Confidence & Lessons Learned from the 2009 H1N1 Vaccination Program

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The New York Times

U.S. Declares Public Health Emergency Over Swine Flu

By DONALD G. McNEIL Jr.
Published: April 26, 2009

Responding to what some health officials feared could be the leading edge of a global pandemic emerging from Mexico, American health officials declared a public health emergency on Sunday as 20 cases of swine flu were confirmed in this country, including eight in New York City.

World now at the start of 2009 influenza pandemic

Dr Margaret Chan
Director-General of the World Health Organization

Statement to the press by WHO Director-General Dr Margaret Chan
11 June 2009

Ladies and gentlemen,

In late April, WHO announced the emergence of a novel influenza A virus.

This particular H1N1 strain has not circulated previously in humans. The virus is entirely new.

The virus is contagious, spreading easily from one person to another, and from one country to another. As of today, nearly 30,000 confirmed cases have been reported in 74 countries.

This is only part of the picture. With few exceptions, countries with large numbers of cases are those with good surveillance and testing procedures in place.

Spread in several countries can no longer be traced to clearly-defined chains of human-to-human transmission. Further spread is considered inevitable.

I have conferred with leading influenza experts, virologists, and public health officials. In line with procedures set out in the International Health Regulations, I have sought guidance and advice from an Emergency Committee established for this purpose.

On the basis of available evidence, and these expert assessments of the evidence, the scientific criteria for an influenza pandemic have been met.

I have therefore decided to raise the level of influenza pandemic alert from phase 5 to phase 6.

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

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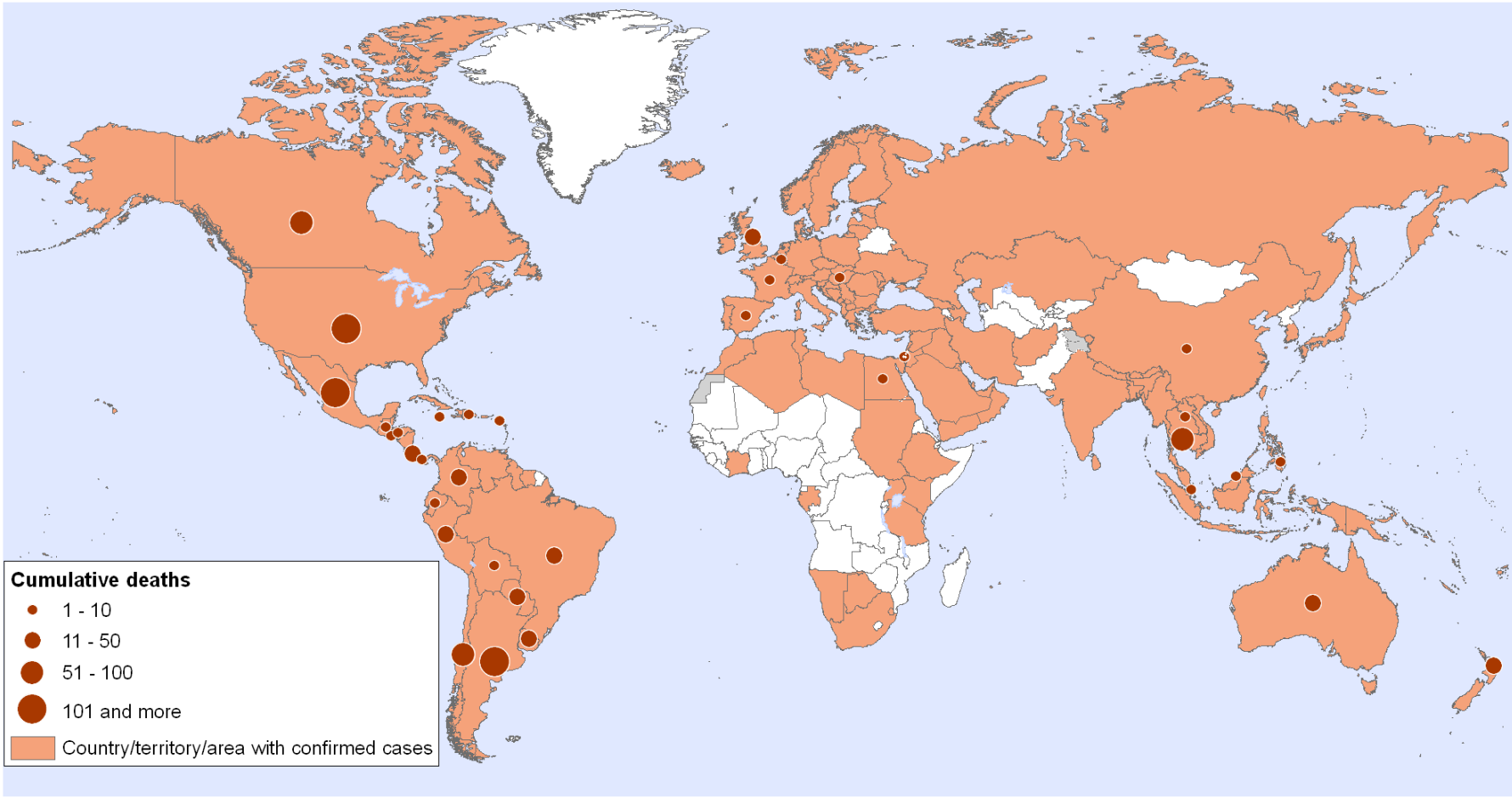
Pandemic (H1N1) 2009

Status as of 31 July 2009

Countries, territories and areas with lab confirmed cases and number of deaths as reported to WHO



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

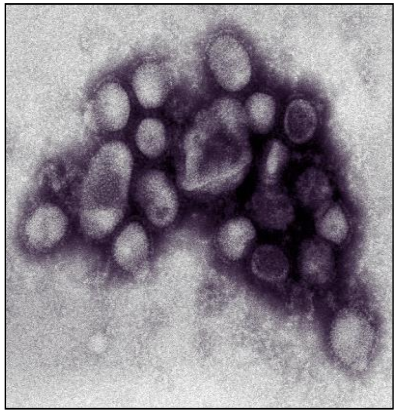
Map produced: 04 August 2009 13:00 GMT

MMWR
Morbidity and Mortality Weekly Report
www.cdc.gov/mmwr

Recommendations and Reports | August 28, 2009 / Vol. 58 / No. RR-10

Use of Influenza A (H1N1) 2009 Monovalent Vaccine

Recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009



DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR DISEASE CONTROL AND PREVENTION

BOX. Initial target groups for novel influenza A (H1N1) vaccination programs and a subset of these target groups to receive vaccine if initial vaccine availability is not sufficient to meet demand*

Initial target groups

ACIP recommends that programs and providers provide vaccine to all persons in the following five initial target groups as soon as vaccine is available (order of target groups does not indicate priority):

- pregnant women,
- persons who live with or provide care for infants aged <6 months (e.g., parents, siblings, and daycare providers),
- health-care and emergency medical services personnel,†
- children and young adults aged 6 months–24 years, and
- persons aged 25–64 years who have medical conditions that put them at higher risk for influenza-related complications.§

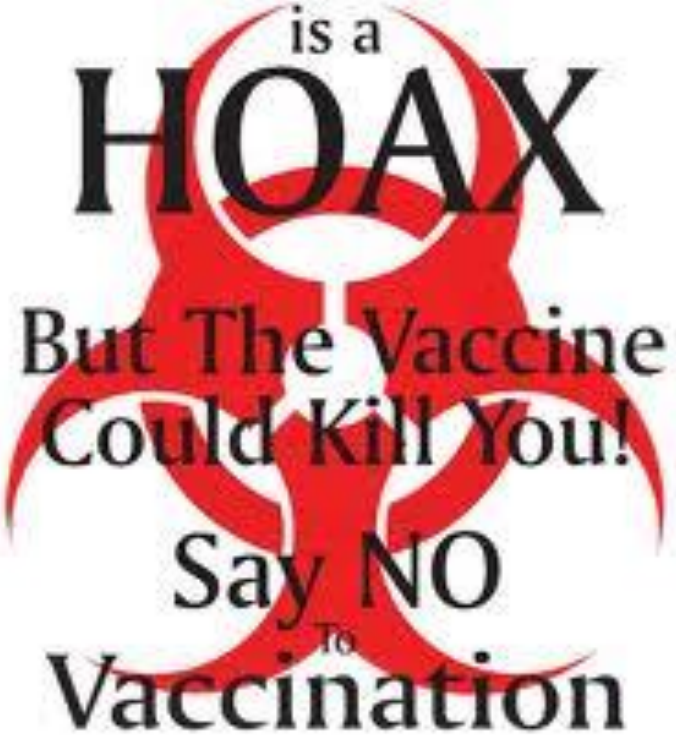
Subset of initial target groups

ACIP recommends that all persons in the following subset of the five initial target groups receive priority for vaccination if vaccine availability is not sufficient to meet demand (order of target groups does not indicate priority):

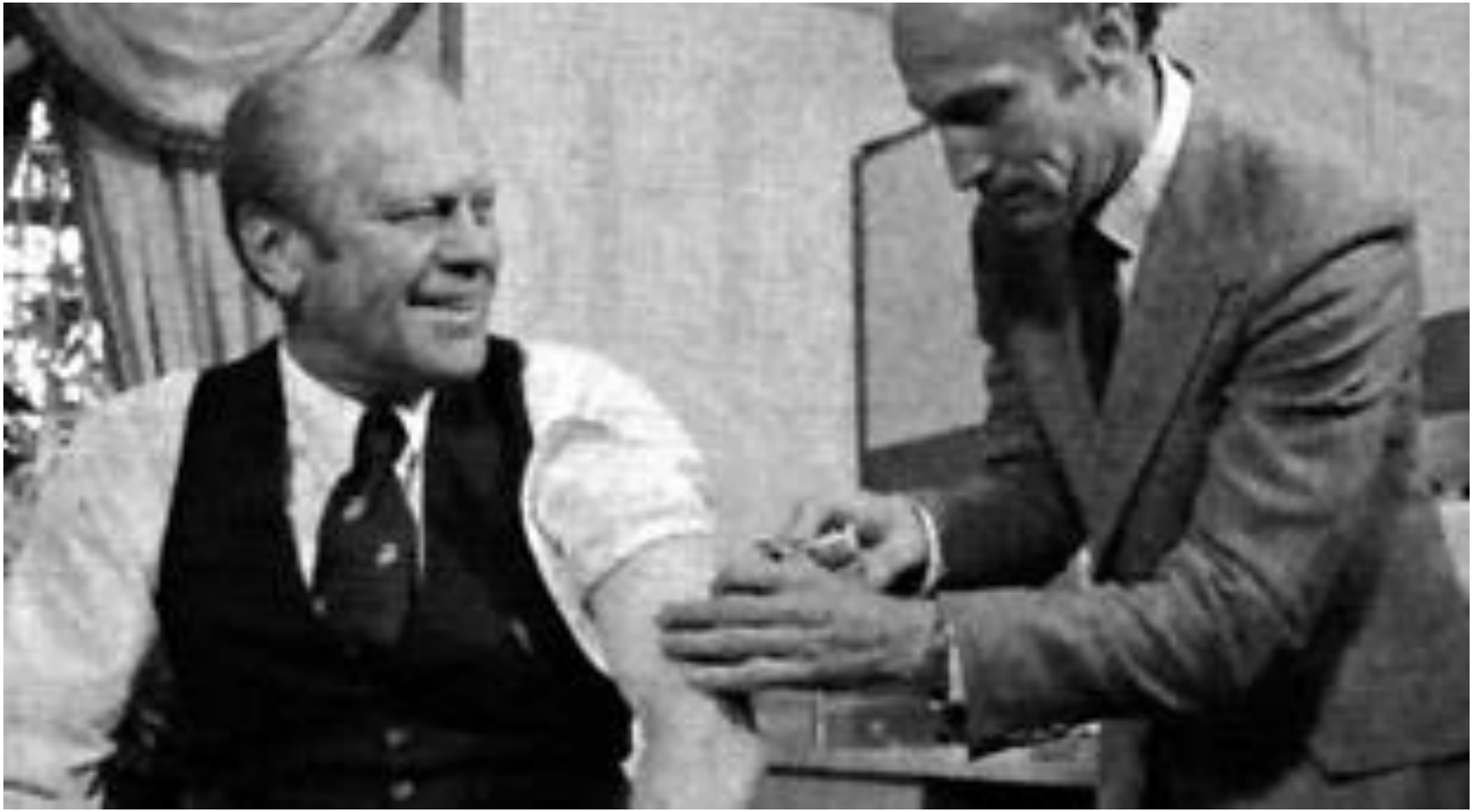
- pregnant women,
- persons who live with or provide care for infants aged <6 months (e.g., parents, siblings, and daycare providers),
- health-care and emergency medical services personnel who have direct contact with patients or infectious material,
- children aged 6 months–4 years, and
- children and adolescents aged 5–18 years who have medical conditions that put them at higher risk for influenza-related complications.§

The Vaccines

2009 H1N1 Vaccines



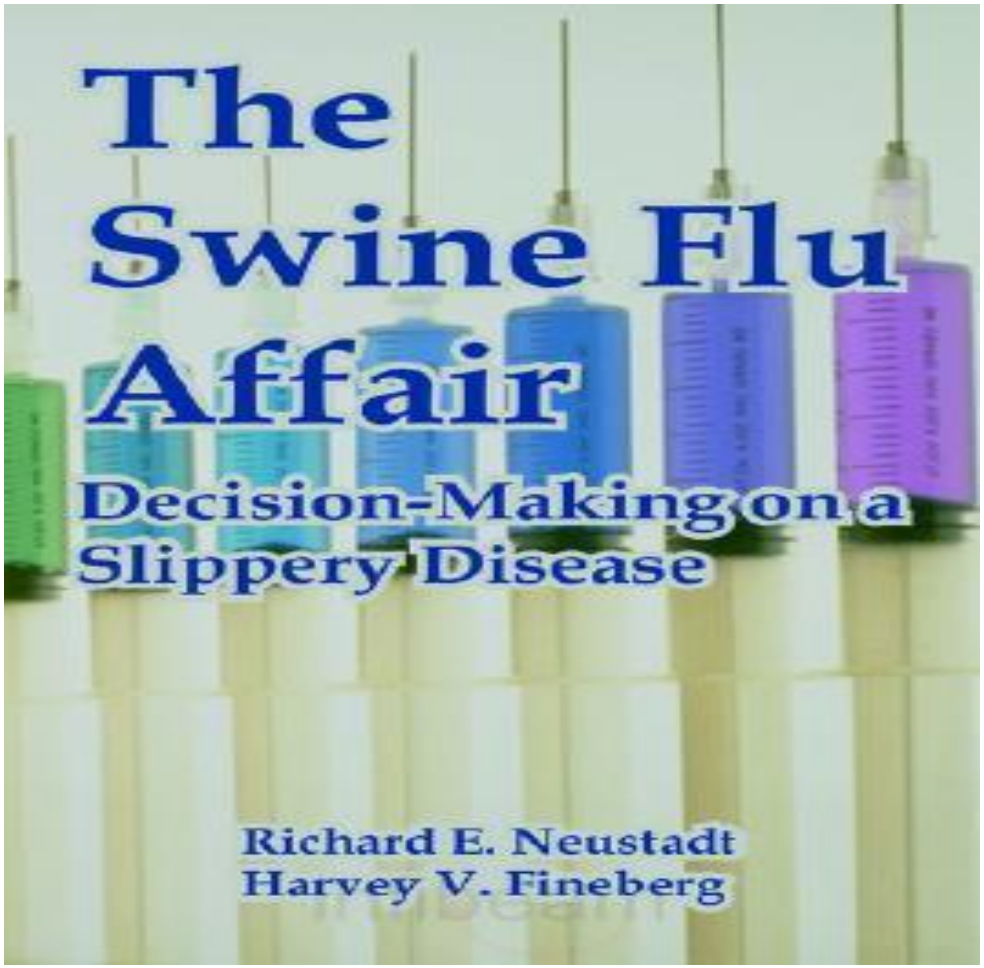
www.theflucase.com



GBS & Influenza Vaccination

- 1976 swine flu vaccination program halted when risk of GBS identified
  - Over 45 million people vaccinated btwn Oct-Dec
    - 500 GBS cases (25 deaths) reported
    - 7 to 8 times increased risk in 42 days post-vaccination (highest is 2-3 weeks) among adults
    - Translated into @ 1 excess case per 100,000 vaccinees
  - Pandemic did not occur as expected
  - Biological mechanism not determined
- Public health and political disaster

Importance of Monitoring H1N1 Vaccine Safety



Monitoring H1N1 Vaccine Safety What is Needed?

- Identify adverse events following immunization and quickly evaluate if caused by vaccine
  - GBS in 1976
- Quickly address spurious associations
  - Pregnant women

Example: Background Rates in Subpopulations

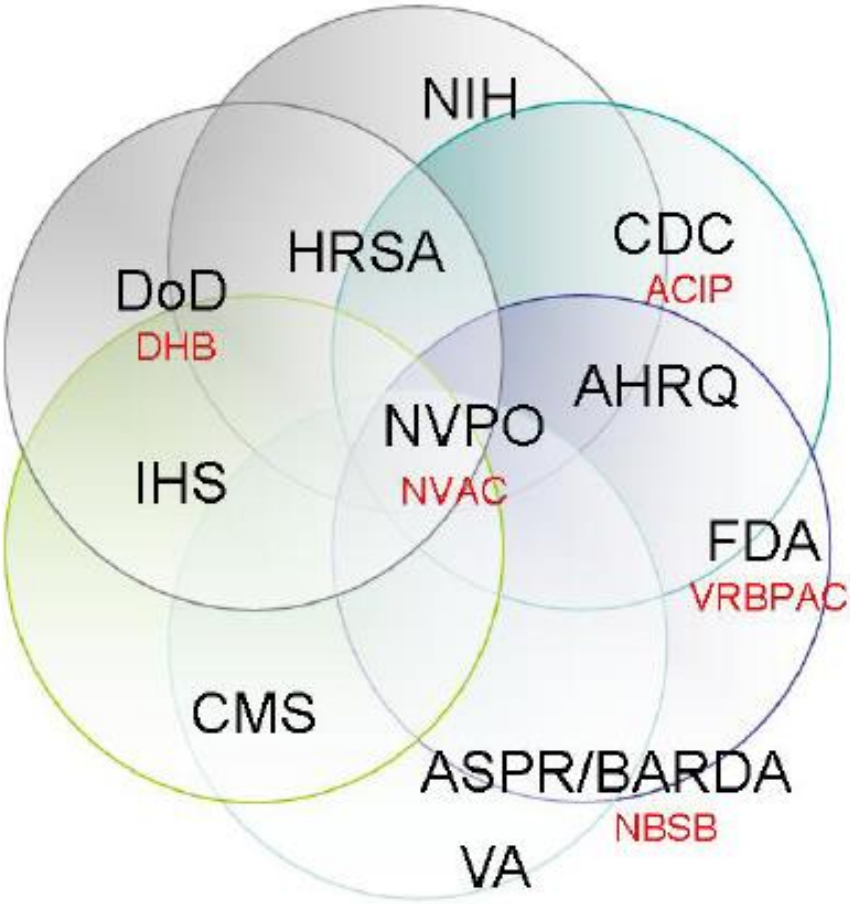
- Pregnant women are listed in Tier 1 in guidance for vaccine allocation
  - 6 million clinically recognized pregnancies in the US each year
  - 15% end in a clinically recognized spontaneous abortion
  - 900,000 clinically recognized spontaneous abortions each year
  - 2,466 clinically recognized spontaneous abortions each day
  - With 50% vaccine coverage, @1,200 spontaneous abortions within 24 hours of vaccination

Monitoring H1N1 Vaccine Safety What is Needed?

- Identify adverse events following immunization and quickly evaluate if caused by vaccine
  - GBS in 1976
- Quickly address spurious associations
  - Pregnant women
- Ability to distinguish between the two

US Vaccine System

- NIH – basic research, vaccine development & evaluation
- FDA – licensure, post-licensure surveillance
- CDC – purchase & promote vaccination, post-licensure surveillance
- NVPO – coordination



Advisory Committees in Red

Brief Review of Safety Monitoring

- Passive Surveillance – VAERS (FDA & CDC)
- Active Surveillance – VSD (CDC)
- Clinical Assessment – CISA (CDC)

Active Surveillance to Evaluate Signals

- Vaccine Safety Datalink (VSD)
  - Large linked database of 8 managed care organizations (MCOs) administered by CDC
  - @ 2% of pop. < 18 yrs.
  - @ 1.5% of pop. > 18 yrs.
  - Includes exposure data (vaccine history), outpatient, ER, hospital and laboratory
  - 20+ years of experience
- CMS, DoD, VA starting to look at influenza vaccine safety (2009)

Force Me to Do What I Want to Do Anyway

Martin Luther King: "We need this Voting Rights Act. You know, we need your help,”

President Lyndon Johnson: "I wanna do it. Make me do it."

National Vaccine Advisory Committee (NVAC) H1N1 Vaccine Safety Subgroup

- Charge: review the current Federal plans for safety monitoring for a 2009 H1N1 influenza vaccine and provide feedback on the adequacy, strengths, weaknesses and considerations for enhancement
- Membership carefully chosen
- Not open to public – recommendations go through NVAC to Assistant Secretary for Health
- Only needed to meet once

National Vaccine Advisory Committee (NVAC)

Recommendations for H1N1 Safety Monitoring

1) Assemble background rates of adverse events that occur in the general population
2) Develop and disseminate a federal plan
3) Enhance active surveillance for signal detection, assessment and confirmation of possible associations between vaccines and adverse events
4) Establish a transparent and independent review of vaccine safety data as it accumulates
5) Develop, and where possible test in advance, a strong and organized response to scientific and public concerns about vaccine safety

Estimates of Coincident, Temporally-Associated Events

Coincident events	Number of coincident events since a vaccine dose: *Within 1 day*	*Within 7 days*	*Within 6 weeks*	Baseline incidence rate used for estimate
Guillain-Barré Syndrome (per 10 million vaccinated people)	0.51	3.58	21.50	1.87 per 100,000 person-years (all ages; UK Health Protection Agency data)
Optic Neuritis (per 10 million female vaccinees)	2.05	14.40	86.30	7.5 per 100,000 person-years in US females
Spontaneous abortions (per 10 million vaccinated pregnant women)	3,970	27,800	166,840	Based on data from the USA (12% of pregnancies)
Sudden death within 1 hour of onset of any symptoms (per 10 million vaccinated people)	0.14	0.98	5.75	Based upon UK background rate of 0.5 per 100,000 person-years

Black *et* al. Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines; Table 6. *Lancet* 2009; 374; Oct. 30 [Epub.]

Federal Plans to Monitor Immunization Safety for the Pandemic 2009 H1N1 Influenza Vaccination Program

Federal Immunization Safety Task Force

U.S. Department of Health and Human Services
Agency for Healthcare Research and Quality
Centers for Disease Control and Prevention
Food and Drug Administration
Health Resources and Services Administration
Indian Health Service
National Institutes of Health
Department of Defense
Department of Veterans Affairs

Preparing the Media

- 3 tabletop exercises with HHS Leadership and the media
- Walk through scenarios highlighting possible events
- See what questions the media might ask and how they would report the issues
- See how the media responded to our responses to situations
- Prepare the media for what was to come

Crisis Brings Opportunity

- Improve active safety monitoring
- Understand relationship between flu vaccine and GBS
- Create independent assessment of safety

Problems with Active Surveillance for 2009 H1N1

- VSD limitations
  - Capturing vaccine exposure
  - Size and consequently timeliness
  - Limited populations (geography and MCOs)
- Solutions
  - Speed development of DoD, VA and CMS
  - Develop new system

Post-Licensure Rapid Immunization Safety Monitoring (PRISM)

- 8 State Immunization Registries captured exposures
- 4 large Health Plans captured some exposures and outcomes
- 38 million people under active surveillance

- Salmon et al, Health Affairs, 2013

Collaborators – Partial List

- **National Vaccine Program Office**
  - Daniel Salmon
  - Kirsten Vannice
- Centers for Disease Control and Prevention
  - Frank deStefano
- Food and Drug Administration
  - Robert Ball
- **America's Health Insurance Plans**
  - Kevin Fahey
  - Barbara Lardy
  - Victor Rhee
- **Public Health Informatics Institute**
  - Ellen Wild
  - Bill Brand
  - Elaine Lowery
  - Therese Hoyle
  - Alan Hinman
  - David Ross
- **Harvard Pilgrim Health Care Institute**
  - Richard Platt
  - Tracy Lieu
  - Grace Lee
  - Jeff Brown
  - Melisa Rett
  - Charlene Gay
  - Katherine Yih
  - Yury Vilk
- **Health Information Systems Consulting**
  - Robert Rosofsky
- **EpiPatterns**
  - Yinong Young-Xu
- **Computer Sciences Corporation**
  - Daniel Foltz
  - Jim Van Dyke
  - Aurelia Ford
  - Jim Roddy
  - John Manson
  - Vic Tandon
- **Cigna**
  - Therese Conner
  - Anthony Sumner
  - Daniel Carmody
  - Ha Nguyen
  - Mark Regine
- **Aetna**
  - Claire Spettell
  - Cheryl Walraven
  - Joaquim Fernandes
  - Yihai Liu
- **Healthcore (Wellpoint, BC/BS)**
  - Peter Wahl
  - Alex Cannon
  - Lori Meyers
  - Greg Daniel
  - Chris Hetrick
- **Humana**
  - David Nau
  - Yihau Xu
  - Amy Ball
- **Arizona State Immunization Information System**
  - Lisa Rasmussen
  - Roger Volp
  - Richard Bradley
- **Florida Shots**
  - Susan Lincicome
  - Pete Garner
- **Georgia Registry of Immunization Transactions and Services**
  - Tracy Culbreath
  - Elizabeth Sullivan
  - Michelle Conner
  - Archie Banks
  - Andre Wilson
- **Michigan Care Improvement Registry**
  - Therese Hoyle
  - Ian Hancke
- **Minnesota Immunization Information Connection**
  - Emily Peterson
  - Diana Jaeger
- **New York State Immunization Information System**
  - Loretta Santilli
- **New York City, Citywide Immunization Registry**
  - Vikki Papadouka
  - Rezaul Kabir
  - Luiz Homem de Mello
- **Pennsylvania Statewide Immunization Information System**
  - Frank Caniglia
  - Mike Jamula
- **Wisconsin Immunization Registry**
  - Dan Hopfensperger

PRISM aims

- Link health plan data and state immunization registry data in new H1N1 vaccine safety surveillance network
- Conduct continuous active surveillance for pre-specified outcomes
- Provide timely information on *unanticipated* potential adverse events

Outcomes Monitored

- Guillain-Barré Syndrome (GBS)
- Demyelinating disease
- Neuropathies
- Seizures
- Encephalitis
- Bell’s palsy
- Other cranial nerve disorders
- Myocarditis
- Ataxia
- Anaphylaxis
- Other allergic reactions
- Spontaneous abortion
- Stillbirth
- Pre-eclampsia

Weekly Monitoring of Counts

- Risk (exposure) windows
  - Periods after H1N1 vaccination
  - 2, 14, 21, or 42 days, depending on outcome
- Comparisons
  - Expected counts based on historical rates after seasonal influenza vaccination, or
  - Unexposed time periods in same persons

PRISM 2009 H1N1 Results

- All outcomes aside from GBS not associated with vaccine
- Chart review done for GBS contributed to US meta-analysis and international study
- PRISM picked up by FDA as vaccine component of mini-sentinel project

NVAC Recommendation:
Independent Vaccine Safety Assessment

Consideration should be given to a transparent and independent review of vaccine safety data as it accumulates. This Vaccine Safety Assessment Committee (VSAC) would be **an independent group of outside experts** with a charge to advise the ASH and/or ASPR on the presence, investigation, interpretation, and implications of possible side effects of H1N1 vaccines. The committee should be **reviewing pre- and post-licensure vaccine safety data accumulated in a timely way and not await activation when a specific signal is declared.** The VSAC should advise on distinguishing spurious from genuine side effects; anticipating and responding to coincident (non-causal) events; evaluating the occurrence, frequency, and seriousness of possible side effects associated with vaccine; programmatic and policy steps to take in response to purported or demonstrated safety concerns; strategies and content of communication about vaccine safety; and such other matters related to vaccine safety that the ASH/ASPR would find useful.

NVAC Recommendation:
Independent Vaccine Safety Assessment

Such an external review would involve an independent group of experts with **no professional or commercial stake in the vaccines or conduct of an immunization program,** to speed and improve response to possible vaccine side effects, to **enhance public confidence**, and to provide focused advice on what can become a scientifically and politically contentious issue. The VSAC may be made up of members of an existing Federal advisory committee, such as NVAC, and supplemented by other vaccine safety experts. The committee would **only assess risks (not consider vaccine benefits) and the committee would be only advisory and not decision making.** The ASH/ASPR would be responsible for assuring programmatic response to the assessment of risk.

SIGNAL ≠ ASSOCIATION ≠ CAUSALITY

Highly Sensitive Systems Result in False Positives

- If initial signal through automated data
  - Check data quality
  - Check whether comparison groups are defined appropriately
  - Repeat analysis with different control group (e.g., concurrent vs. historical) or different vaccine
  - Check for temporal clustering of outcomes during a post-vaccination time window
  - Adjust for confounding, e.g., stratified and multivariate analyses
  - Review charts to confirm/exclude cases and obtain additional information on potential confounders
- Historically, 90% of signals turn out to be spurious

Policy Questions

- How to be responsibly transparent?
  - Need for process that is credible, especially at times of crisis
  - If too much raw data become publicly available we may cause undue alarm
- Who should manage process?

Independent Assessment

National Vaccine Advisory Committee H1N1 Vaccine Safety Risk Assessment Working Group (VSRAWG)

VSRAWG Members

Marie McCormick[1]	*NVAC*
Stephen Cantrill	*National Biodefense Science Board (NBSB)*
John Clements	*Defense Health Board (DHB)*
Vicky Debold	*Vaccines and Related Biological Products Advisory Committee (VRBPAC)* Public Rep
Kathryn Edwards	*Institute of Medicine (IOM); Formerly ACIP and VRBPAC*
Theodore Eickhoff	*VRBPAC*
Susan Ellenberg	*IOM*
Laura Riley	*NVAC*
Mark Sawyer	*ACIP*

VSRAWG Charge

To conduct independent, rapid reviews of available federal immunization safety monitoring data for the 2009 H1N1 influenza vaccines

VSRAWG Methodology

- Created on October 30, 2009
- In-person meeting reviewed
  - Influenza vaccine safety literature from 1967 to 2009
  - Protocols/analytic plans from each vaccine safety monitoring system
  - Clinical trials data
- Ongoing Process
  - Bi-weekly calls through vaccine program, then monthly
  - Received vaccine safety data from each system via the Federal Immunization Safety Task Force (ISTF)
  - Discussed and interpreted data
  - 20 total meetings

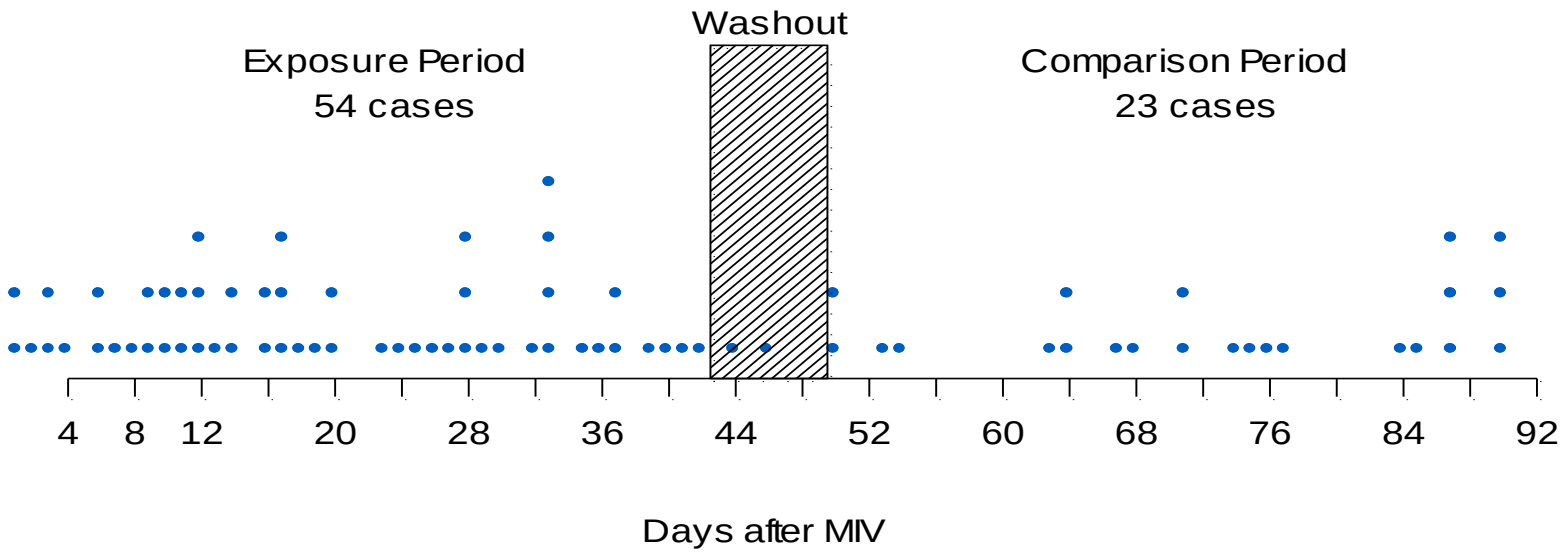
VSRAWG Reports

- Reports included
  - Summary of data
  - Assessment of data strengths and limitations
  - Considerations for follow-up studies
- 7 VSRAWG reports were provided to the NVAC
    - December 16, 2009, January 20, 2010, February 26, 2010, March 23, 2010, April 23, 2010, June 2, 2010, January 31, 2012 (final)
- Available on NVPO website at: http://www.hhs.gov/nvpo/nvac/reports/index.html

VSRAWG Conclusions

- Initial “weak signals” for ITP, Bell’s Palsy, and GBS
- Publicly reported with little attention
- ITP & Bell’s Palsy turned out to be spurious

Distribution of Guillain-Barré syndrome Onset Days Post Influenza A (H1N1) 2009 Monovalent Inactivated Vaccine (MIV)



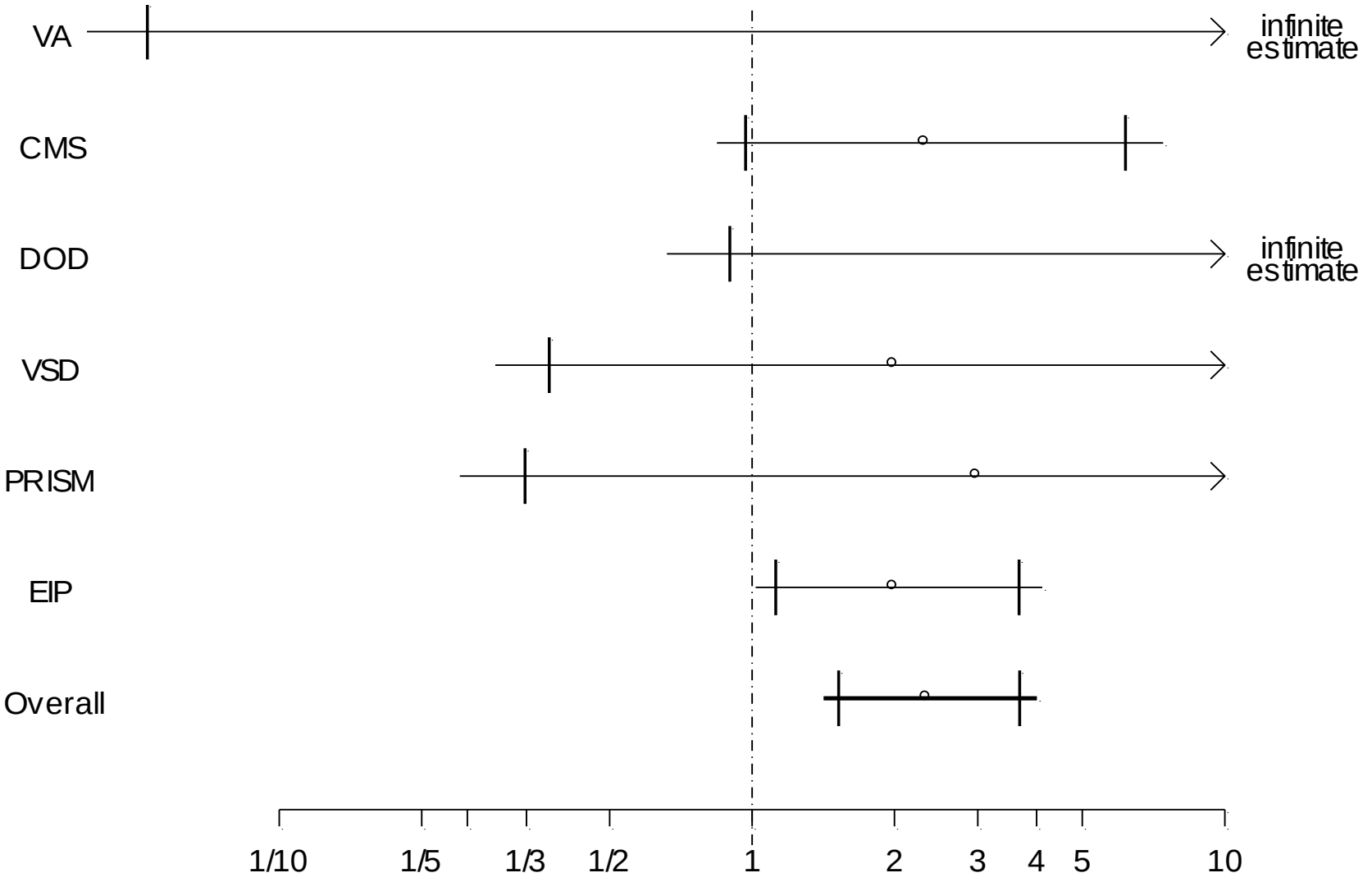
Exposure window days 1-42

Washout period" days 43-49

Comparison period days 50-91

Salmon, Lancet, 2013

Incidence Rate Ratio (IRR) and 90% and 95% Confidence Intervals (CI) for risk of Guillain-Barré syndrome Associated with Influenza A (H1N1) 2009



Salmon, Lancet, 2013

Overall: 2.35; 90% confidence interval (CI) 1.53-3.68; 95% CI 1.42-4.01; P Value 0.0003

Attributable Risk for Guillain-Barré syndrome (GBS) Associated with Influenza A (H1N1) 2009 Monovalent Inactivated Vaccines (MIVs) by Age Category

Age (years)	IRR	Background cases per 100,000 person-years	Background cases per million (42 days) risk windows	Excess (attributable) cases per million vaccinations
<18	2.33	0.69	0.79	1.05
18-64	2.50	1.20	1.38	2.07
65+	2.20	2.24	2.58	3.09

Background rates based upon Sejvar et al, Neuroepidemiology, 2011

Salmon, Lancet, 2013

Confidence Lessons Learned from 2009 H1N1 Sample Size of 1

- Most notable is what didn't happen
- Safety monitoring
  - Dependent on infrastructure
  - We can detect extremely small risks and rule out many others
- Did we "immunize" the media from safety sensationalism?
- Public can be trusted with preliminary data
- Rapid independent review is
  - Feasible
  - Objective
  - Well received