidm: Three of the Four Antigens are Components of Novel Covalent Pili



- **gram-neg pili formed by non-covalent interactions between pilin subunits, but**
- **gram-pos pili formed by covalent polymerization of adhesive pilin subunits**
- **Studies in 3 strep pathogens indicate that the genes encoding the pilin subunits and assembly enzymes were acquired en bloc by horizontal transfer of a pathogenicity island.**

Lauer et al: Genome analysis reveals pili in Group B Streptococcus. Science 2005

Maione et al.: Identification of a universal Group B streptococcus vaccine by multiple genome screen Science 2005

Telford et al. Pili in gram-positive pathogens. Nat Rev Microbiol 2006

GBS Vaccine Progress Has Spanned Over a Decade and Involved Brilliant Work: But Challenges Remain

- **How to demonstrate efficacy**
  - **Will require either an 'impossible' field trial (vaccination prior to or during pregnancy and follow-up of infants), *or***
  - **Acceptance of an antibody surrogate based on epidemiological and / or animal data**
- **Vaccination during pregnancy; flu vaccines as a model**
  - **CDC recommends flu vaccination for pregnant women, but**
  - **Safety not established; obstetricians in a bind**

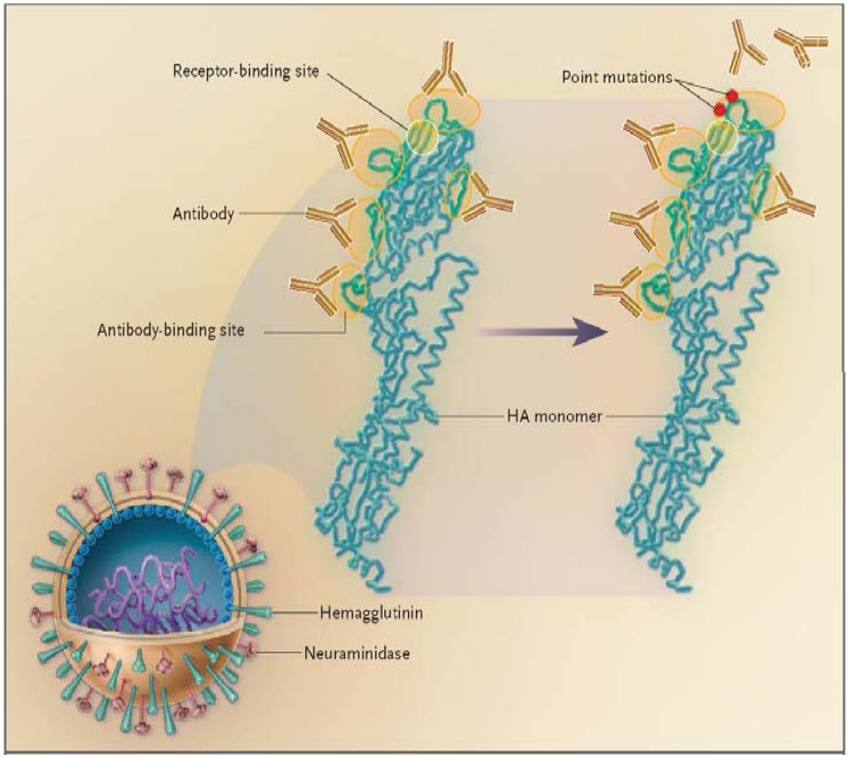
Preparing For Flu Season:
The Race with Influenza Virus

The virus always has the inside track.

Flu Vaccines Can't Be Stockpiled: Every Year A New Vaccine

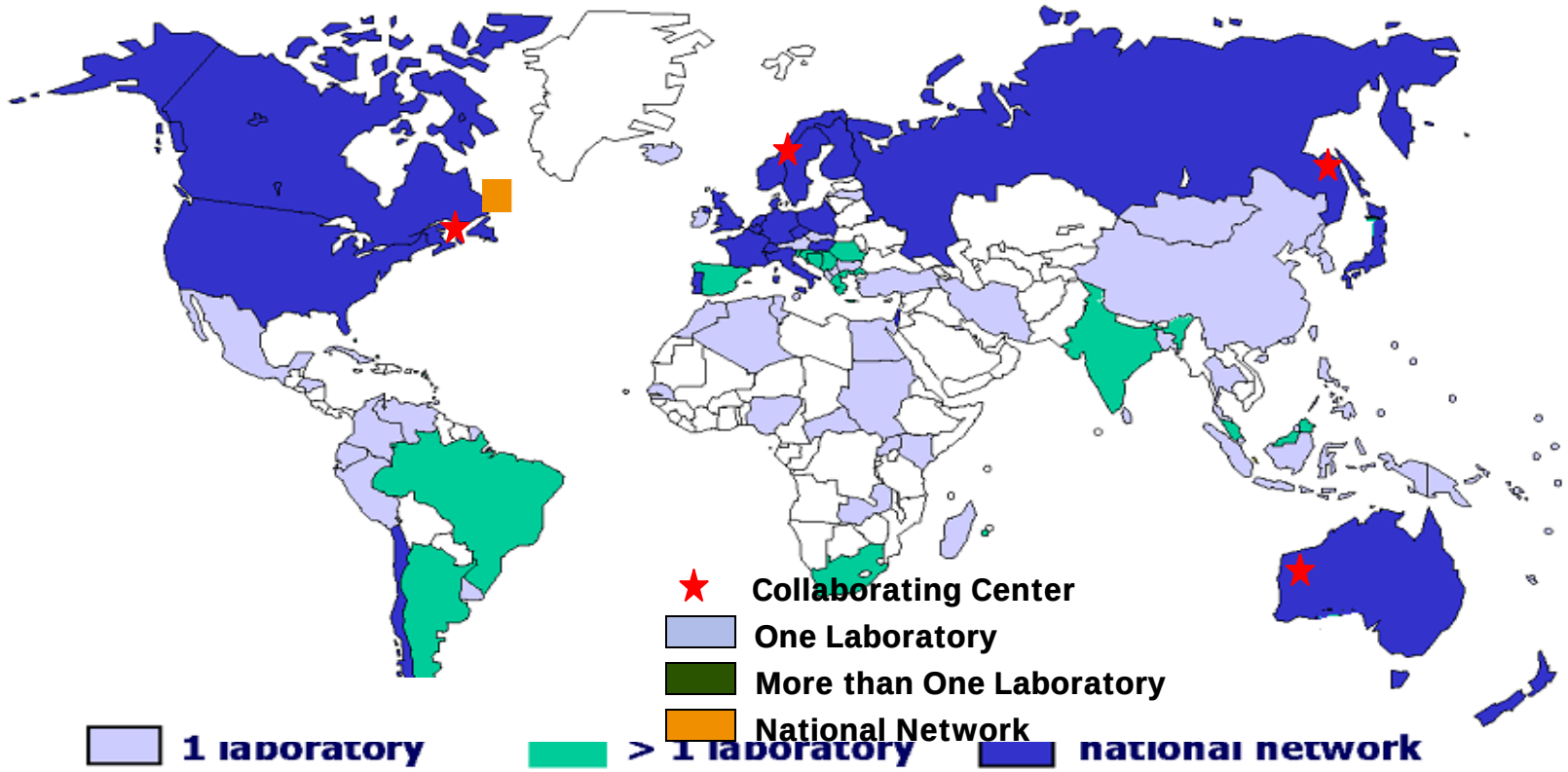
Influenza: Antigenic Drift and Shift Explains Why You Need a Shot Every Year & Why Pandemics Occur

- **Antigenic drift**
  - Relatively minor mutations
  - Anti-hemagglutinin antibody responsible for protection against infection
  - Segmented genes prone to recombination
  - Mutations occur in antibody binding sites
  - **Reason for annual vaccination**
- **Antigenic Shift**
  - "New" viruses arising from drastic changes in hemagglutinin with or without changes in neuraminidase
  - Occurs when 2 different viruses co-infect a single host and re-assortment of the genome segments occurs
  - **Can lead to pandemic**
- **Q5yr vaccine: Need an antigen that doesn't change**



The Front Line Against Influenza: WHO Influenza Surveillance Network

- National Influenza Centers: 112 institutions from 83 countries
- Four WHO Collaborating Reference Centers: Atlanta, London, Melbourne, Tokyo
- Determine which influenza viruses are circulating; where and when
- Assess unusual events: unusual viruses with pandemic potential
- 175,000 patient samples and 2000 virus samples submitted annually
- Most virus samples sequenced to assess drift / shift

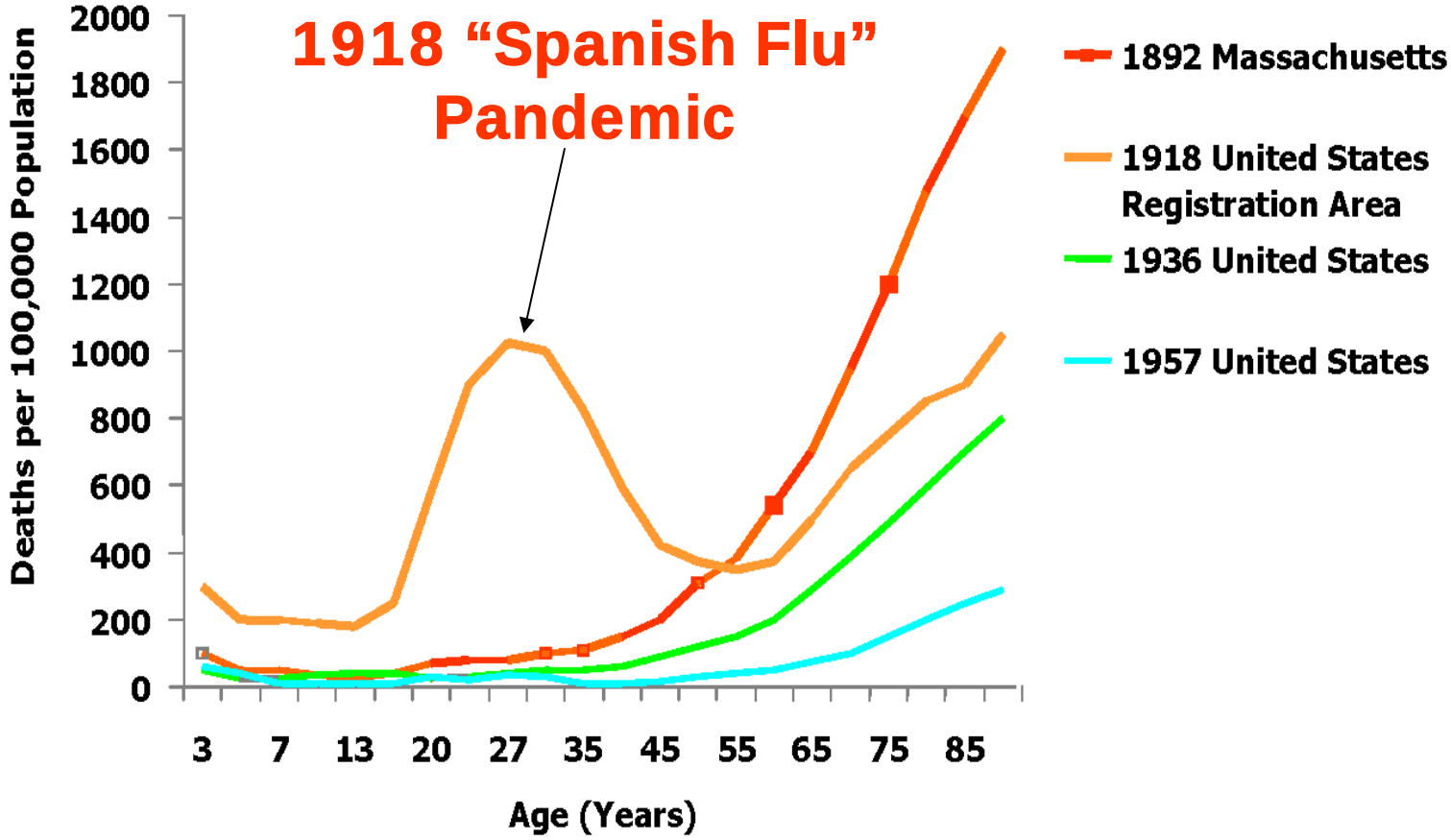


Influenza Pandemics Of The 20th Century Prior to the 2009 H1N1 Pandemic

1918: “Spanish Flu”	**1957: “Asian Flu”**	**1968: “Hong Kong Flu”**
20-40 million deaths	1-4 million deaths	1-4million deaths
A(H1N1)	A(H2N2)	A(H3N2)

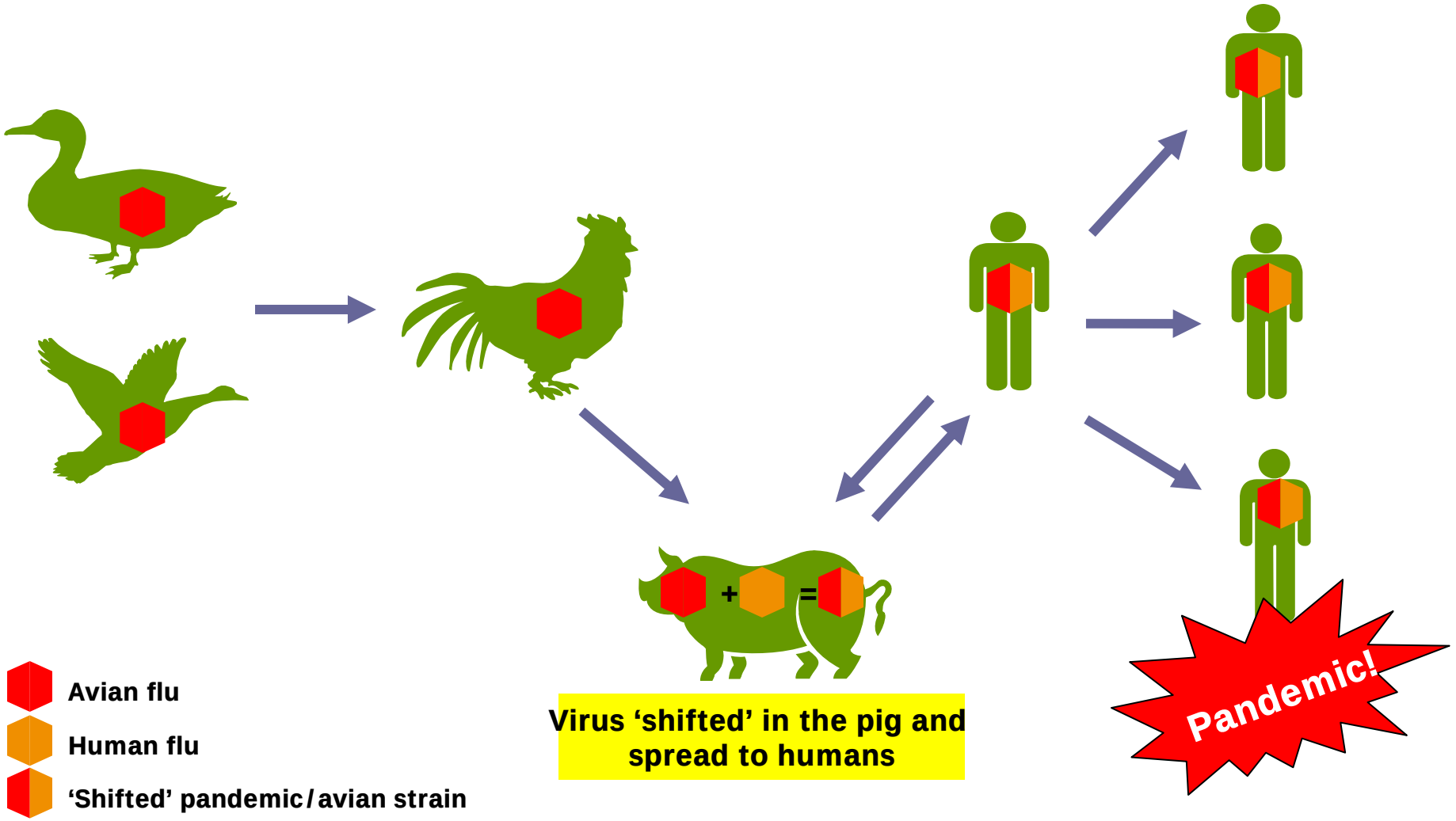
Credit: US National Museum of Health and Medicine

Mortality Rates in Different Influenza Epidemics



Am J Med 1987, 82:20-25

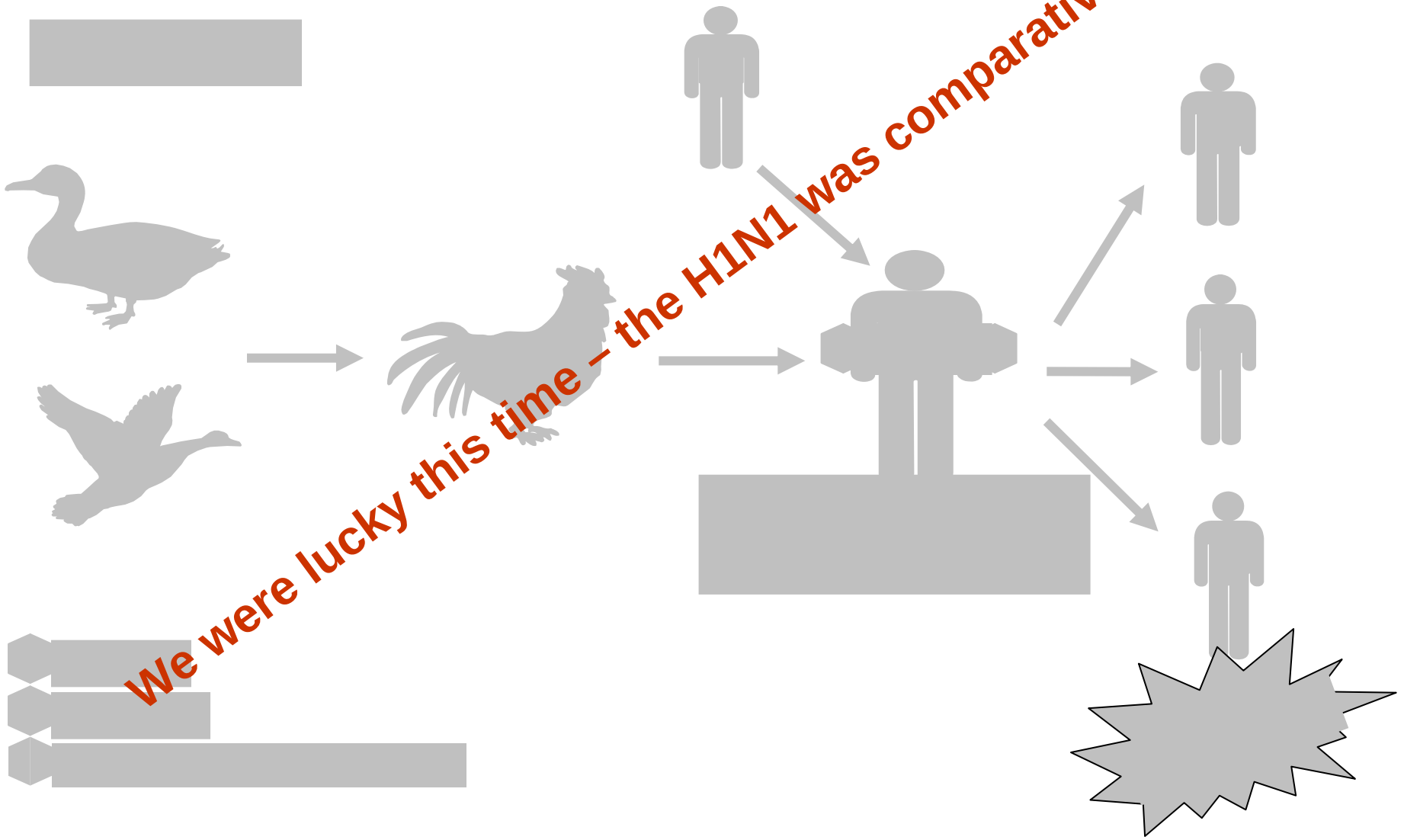
Traditional Scenario:
Genetic re-assortment of Avian Virus in Pigs



Vaccine Strain Selection (US)

- **January:**
  - WHO makes recommendations for the Northern Hemisphere vaccine.
- **February:**
  - FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) reviews worldwide surveillance data.
  - VRBPAC usually makes an initial recommendation about at least one of the three strains to be included in the vaccine (in coordination with WHO).
- **March:**
  - VRBPAC finalize the recommendations for the U.S. influenza vaccine.
  - CDC provides manufacturers with seed virus and necessary reagents.
- **2010-11 vaccine consists of:**
  - an A/California/7/2009 (H1N1)–like virus;
  - an A/Perth/16/2009 (H3N2)–like virus;
  - and a B/Brisbane/60/2008–like virus.
- **The H1N1 virus is the same pandemic 2009 H1N1 vaccine virus as was used in the 2009 H1N1 monovalent vaccine**

Emerging Scenario:



Pandemic Threat Helped Trigger New Flu Production Process

- Traditional approach: grow virus in fertilized chicken eggs
  - Pros: been used for 50 years and safe
  - Cons: Need ~300M eggs, long lead time, prone to contamination (Flu plant contamination killed Chiron), if a pandemic kills the chickens, you get no eggs!

- Emerging approach: mammalian cell culture (MDCK cells)
  - Pros: more readily scalable, shorter lead time, better pandemic preparedness, potentially better adapted to humans
  - Cons: big investment for a commodity vaccine

- First flu cell culture vaccine (Optaflu)
  - Approved in EU:
  - In development in US: