Vaccination in the prevention of lower respiratory tract infection

April 29th 2010
Influenza Vaccination

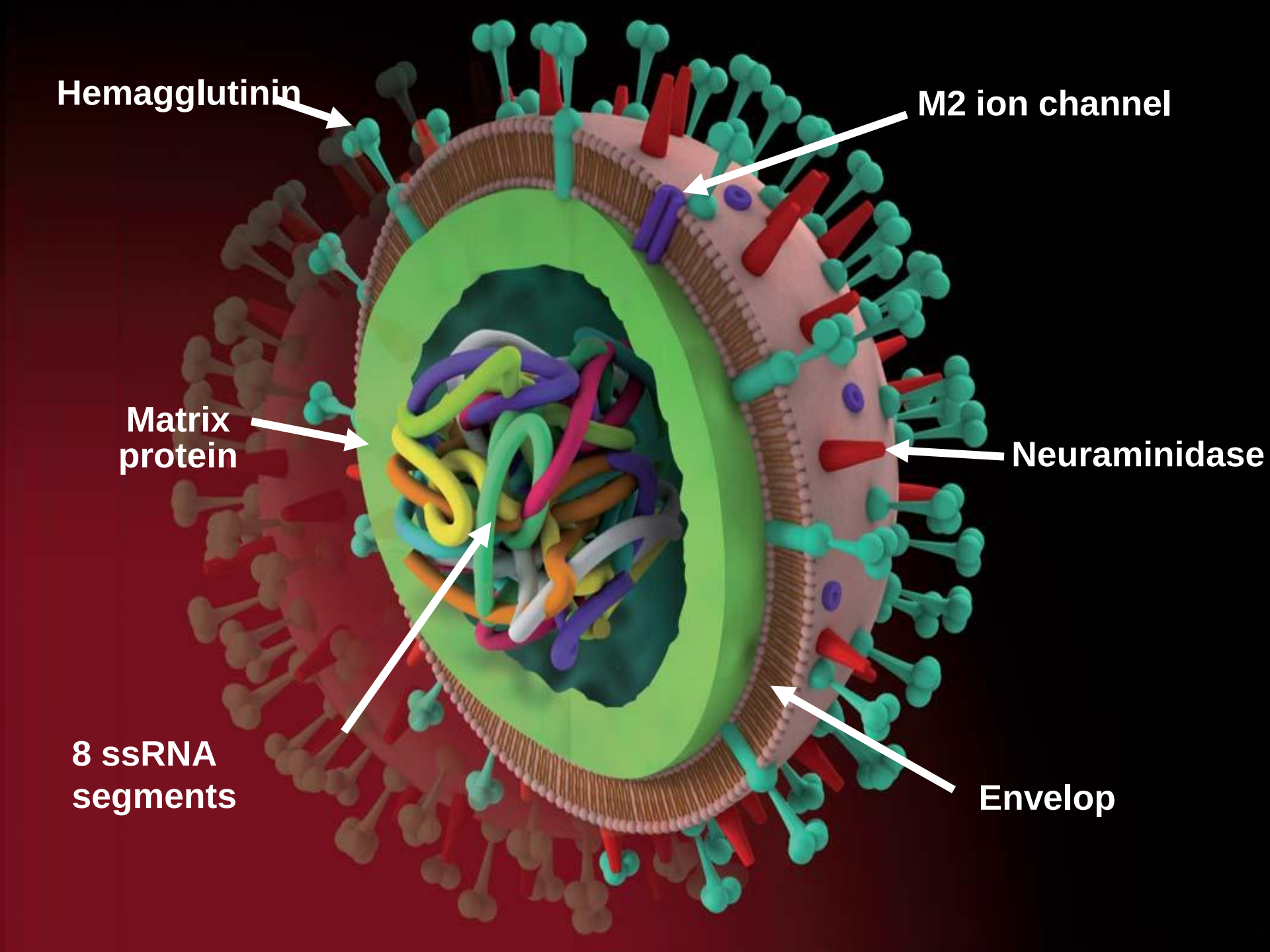
Pierre Van Damme, MD, PhD
Centre for the Evaluation of Vaccination (CEV)
Vaccine & Infectious Disease Institute

Vaccine & Infectious Disease Institute

Universiteit Antwerpen

Influenza vaccines

- Development dates back to 1940s
- Influenza virus discovered in 1933
- ‘influenza’
- First inactivated whole cell vaccines
- split & subunit vaccines were developed:
  - Higher purity and better tolerability
  - Consist of surface antigens (HA and N) with only few residual amounts of internal virus proteins
- All licensed seasonal influenza vaccines contain each of the three circulating human influenza viruses (15 mcgr/strain): 2 A-like and 1 B-like


Hemagglutinin
M2 ion channel
Matrix protein
Neuraminidase
8 ssRNA segments
Envelop

Airborne transmission through large droplets

Airborne transmission through aerosolisation

Direct contact: Passing infectious secretions to another person

Over the Week End
DON'T TELEPHONE
Unless It Is Absolutely Necessary

During the present week our operating force has been seriously depleted by Spanish Influenza.

The shortage of operators continues to increase.

Only a radical decrease in the number of calls will save the situation.

Will you help us meet the emergency over the week end by refraining from using the telephone except for indispensable calls?

Cards asking for the voluntary restriction of calls have been mailed to all subscribers. A supply may be secured on application at any of our Commercial Offices. Will you please place one near your telephone as a reminder for *yourself, your family* or *your employees,* that no telephone calls are to be made unless they are absolutely necessary?

NEW YORK TELEPHONE COMPANY

Influenza vaccines

- Annual re-vaccination is needed
  - To update specificity of the human immune system with regard to the antigenically drifted seasonal influenza viruses
  - Effective re-vaccination requires sufficient high residual immunity!
    - Weaker response in naïve children (unprimed)
    - Consideration of two doses of pandemic influenza vaccine in unprimed individuals!

Influenza vaccines: safety in children

- Good local and systemic tolerance
- RCT in 1-15y olds: mild fever in 4.6-11.5%
- VAERS – US, 1990-2003: passive reporting system
  - Fever, urticaria, seizures, local reactions
- Administration of multiple doses is safe and well tolerated
- Guillain-Barré Syndrome (GBS): no association in the years other than 1976

Ref: Neuzil, PIDJ 2001; Hoberman A, JAMA 2003;McMahon Pediatrics 2005; Hambidge, JAMA 2005; Goodman, Pediatrics 2006.

Elevated risk of Guillain-Barré Syndrome after vaccination in 1976

October 1st, 1976:	first swine flu shots are given
December 2nd, 1976:	CDC begins investigation of cases of Guillain-Barré
December 14th, 1976:	CDC issues press release on Guillain-Barré (54 cases; 30 received influenza vaccination anywhere from 1 to 30 days before onset of symptoms).
December 16th, 1976:	Because of an increase in the number of reports of Guillian-Barre syndrome (GBS) following A/New Jersey influenza vaccination, the National Influenza Immunization Program was suspended and nationwide surveillance for GBS was begun.

The surveillance uncovered a total of 1098 patients with onset of GBS from October 1, 1976, to January 31, 1977. A total of 532 patients had recently received an A/New Jersey influenza vaccination prior to their onset of GBS. The period of increased risk was concentrated primarily within the 5-week period after vaccination, although it lasted for approximately 9 - 10 weeks.

Schonberger LB, et al. Am. J. Epidemiol. 1979; 110: 105-123.

How can the association between swine flu vaccination and GBS be explained?

- Chicken eggs are used in the production process of influenza vaccines
- *Campylobacter* is an endemic infection among chickens
- *Campylobacter* is a known cause of Guillain-Barré syndrome
- Experts speculate that a *Campylobacter* contamination had occurred in some lots of the 1976 vaccine

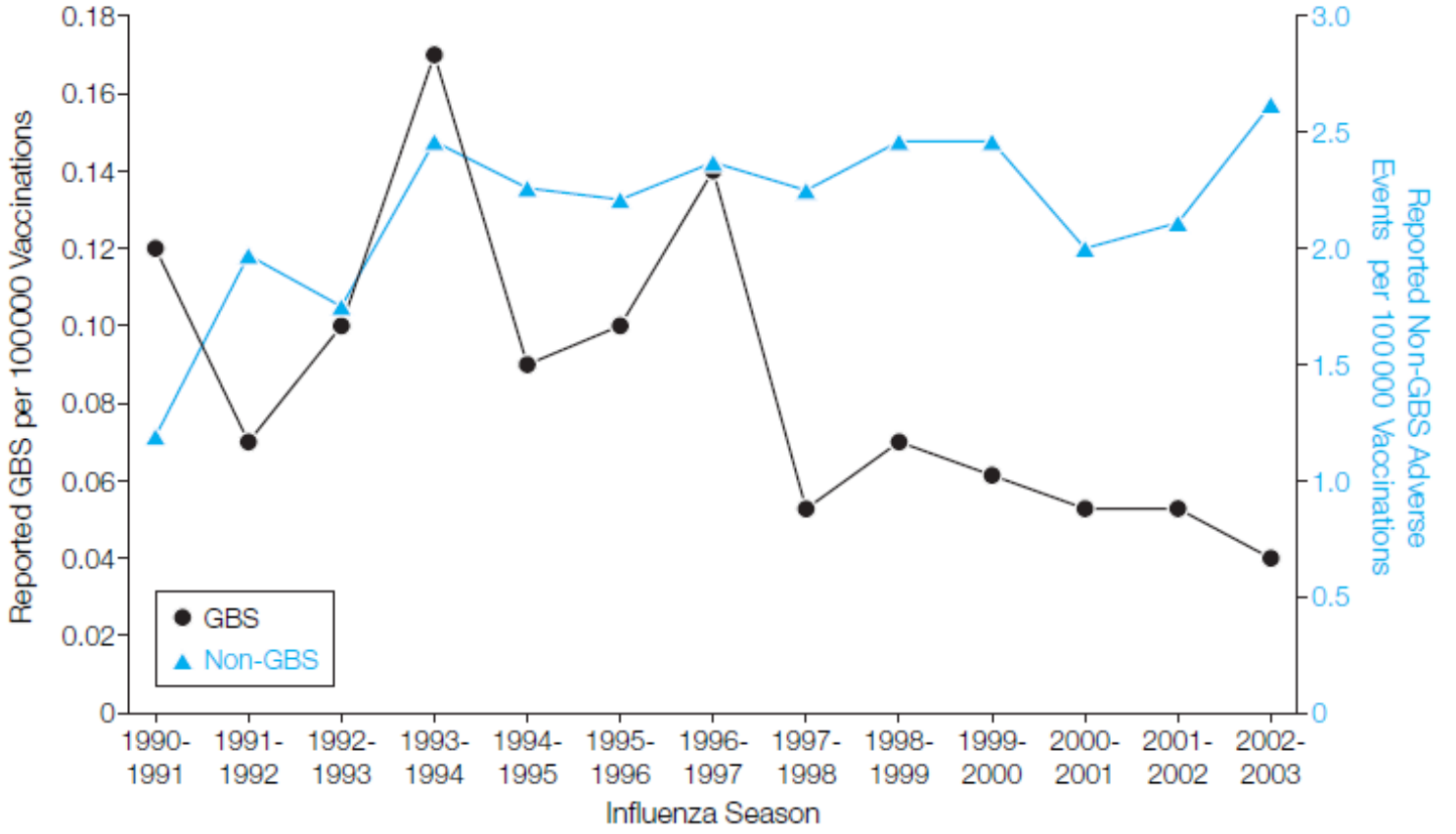
Haber P, et al. Guillain-Barré Syndrome following influenza vaccination. JAMA 2004; 292: 2478-2481.

Why today an association between influenza vaccination and GBS is unlikely?

- More demanding GMP standards for influenza vaccine production are used today versus 1976.
- Due to enhanced food safety interventions *Campylobacter* infections in humans decreased 28% in the US from 1996 to 2003.
- The vast majority (>99%) of patients with GBS have not recently received a vaccination.
- The benefits of influenza vaccination generally outnumber the supposed risk of developing GBS

Haber P, et al. Guillain-Barré Syndrome following influenza vaccination. JAMA 2004; 292: 2478-2481.

Rates of GBS and non-GBS reports following influenza vaccination, VAERS 1990-2003



GBS indicates Guillain-Barré syndrome; VAERS, Vaccine Adverse Events Reporting System.

Haber P, et al. Guillain-Barré syndrome following influenza vaccination. JAMA 2004; 292: 2478-2481.

general comment on safety in children

- Influenza vaccines are safe and well-tolerated in healthy children over 6 months of age
- Post-licensure surveillance of rare serious adverse events after introduction of influenza vaccinations are encouraged
- Children with mild to moderate egg allergy could safely receive influenza vaccines

(James J et al. J of Pediatrics, 1998)

Efficacy of influenza vaccines – general comments

- Strain-specific antibodies against HA are the primary immune mediator against protection
- Antibodies against NA may reduce severity, through enhancing virus clearance
- HI titre of 1/32 or 1/40 often regarded as ‘protective’, but no strict ‘correlate of protection’

EMEA / CHMP criteria for evaluating the immunogenicity of influenza vaccine with HI test

Criterion	18–60 years	>60 years
Seroconversion rate or significant increase - Proportion of individuals who seroconvert *(D0 titer <10 & D21 titer ≥40)* - Proportion of individuals with at least 4 fold increase in antibody titer at day 21 post-vaccination (*D0 titer ≥10 & ≥4-fold increase on D21)*	40%	30%
Mean geometric increase or GMTR Geometric Mean Titres Ratio *(GMT_{D21}/GMT_{D0})*	>2.5	>2.0
Seroprotection rate Proportion of individuals achieving an antibody titer of ≥40 at day 21 post-vaccination *(with titer ≥40 on D21)*	>70%	>60%

At least one criteria for each strain should be met

1 European Agency for the Evaluation of Medicinal Products. *Note for guidance on harmonization of requirements for influenza vaccines*. March 1997; CPMP/BWP/214/96. p17-18

Efficacy of influenza vaccines – general comments

- a titre of 1/32 or 1/40, represents the level at which approximately 50% of individuals will be protected (depending from age, …)
- In naive subjects, antibody will peak by 4 weeks; in primed subjects it will peak by 2-4 weeks.

Efficacy of influenza vaccines – general comments

- Depends from many factors:
  - Matching with circulating strain
  - Outcome measures:
    - Confirmed influenza cases (86%)
    - ILI (34%) (Bridges et al. JAMA 2000)
    - Pneumonia
- When less specific outcomes are used, co-circulation of other infectious diseases causing similar symptoms will reduce the calculated effectiveness.

Efficacy of trivalent inactivated vaccine (TIV) in healthy children

- Data in children 6m-18 years
- Focus on 6-23m olds, 2-4 y olds, 5 y & older
- Outcome criteria for efficacy:
  - Lab confirmed case (culture +, sero+)
  - Influenza-like illness (ILI) – ‘effectiveness’
- Large heterogeneity of studies:
  - Site, timing to epidemic, kind of epidemic, study design, sample size, type of vaccine, …

Efficacy of trivalent inactivated vaccine (TIV) in healthy children

- Lab proven influenza: 31-91.4% efficacy (ECDC report)
- Meta-analysis:
  - Demichelli, 2006 (Cochrane): 59% eff (> 6y 64%)
  - Jefferson, 2005 (Lancet): 14 RCT: 65% eff.
  - Few studies under the age of 2 years!
- For children 1-18 years of age efficacy has been demonstrated: 59% (95% CI:31-71%).
- Increasing evidence of indirect effect to society!

Efficacy of trivalent inactivated vaccine (TIV) in healthy adults

- Cochrane systematic review, 2007
- Lab confirmed influenza:
  - 80% efficacy (95% CI: 57-91%): good match
  - 30% efficacy (95% CI: 27-41%): bad match
  - Reduction in medical visits by 42%, illness days by 0.5
- ILI:
  - 30% efficacy (95% CI: 27-41%)

Efficacy of trivalent inactivated vaccine (TIV) in < 65y olds

- Individual studies:
- 5y placebo-controlled study (Edwards, JID ‘94):
  - 70-79% reduction of confirmed cases
- 5y placebo-controlled study (Keitel, Vaccine, ‘97)
  - 47-73% reduction of confirmed cases
- 3y study in HCW (Wilde, JAMA ‘99)
  - 88-89% reduction in confirmed cases
  - 29% reduction in febrile resp. illness
  - 53% reduction in work absenteism

Efficacy of trivalent inactivated vaccine (TIV) in > 65y olds

- Individual studies:
- VE: 58% for lab confirmed influenza (Govaert, ’94)
- VE: 56% resp.illness, hosp. 48%, deaths 68% (Gross, ‘95)
- VE: 52% hosp., 70% death (Nicholl, ‘99) – good match
- VE: 19-24% hosp.; deaths: 35-61% (Nordin, ‘01) – poor match

Efficacy of trivalent inactivated vaccine (TIV) in elderly

- Cochrane systematic review, 2010
- 4 studies, N=6894:
  - ILI: 41% (95% CI: 27-53%)
- 3 studies, N=2217:
  - Lab confirmed influenza: 58% effica. (95% CI 34-73%)

Influenza vaccination: collective protection

- Potter J et al. JID, 1997, 175: 1-6
  - 12 geriatric instutions
  - vaccination of personnel and/or residents
  - Vaccination of personnel = effect on residents:
    - reduced mortality
    - reduced ILI and confirmed influenza cases
  - vaccination residents:
    - No significant reduction in mortality
    - Reductionin influenza cases

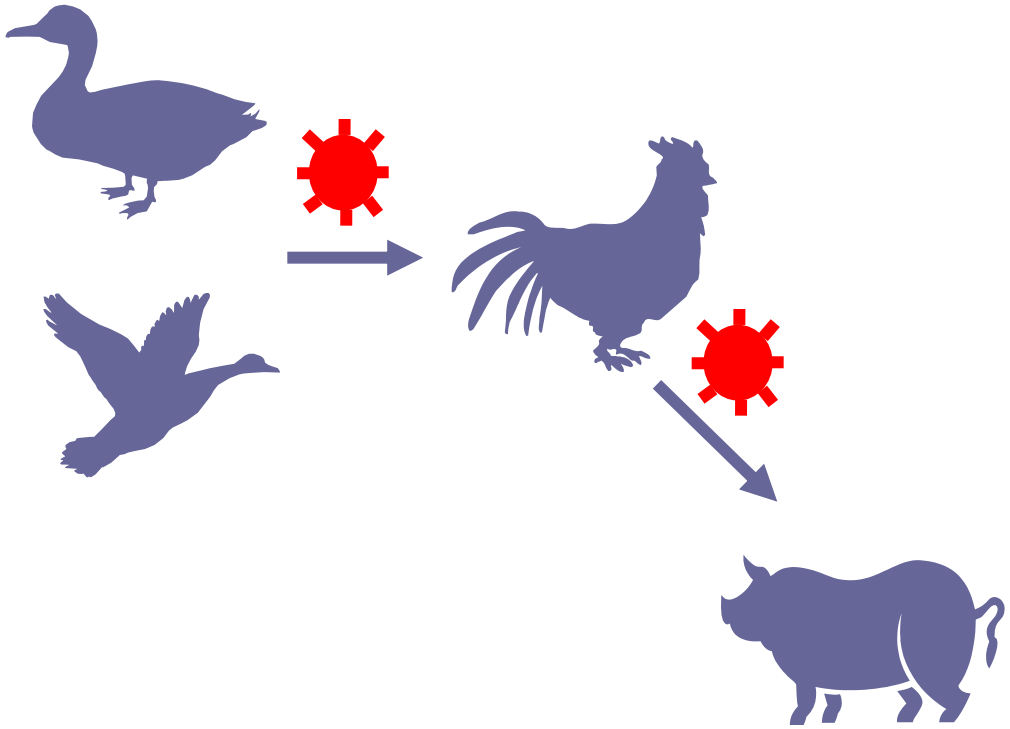
Influenza vaccination

Group	PersVacc/ ResVacc	Pers Vacc/ Res0	Pers0/Res Vacc	Pers0/Res 0
N	230	260	308	261
Mortality	25 (11%)	25 (10%)	56 (18%)	42 (16%)
Mortality ass. Pneumonia	10 (4%)	15 (6%)	24 (8%)	23 (9%)
Viral illness	24 (10%)	58 (22%)	75 (24%)	59 (23%)
ILI	2 (1%)	20 (8%)	19 (6%)	23 (9%)

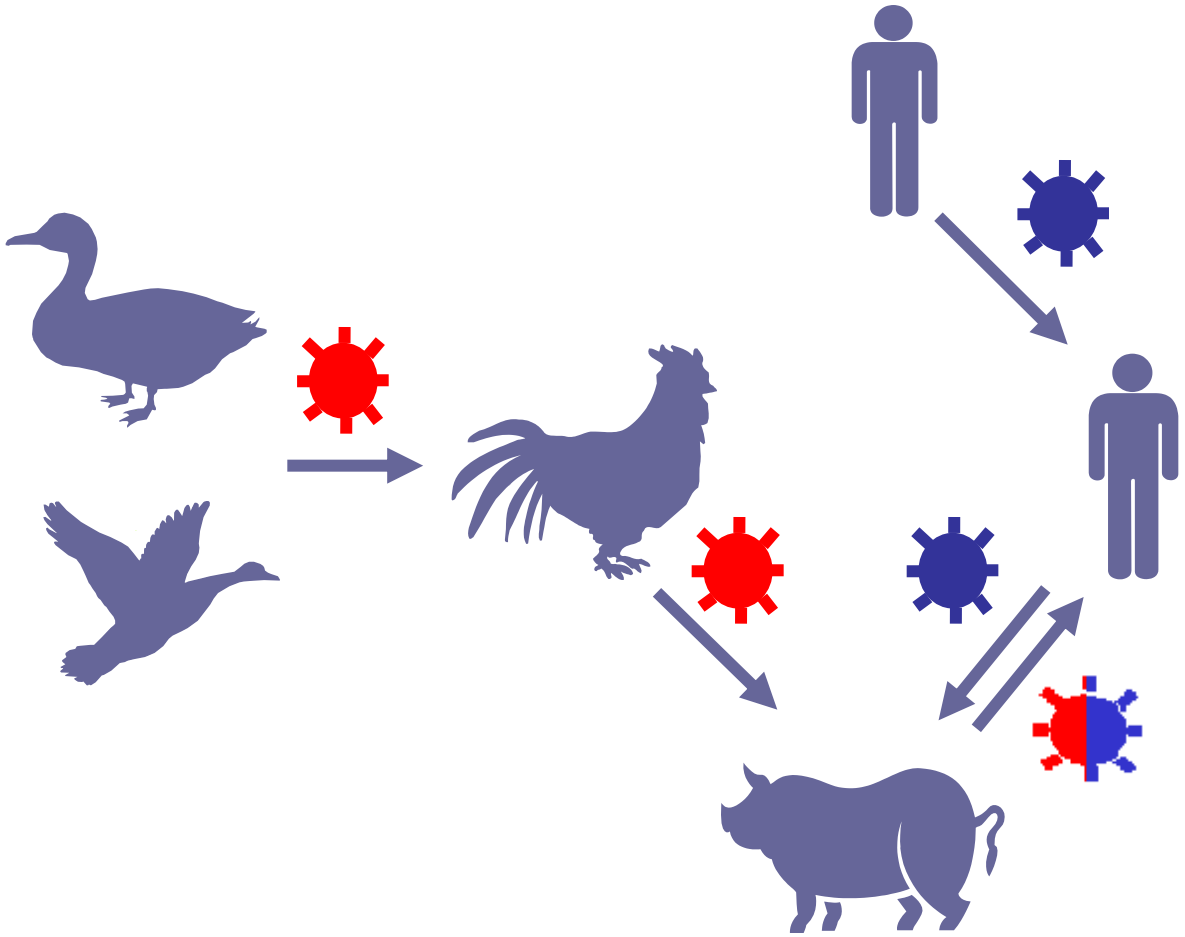
Evolution in influenza vaccines

- For better efficacy and immunogenicity:
  - Addition of adjuvants
  - Intradermal administration
  - Attenuated vaccines /mucosal vaccines
  - Quadrivalent vaccines

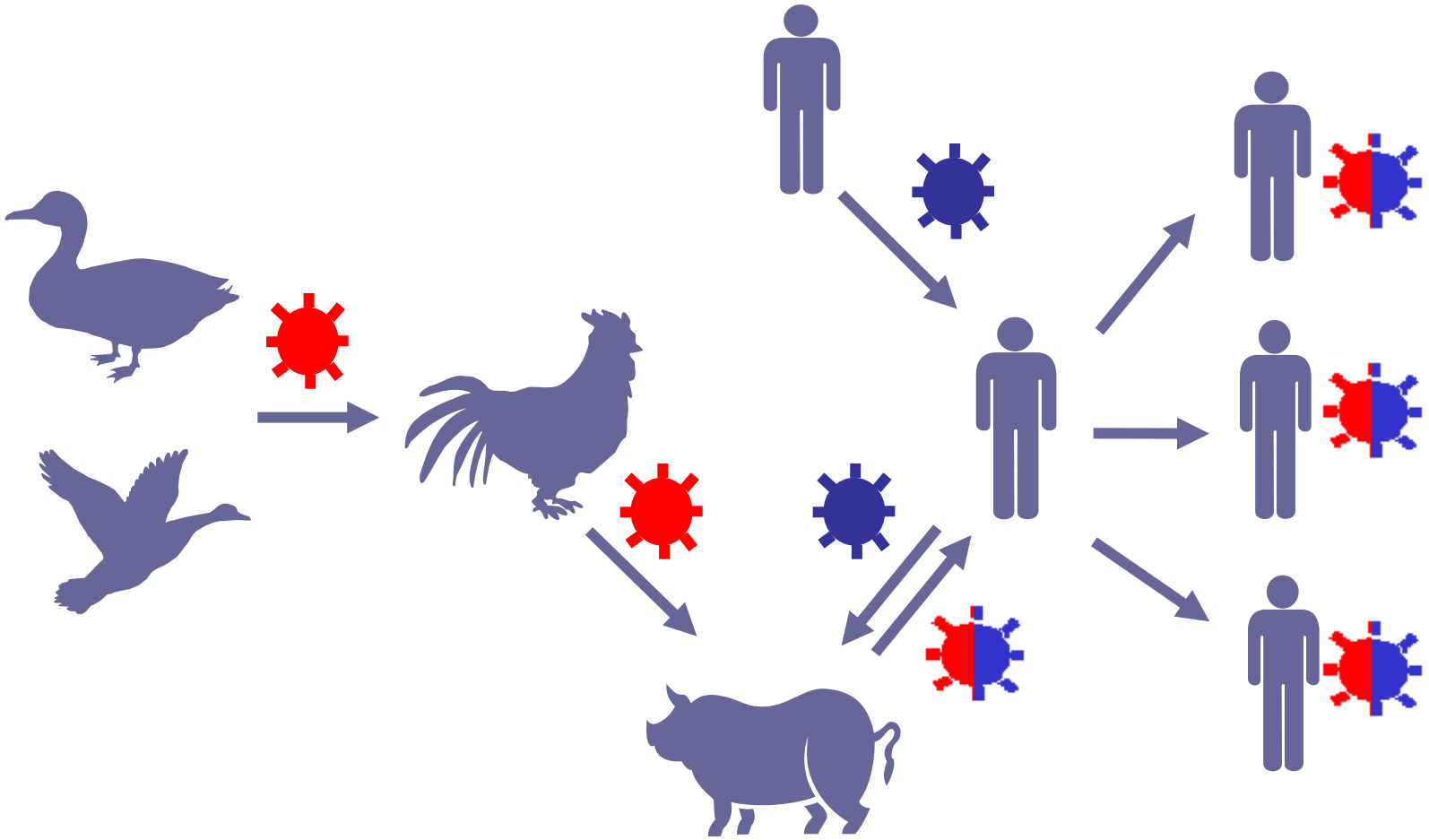
REASSORTMENT IN PIGS



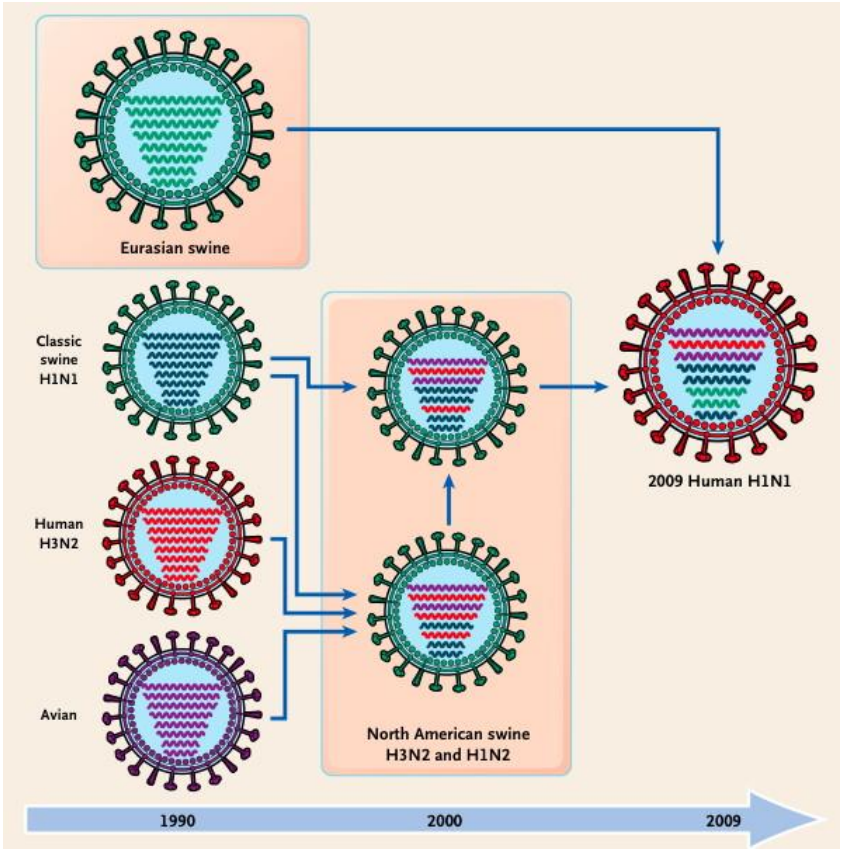
REASSORTMENT IN PIGS

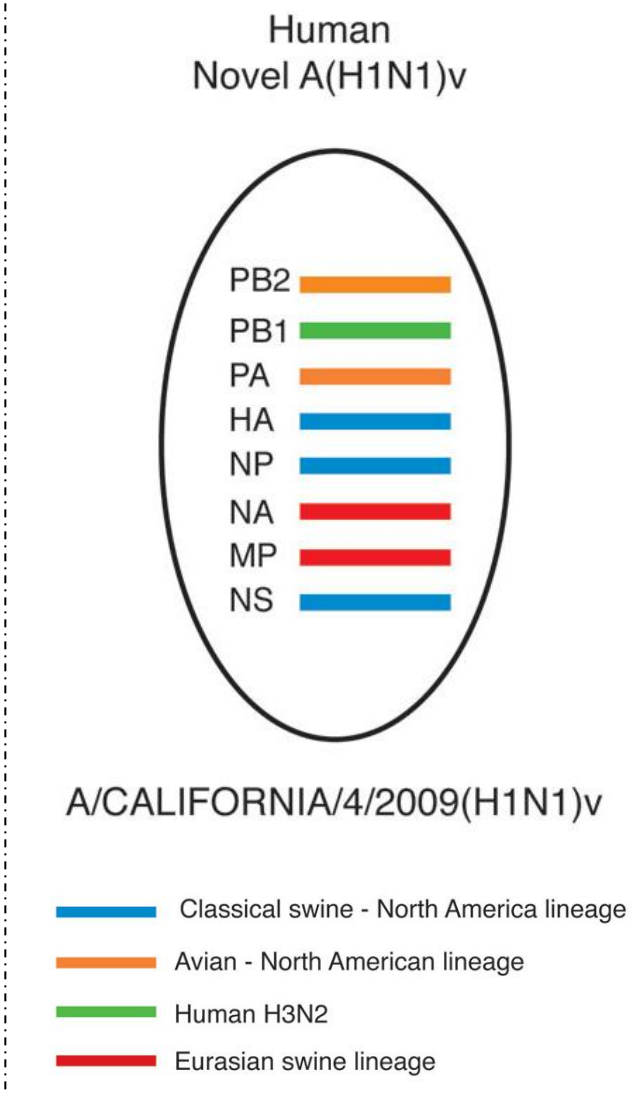


REASSORTMENT IN PIGS



Genotypes of the triple-reassortant strain in recent cases of people infected with the new influenza A (H1N1) virus





Novel Swine Origin Influenza A (H1N1) Virus Investigation Team. NEJM 2009; 360: 2605-2615.

Influenza: 2009-2010

- April 17, 2009:
  - CDC reported a new strain of swine flu virus infecting two children in California
- 18 cases of respiratory illness in Mexico, confirmed by the PH Agency of Canada, of which 12 being genetically identical to the Californian virus.
- ”Mexican flu”
- “Swine flu”
- “H1N1 flu”
- “A/H1N1v 2009”
- “A/California/4/2009(H1N1)v”

Pandemic influenza 2009: first data on disease burden

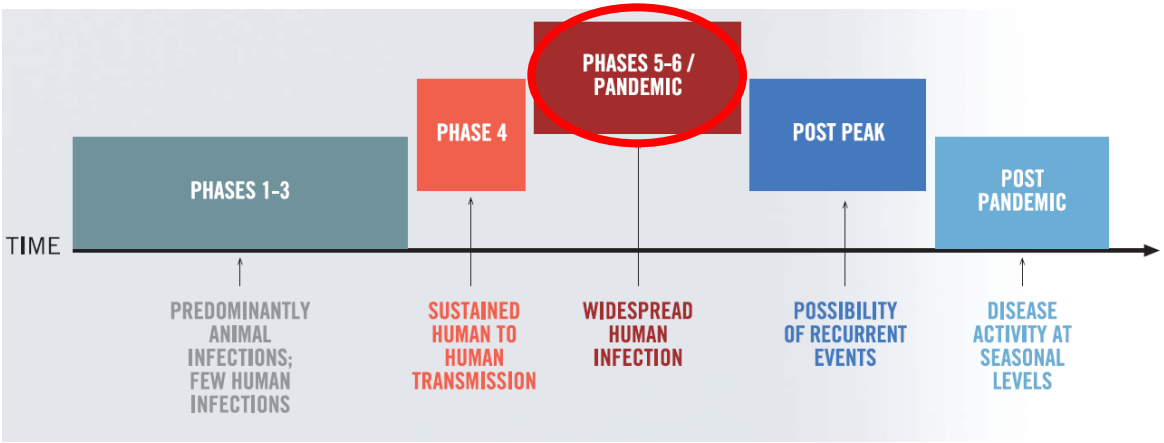
- Particular interest in children, young adults, pregnant women, people with underlying diseases
- Reasons:
    - Background immunity
    - Underlying disease
    - Virulence
    - Activity of the immune system
    - Immune suppression

Declaration of a phase 6 on June 11th, 2009

« The world is now at the start of the 2009 influenza pandemic. »

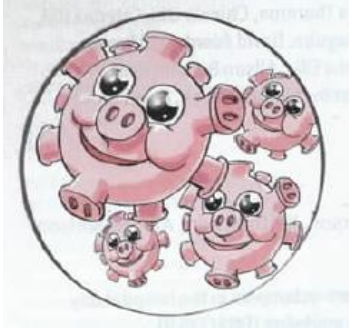
« I understand that production of vaccines for seasonal influenza will be completed soon, and that full capacity will be available to ensure the largest possible supply of pandemic vaccine in the months to come. »

Phase 4
28 April 2009



Phase 5
30 April 2009

http://www.who.int/csr/disease/avian_influenza/phase/en/



Current situation

- Concerns about the global response is rising! (see discussion on the ash cloud)
- Health committee of the Council of Europe and WHO have announced separate inquiries!
- Influence of the pharmaceutical industry on WHO has been critised!

Current situation - 2

- First pandemic for 40 years has not behaved as expected
- We cannot relax yet, as the virus can mutate
- If it does not mutate, can the level of illness caused up to now justify the label ‘pandemic’?

- It is easy to be wise after the event….

Current situation - 3

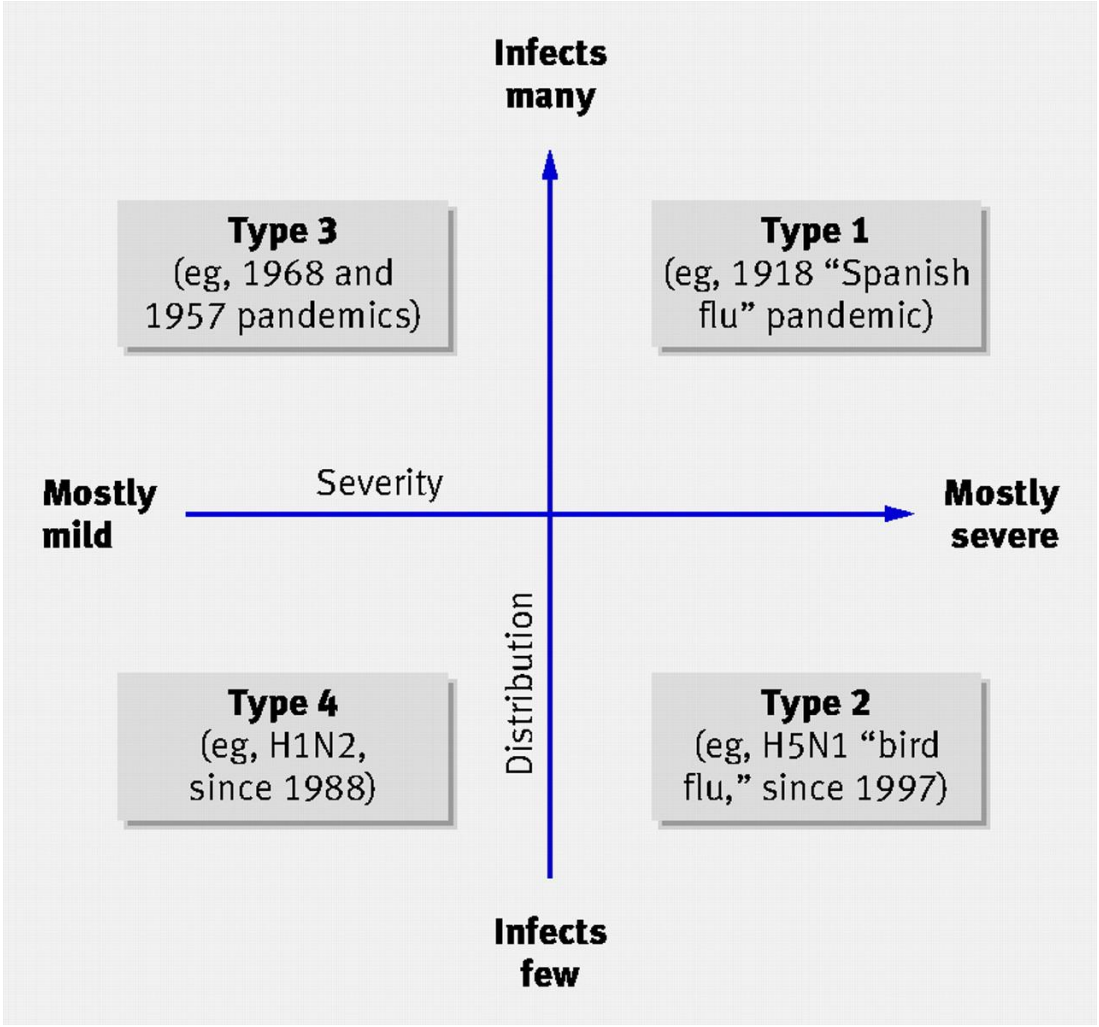
- History learns that:
- “The influenza virus is capricious, the disease elusive and our remedies imperfect”, J. Laurence, Lancet, Jan 30, 2010

- “We did what we did on pretty good grounds, it happened that it was the wrong virus, so far”, D. Salisbury, March 2010

H1N1 “lessons learnt” Workshop, Bussels, March 22, 2010

- Remaining issues:
- Way in: Many industrialized countries had sleeping contracts with manufacturers since < 2007, which were triggered once phase 6 was declared.
- Way out: when de-declaring phase 6, vaccines become un-licensed in some areas of the world!
- Link of the WHO phasing declaration and the licensing contracts is an issue.
- As H1N1 vaccine is licensed as a seasonal flu vaccine in the US, it becomes un-licensed by July 1, 2010.

Fig 2 Proposed classification of impact of new infectious diseases



Doshi, P. BMJ 2009;339:b3471

BMJ

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Recommendations of the Strategic Advisory Group of Experts (7 July 2009)

- The experts identified three different objectives that countries could adopt as part of their pandemic vaccination strategy:
  - protect the integrity of the health-care system and the country's critical infrastructure;
  - reduce morbidity and mortality; and
  - reduce transmission of the pandemic virus within communities.

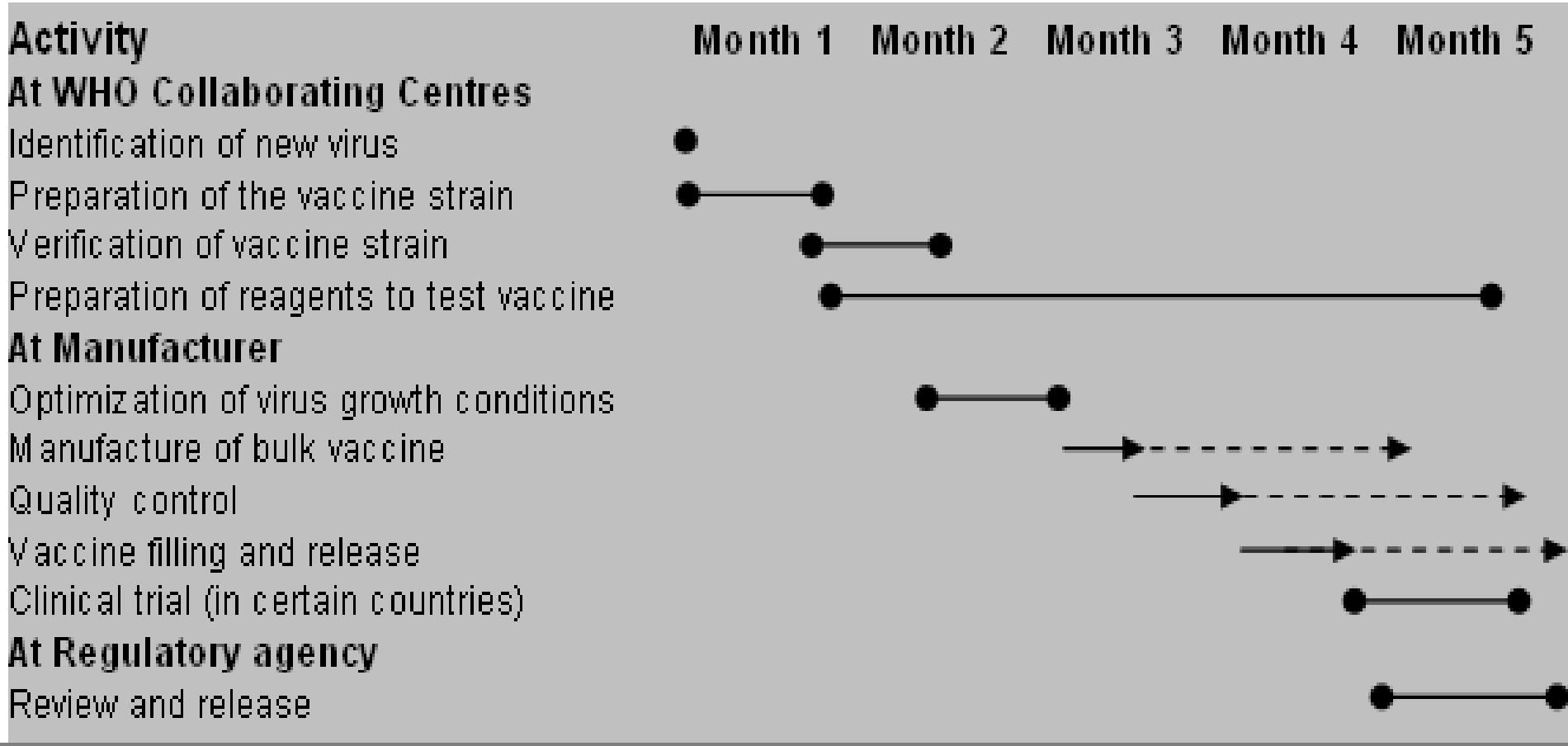
WHO. Available at:http://www.who.int/csr/disease/swineflu/notes/h1n1_vaccine_20090713/en/index.html

Recommendations of the Strategic Advisory Group of Experts (7 July 2009)

The following recommendations were provided to the WHO Director-General:

- All countries should immunize their health-care workers as a first priority to protect the essential health infrastructure. As vaccines available initially will not be sufficient, a step-wise approach to vaccinate particular groups may be considered.
- SAGE suggested the following groups for consideration, noting that countries need to determine their order of priority based on country-specific conditions:
  - pregnant women;
  - those aged above 6 months with one of several chronic medical conditions;
  - healthy young adults of 15 to 49 years of age;
  - healthy children;
  - healthy adults of 50 to 64 years of age;
  - healthy adults of 65 years of age and above.

WHO. Available at:http://www.who.int/csr/disease/swineflu/notes/h1n1_vaccine_20090713/en/index.html



seasonal flu vaccines takes 9-10 months
pandemic flu vaccines took 5-6 months
by the time decision is taken, ……!!!

Belgium, data sentinel practice

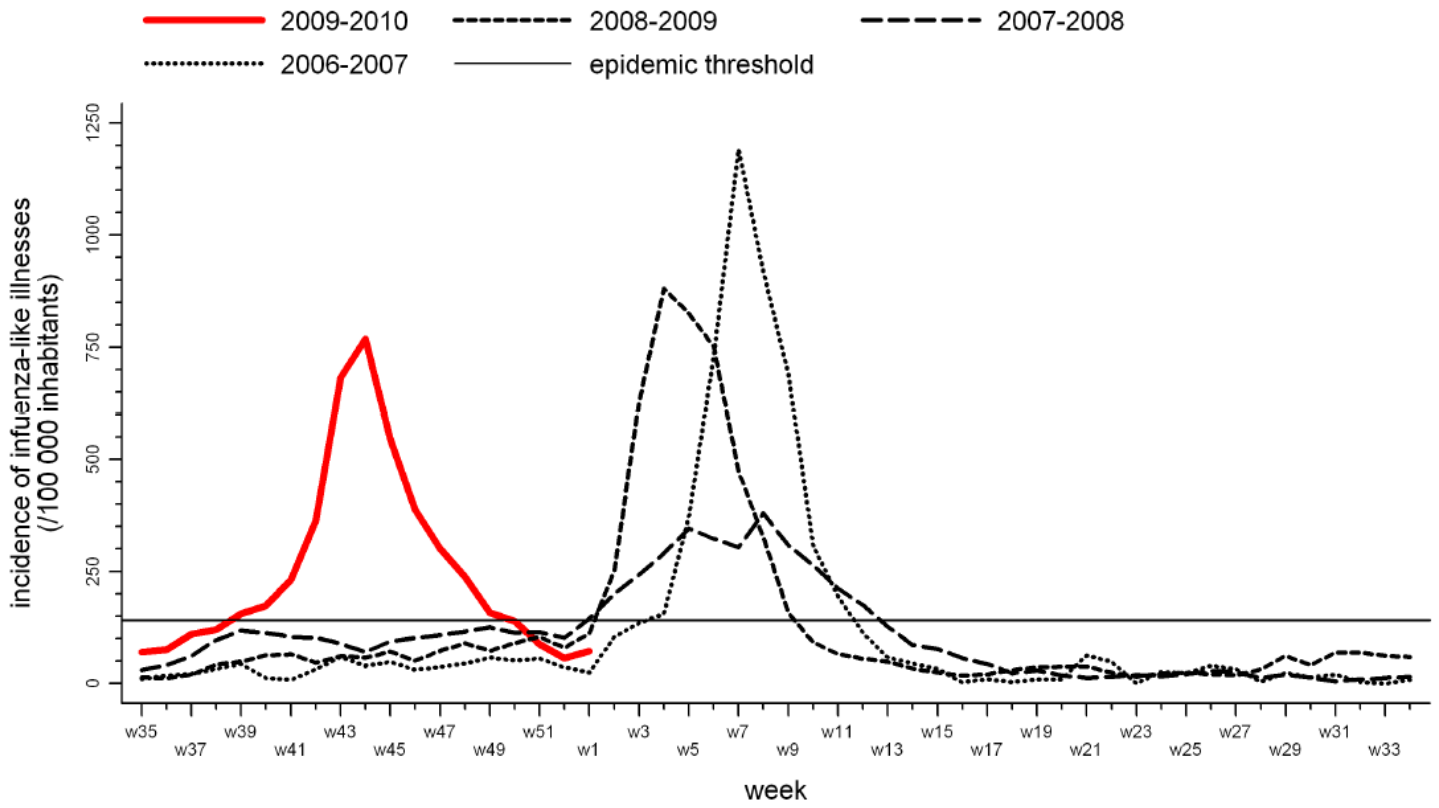


Figure 1: GP: Evolution of ILI incidence

©Scientific Institute Public Health, Brussels, 13 Jan 2010 14:22:03

TABLE 1

Overview of vaccines against pandemic influenza A(H1N1) available in the European Union in October 2009

Name, producer	Product description	Culture medium	Haemagglutinin-content	Adjuvant emulsion	Number of doses
Celvapan, Baxter	Inactivated, whole wild-type virus A/California/7/2009 (H1N1)v	Cell-culture	7.5 µg	None	All > 6 months 2 x 0.5 mL
Pandemrix, GSK	Inactivated, split-influenza, reassortant, A/California/7/2009 (H1N1)v-like strain	Egg-culture	3.75 µg (per adult dose)	AS03	>10 years 2 x 0.5 mL
			1.875 µg (per pediatric dose)		6 months – 9 years 2 x 0.25 mL
Focetria, Novartis	Inactivated, surface-influenza antigens (haemagglutinin and neuraminidase), reassortant, A/California/7/2009 (H1N1)v-like strain	Egg-culture	7.5 µg	MF59	All > 6 months 2 x 0.5 mL
Fluval P, Omninvest	Inactivated, whole reassortant virus A/California/7/2009 (H1N1)v-like strain	Egg-culture	6 µg (per adult dose) 3 µg (per pediatric dose)	aluminium phosphate	Adults and adolescents > 12 years 1 x 0.5 mL Children 3-12 years 1 x 0.25 mL Children 6 months - 3 years* 1 x 0.25 mL (*decision pending)

Johansen K et al. Eurosurveillance 2009; 14 (41): pii=19361

TABLE 2

Overview of thiomersal and immunostimulating compounds* included in vaccines against pandemic influenza A(H1N1) available in the European Union in October 2009

	Thiomersal	Adjuvant emulsion
Celvapan, Baxter	No	None
Pandemrix, GSK	5 µg (per adult dose) 2.5 µg (per pediatric dose)	**AS03** squalene* 10.69 mg α-tocopherol* 11.86 mg polysorbate 80 4.86 mg per adult dose; half the above amounts per pediatric dose
Focetria, Novartis	50 µg	**MF59** squalene* 9.75 mg polysorbate 80 1.175 mg sorbitan trioleate 1.175 mg
Fluval P, Omninvest	50 µg (per adult dose) 25 µg (per pediatric dose)	aluminum phosphate 0.33 mg Al^{3+} (per adult dose) 0.165 mg Al^{3+} (per pediatric dose)

Adjuvanted vaccines: oil-in-water emulsions

- Allow reduction of the Ag content in the pandemic vaccines (factor 2 to 8, versus seasonal flu vaccine)
- Expected to induce more cross-protection against similar H1N1 strains
- squalene: natural intermediate product of human cholesterol and a component of cell membrane
- Tocopherol: = Vit E

Antibody response to 7.5mcgr MF59-adjuvanted vaccine (NEJM, 2009; 361)

Day 0	**18-50 y**	**EMEA criteria**
GMT	6.2	
SP %	12	
Day 21		
GMT	172.5	
GMTR	27.9	> 2.5
SC %	76	➢40
SP %	80	>70

Antibody response to non-adjuvanted vaccine, 15 mcgr (Australia) (NEJM, 2009, 361)

Day 0	**18-49 y**	**50-64 y**
GMT	21.4	19.3
SP %	32.8	33.9
Day 21		
GMT	306.9	157
GMTR	14.3	8.1
SC %	75.9	66.1
SP %	100	93.5

Antibody response to non-adjuvanted vaccine, 15 mcgr (SP) (Lancet, 2009, Dec 16)

Day 0	**18-64 y**	**>65 y**
GMT		
SP %	26	25
Day 21		
GMT	1405	390
GMTR	64.3	21.3
SC %	96	89
SP %	98	93

Safety of H1N1-vaccines

- Foeto-toxicity, embryotoxicity tested at PEI, Germany
- Experience with MF59 in > 45 million vaccines administered, since more than 10 years
- Experience with AS03 in influenza vaccines, H5N1 vaccines, malaria vaccines, … (> 45.000 doses administered)

Safety of H1N1 vaccines

- Sudden, large programmes
- In different age groups of the population
- Awareness of the background rates of potential adverse events is crucial
- See: Black S et al. Importance of background rates of disease in assessment of vaccine safety during mass immunization with pandmic H1N1 influenza vaccines. Lancet online October 31, 2009.

Safety of H1N1 vaccines

- Black S et al. Importance of background rates of disease in assessment of vaccine safety during mass immunization with pandmic H1N1 influenza vaccines. Lancet online October 31, 2009.
- If a cohort of 10,000,000 individuals was vaccinated in the UK, within 6 weeks post-vaccination, as coincident background cases:
  - 21.5 cases of GBS would be expected
  - 5.75 cases of sudden death
- Similar calcualtions for the US scenario for female vaccinees:
  - 86.3 cases of optic neuritis/ 10,000,000 population within 6 weeks
  - 3970 spontaneous abortion/10,000,000 vaccinated pregnant women, within 1 day of vaccination

Safety of H1N1 vaccines

- Against such background safety reports need to be understood:
- www.fagg.be: Belgian and EU data
- www.sma.be: Swedish data on Pandemrix

Safety of H1N1 vaccines

- For Belgian data (by January 2010):
- On a total of 724,051 registered vaccinees (= denominator), but more than 2,000,000 doses distributed (= other denominator):
  - 166 reports of 651 adverse events after administration of Pandemrix
  - Local reactions are the most frequently reported AE
  - Reports are in line with the EU-data and with what could be expected

Safety of H1N1 vaccines

- For Swedisch data (By December 2009):
  - 4 million individuals vaccinated and regsitered. 3000 AE reported
  - Mostly local symptoms, ILI-symptoms (all resolved within quickly, some lasting up to 5-7 days)
  - Allergic reactions – 3 anaphylactic shoks (in individuals with known egg allergy)
  - Reactions in children: (102,000 children < 3y – 450,000 children 3y-13y vaccinated)
    - Convulsions, dizziness, facial palsy, ….
  - Pregnant women (> 31,000 vaccinated):
    - 6 spontaneous abortion and 1 intra-uterine death

Interpretation: consistent with what was expected, and not higher than the background rate of these syndrome/diseases


YOU LITTLE BASTARD.
YOU'VE KILLED US ALL.