Immunization Before the Next Pandemic?
Risks, Benefits and Pathways

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Director, Center for Biologics Evaluation and Research,
IDSA, Washington, DC, May 19,2008

Overview

- *Framing the major issues*
- *Some “lessons of history” from 1976*
- *New pandemic vaccines – special considerations and safety database issues*
- *Some potential pathways*
- *Audience input*

The issue and hypothesis, at their simplest and boldest….

- A pandemic is a pandemic because a highly pathogenic virus, transmissible from person to person, emerges against which broad populations have no significant protective immunity, so…
- If the population had significant immunity, could we prevent the next pandemic?
  - *In reality, a range of potential approaches, benefits and risks exist for pre-pandemic vaccine use*

Predicting risk-an uncertain science

- Probability, timing, severity and identity of future pandemics are unknown
- H5N1 persists and changes – and other serotypes will remain/emerge as threats
- Evidence of increased human-human transmission, perhaps accompanied or, someday, predicted, by relevant changes in the virus, may or may not presage a pandemic
- Waiting for such evidence may leave limited time for vaccine production and administration
- These uncertainties complicate strategy and planning

Why consider immunization prior to (or early in) a possible pandemic?

- Despite progress with and promise of newer technologies, including antigen sparing, time for production/availability remains long (>3 mo with current methods) and global surge capacity limited
- Unlikely to sustain vaccine industrial base for what may be ~ every 40-60 year threats or events
- Conversely, increased US investments and capacity provide opportunities for prepandemic options
- Increasing evidence supports priming and cross-protection among heterologous H5 strains, appears increased with novel adjuvants
- Modeling suggests benefits to early use of vaccine, even of limited efficacy, and even in single doses

Vaccination Timing Options: Overview

- *During a pandemic, using pandemic strain*
  - Pros - Clearest benefit/risk (though even with proven vaccine, strain change could conceivably have unforeseen AEs)
  - Con- too little, too late
- *In an "emerging" pandemic*
  - Vaccination can begin quickly if stockpiled
    - Can target areas/individuals at high initial risk
    - Temporizing strategy until matched vaccine available
  - Benefit/risk ratio clearer than inter-pandemic use
    - Although feared pandemic still could "fizzle"
  - Expensive, need large stockpiles
    - Potential need to replace/rotate stockpiles

Vaccination Timing Options: Overview

- *"Pre-pandemic"*
  - *Truly inter-pandemic – though may be variable risks from theoretical to current status w/ avian/zoonotic threat)*
  - Options: separate or related to annual immunization
    - » Generally or to populations w/ increased risk/need
    - » Strategy could provide priming and/or full protection
    - » Complexities of administration if different dosing/form
  - If successful, could blunt or prevent pandemic
    - » Individual and public health and economic benefits, require less surge capacity, reduce need for emergency measures, risk communication, administration, stockpiles
  - Strain mismatch and likely reduced efficacy
    - » May still reduce death, hospitalization, infectivity
  - Uncertain pandemic risk increases safety concerns and reduces risk tolerance
    - » *Better prediction of a strain's pandemic risk and potential needed and could transform preparedness*

Models Suggest Potential for Significant Vaccine Effects: Impact of vaccine delay and of prevaccination

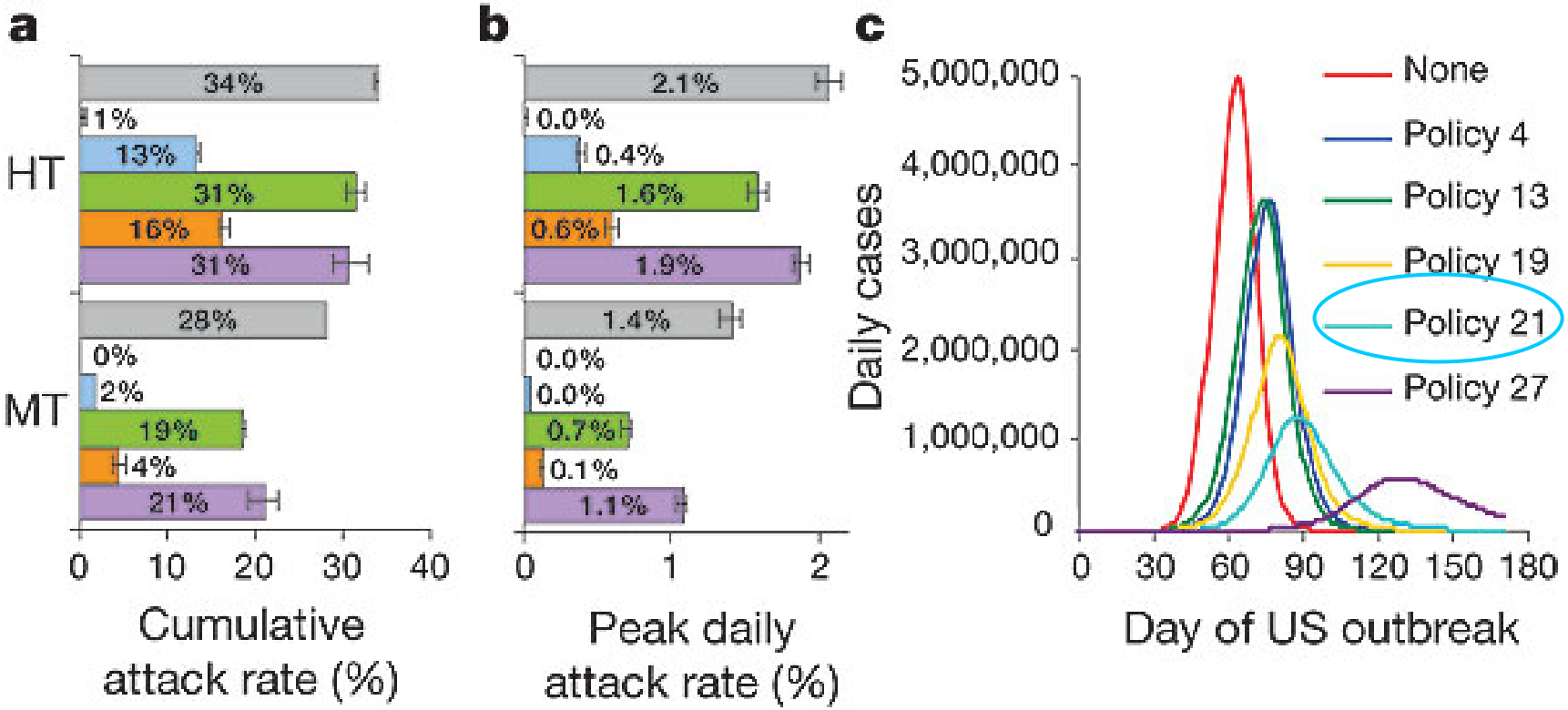

Figure a, b: effects of mass vaccination beginning on day 30 (second bar down), 60 (blue) or 90 (green) after first case for high/low transmissible virus Fig. c - Policy 21 = pre-vaccination of 20% of population (VE30%), prioritizing children, added to household quarantine, school closure, next day Rx and household Px - *Ferguson, Cummings, Fraser, et al Nature 442, 448-452(27 July 2006)*

Early immunization strategies: many unanswered questions

- How can we better measure and predict both protection and cross-protection?
  - Unknown/uncertain for non-HA antigens or LAIV
  - How do animal models contribute?
- What dose and dose intervals are needed for priming? Boosting?
- How durable is priming? Are specific levels of Ab needed, and must they be maintained?
- *Caveats:*
  - *Some answers may be serotype, clade or even virus specific, and may defy prediction*

Lessons of History: The 1976 Swine Influenza Experience

“Those who cannot remember the past are condemned to repeat it"

Swine Flu

- Timeline
- Observations
- Some major lessons learned

"Skepticism, like chastity, should not be relinquished too readily"

Coincidence: 2/13 Kilbourne editorial alerting that we are due for pandemic with cartoon in NY Times

pg. 32

Flu to the Starboard! Man the Harpoons! Fill 'em With Vaccine! Get the Captain! Hurry!

By Edwin D. Kilbourne

Holbrifter

World-wide epidemics, or pandemics, of influenza have marked the end of every decade since the 1940's — at intervals of exactly eleven years — 1946, 1957 and 1968. A perhaps simplistic reading of this immediate past tells us that 11 plus 1968 is 1979, and urgently suggests that those concerned with the public health had best plan without further delay for an imminent natural disaster.

Since the virus of influenza was first isolated in 1933, it has been measured, dissected and chemically analyzed with the assumption that its tiny particle holds the secret of its unique ability to persist into the twentieth century as the last great plague of man. In truth, the influenza virus particle will reveal the secret of its unusual mutability when the function of its genes and proteins can be understood.

The basic structure of the virus is now known, its proteins and genes counted and numbered and subject to deliberate laboratory manipulation, yet we have no answer to its predictable disappearance every ten years and its periodic replacement by new mutants to which the whole world is susceptible.

Reasonably effective vaccines for influenza have been available for thirty years, but not even recent pandemics have been significantly influenced by human intervention. Whenever pandemic influenza next appears, we must improve upon our well-intentioned but uncoordinated individual efforts of the past that have resulted in ambiguous advice to the public and inadequate production and maldistribution of vaccine.

The initial introduction in 1968 of the currently circulating Hong Kong subtype of influenza virus witnessed within the United States alone the occurrence of more than 50 million illnesses and 19,000 influenza-associated deaths (and 1968 was not our worst pandemic year). The economic burden of such a disaster is not easily calculated but in 1968-69 approached $4 billion if losses in earnings are added to total medical costs.

If, then, we accept pandemic influenza as a disaster and are concerned about its apparent predictability, what can be done about the predictable disaster of circa 1979?

Much can be done without a single new scientific development. Our present vaccine policy is not carried out in practice. This policy recommends the preferential immunization of the estimated 45 million Americans unusually susceptible to influenza complications (pneumonia and death) even in interpandemic years.

But only about 20 million doses of vaccine are produced annually, and of

for Disease Control, to insure adequate production of vaccine by the private sector and its appropriate distribution. Achievement of this objective may require governmental subsidizing of industry with the probability of occasional overproduction of vaccine—but discarded vaccine should be weighed against discarded lives.

Although present vaccines do not

yielded practical dividends in enhancement of vaccine production by the use of genetically modified viruses—thus shortening the production lag responsible, in part, for past vaccine shortages in pandemic years.

Meanwhile, research on new live virus vaccines as well as basic studies should be accelerated so that these and other new approaches to the

The Story Plays Out: Timeline

- **2/4/76: Pvt. David Lewis, 18 y/o dies of pneumonia at Ft. Dix, NJ (then in midst of one month flu epidemic)**
- **2/12: Lewis isolate and 4 others: Swine flu cross reactive with 1918 serum.**

The Story Plays Out: Timeline II.

- **2/14: Emergency meeting at CDC: studies planned, serology on and off base and nationally. Decision to make reagents and reassortant "just in case"**
- **2/19: CDC Press Conference: intent low key but press evokes 1918 – showing pictures**
- **2/20: Meeting at FDA: "better safe than sorry"**
- **Serologies - 13+ among recovered at Ft. Dix, up to 500 + in asymptomatic, none positive outside area, no further cases but "will it reappear in Spring"?**
- **2/27: E. Kilbourne distributes reassortant to FDA and FDA to manufacturers**

The Story Continues: III

3/9: CDC meeting/Kilbourne: "Better a vaccine without an epidemic than an epidemic without a vaccine" - reasonable

BUT THEN RAMP UP OF CERTAINTY AND RHETORIC ON RISK OF PANDEMIC AND SEVERITY OF VIRUS OCCURS

3/10: ACIP: Pandemic a *"possibility"*, rec. make vaccine and vaccinate - Alexander: "What information might make you change your mind"? Not explored. Stockpiling viewed impractical, delivery challenge, perhaps not enough time.

3/13 Sencer (CDC head) memo to Secy: likelihood unknown but a *"strong possibility.* Secy. Matthews to OMB: *"indications are that we will see a return of 1918 flu…with 1 million deaths"*

3/15: Briefing of President – possible risks not discussed, Ford asks dissenters to speak with him in Oval Office – no takers

3/24: Meeting at White House with Salk, Sabin, "No one knows how serious a threat…inoculate every man, woman and child"

Ford Urges Flu Campaign To Inoculate Entire U.S.

He Will Ask Congress for $135 Million to Make Vaccine for a New Virus to Avert Fall and Winter Epidemics

By HAROLD M. SCHMECK Jr.
Special to The New York Times

WASHINGTON, March 24— President Ford called today for a Government-supported campaign to vaccinate the entire United States population against a new influenza virus to forestall possible epidemics next fall and winter.

Mr. Ford said he would ask Congress tomorrow for an appropriation of $135 million to produce the vaccine.

In terms of size and intensity, no comparable vaccination effort has ever been attempted in this country. It would be a cooperative effort involving Federal, state and local public health forces and private groups and individuals.

Mr. Ford said it was "a subject of vast importance to all Americans."

In recent days, he said, he has been consulting with experts from Federal agencies and industry and with other authorities on vaccines and influenza from the scientific community.

In addition to asking Congress to appropriate money to insure production of enough vaccine to inoculate every man, woman and child in the United States, the President said he was "asking each and every American to receive an inoculation this fall."

He said he had also directed F. David Mathews, Secretary of Health Education and Welfare, and Dr. Theodore Cooper, Assistant Secretary for Health, to develop plans through which the vaccine can be made available to everyone during the months of September, October and November.

To date, only small experimental batches of vaccine against the new virus have been produced. None have yet been released for use. It is expected to be mid-to-late summer before large amounts have been produced, tested and released as safe and effective by the Food and Drug Administration's Bureau of Biologics.

The vaccination would be

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The Story Continues

- **Congress appropriates $ 135 million**
- **Vaccine makers switch from annual vaccine after 30-40 mill production**

- ***3/24:The Critics Emerge***
  - **CBS News/Cronkite/NYT: premature, unwise**
  - **4/2: Goldfield, NJS epidemiologist: bad idea- *"15% of the population will suffer a disability"***
  - **Sabin starts arguing for stockpile approach**

pg. A2

. . . mass immunization impossible

Sabin, Salk Split Over Flu Shot Plan

By Victor Cohn
Washington Post Staff Writer

Dr. Albert Sabin—developer of the oral vaccine and an original backer of a plan to vaccinate 200 million Americans against swine flu this year—told a House health subcommittee yesterday that only older and high-risk persons should be injected now unless swine flu appears.

But Dr. Theodore Cooper, assistant secretary for health, and Dr. Jonas Salk, developer of the first polio vaccine, disagreed and said swine flu vaccination should proceed.

They disputed Sabin's contention that "the original plan for mass vaccination of every man woman and child"—ordered last March by President Ford—"is no longer possible" because of "new findings" about limitations of the test vaccine produced so far.

Salk said even partial immunization of the population might prevent the spread of the potentially deadly swine flu — the kind that unexpectedly killed a soldier at Fort Dix, N.J., last winter and the kind, that probably killed 550,000 Americans in 1918-19.

Cooper said that if swine flu appears it will spread too fast to apply Sabin's new plan, which calls for limiting vaccinations to "15 to 20 million" persons over 65 or chronically ill, stockpiling more vaccine and forming national volunteer brigades to give it swifty if and when needed.

Sabin's testimony, however, was only one of the possible roadblocks to mass vaccination that loomed yesterday.

The four firms expected to make the vaccine said they have been able to buy either none or scarcely any of the liability insurance required to protect them from lawsuits that may result from actual or alleged adverse reactions. They said they can't afford to take all the risks, and repeated pleas for quick passage of a law to indemnify them against judgments except where they are negligent.

Congress must pass such a l "by early July" if the firms to make vaccine in time for m shots this summer and fall, s Ivan Husovski, president of Merrell-National Laboratories.

Cooper backed the companies' plea, calling the vaccine program "in jeopardy" unless all four makers—Merrell, Merck, Warner-Lambert and Wyeth—are able to move quickly. He called the refusal to write liability insurance "incredible" and "wholly irresponsible."

But Leslie Cheek, vice president of the American Insurance Association —whose 138 members write most of the nation's product-liability and medical-malpractice policies — said "the risks in a massive swine flu program are unknowable and uninsurable" in view of the "enormous number of potential claims, both meritorious and otherwise," that might be made by anyone who suffers an illness after a flu shot.

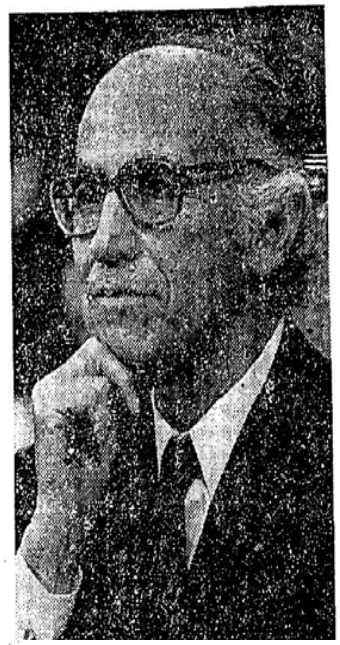
During a day of testimony, health subcommittee members raised questions about the advisability of protecting private drug makers against patients' claims.

But Rep. Henry Waxman (D-Calif.) said "we've been stampeded into passing" legislation to make the mass vaccination possible this year, and "now we're being stampeded" into a law that might set a bad precedent for other public health programs in which private firms might be reluctant to participate.

Salk backed an indemnity law but only against swine flu shots, not against effects of other vaccines including Sabin's oral polio vaccine, where some paralyzed persons have won law suits claiming they were not informed about possible ill effects.

Sabin—who claimed in such cases that his vaccine was not to blame—based his plea for delaying mass swine flu shots in large part on the argument that tests so far show poor protection of persons under age 24...

He said health officers would be better off saving most of the vaccine until it is definitely needed, and trying meanwhile to immunize



Vaccines for Swine Flu Flunk Tests in Children

Therman E. Evans

Blacks' Fear of the Swine-Flu Shots

Black people across the country have not been getting swine-flu vaccinations. Inner-city clinics have reported a low level of participation by the urban poor generally and blacks specifically. In Birmingham, for example, as of the first week in November, 7,000 people in white neighborhoods had been immunized but only 124 in black neighborhoods.

The reason most often cited is fear of the effects of the vaccine itself. The director of Washington's flu program has said that the low level of education among some poor people and some blacks fostered fear of the vaccine, despite findings by the Center for Disease Control that it was safe.

I have talked with blacks at all levels —professional and nonprofessional, old and young, high-income, middle-income, low-income and no income—across the country. The responses to the question, "Have you gotten your swine-flu shot?" have been fairly consistent. They all seem to involve a fear that the evidence supporting the program was shaky and that some of their professors, experts in the area, were not convinced—so neither were they.

Two black ministers, with large congregations in a large midwestern city, have already advised their members not to take the shots. One of these ministers was convinced that the swine-flu effort was a part of a genocidal thrust against black people, and that the shot taken by President Ford was only water. Many blacks who are members of fundamentalist churches have explained their refusal to get the shot by saying that the Lord will take care of them.

Dr. Evans is president of the D.C. Board of Education.

A black bureaucrat in the Public Health Service said, "The swine-flu program was shaky and that some of their professors, experts in the area, were not convinced—so neither were they."

vestigation thus far, it would appear that the influenza caused by the swine-like virus is no more virulent than that caused by recently circulating strains of influenza." Such statements, plus differing findings by various medical experts, black and white, have fostered confusion and fear.

The identification of the massive inoculation program with the politics of the Republican administration is also important. The President's visible involvement automatically produced paranoia in many blacks. The program was assumed to be a political effort to help elect him, rather than a medical effort to protect the population. This point seemed more substantial because Ford has vigorously supported this $135-million "health effort"—about which there is much uncertainty and differing expert opinions—but vetoed health, education and welfare programs about which there was clarity and consensus.

Another important factor is this

JLG5-08

What can go wrong, will?

- **6/2: Parke Davis vaccine mix up**
- **Studies show young need 2 doses, don't tolerate some vaccines**
- **July: UK: Intentional inoculation – mild disease**
- **May-June: Manufacturers unable to get liability, refuse to produce further and seek indemnification**

No Insurance No Flu Vaccine, Producers Say

By Stuart Auerbach
Washington Post Staff Writer

President Ford's program to protect all Americans against a possible swine flu epidemic next winter is on the ropes because no one wants to insure the makers of the vaccine.

Government officials failed in day-long meetings rise in our view to a substantial number of claims," Cheek continued.

Health Subcommittee Chairman Paul G. Rogers (D-Fla.) suggested yesterday's meeting in an effort to draw up a contract between the vaccine makers

Error Cited In Making Flu Vaccine

By Stuart Auerbach
Washington Post Staff Writer

A drug company used the wrong strain of virus to make vaccine against swine flu, possibly delaying for six weeks a government campaign for the early immunization of high-risk groups, officials said yesterday.

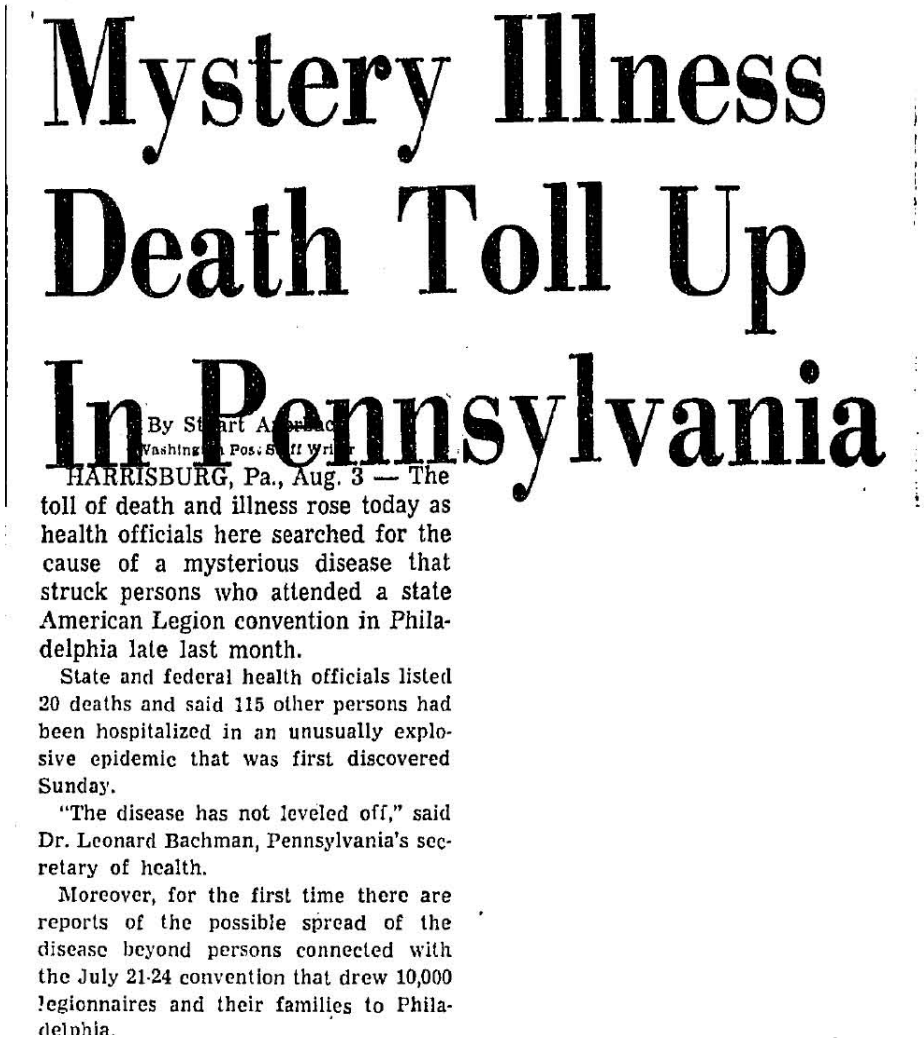
The mistake—estimated at 2 million doses by Public Health Service officials—was discovered last week by the Department of Health, Education and Welfare during routine checks on the vaccines being used in tests to determine the doses needed to provide protection.

"The company, Parke-Davis, has since changed strains and has significantly increased its production," Dr. Theodore Cooper, HEW's assistant secretary for health, said yesterday.

"Although the company's output has increased," he

Legionnaire's Reignites Fears

- Epidemiologist letter to NYT warns of side effects that will occur after vaccine and merely by coincidence: 2300 strokes, 7000 MIs, 45 encephalitis cases, 9000 pneumonia
- August 1- *serendipity*- Legionnaire's outbreak, initially thought Swine flu, reinvigorates program and Congressional concern
- 8/12 indemnification signed by President



Mystery Illness Death Toll Up In Pennsylvania

By St[illegible] Washing[illegible] Post Staff Writer

HARRISBURG, Pa., Aug. 3 — The toll of death and illness rose today as health officials here searched for the cause of a mysterious disease that struck persons who attended a state American Legion convention in Philadelphia late last month.

State and federal health officials listed 20 deaths and said 115 other persons had been hospitalized in an unusually explosive epidemic that was first discovered Sunday.

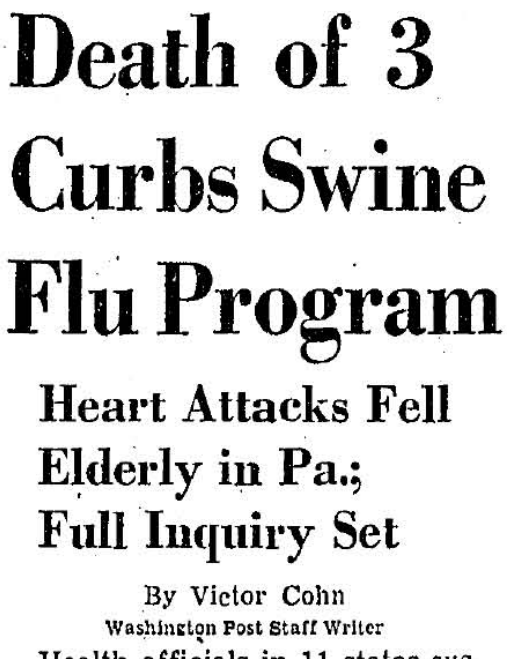
"The disease has not leveled off," said Dr. Leonard Bachman, Pennsylvania's secretary of health.

Moreover, for the first time there are reports of the possible spread of the disease beyond persons connected with the July 21-24 convention that drew 10,000 legionnaires and their families to Philadelphia.

Vaccination Begins: 10/1/76

Trouble comes fast- media right there with it

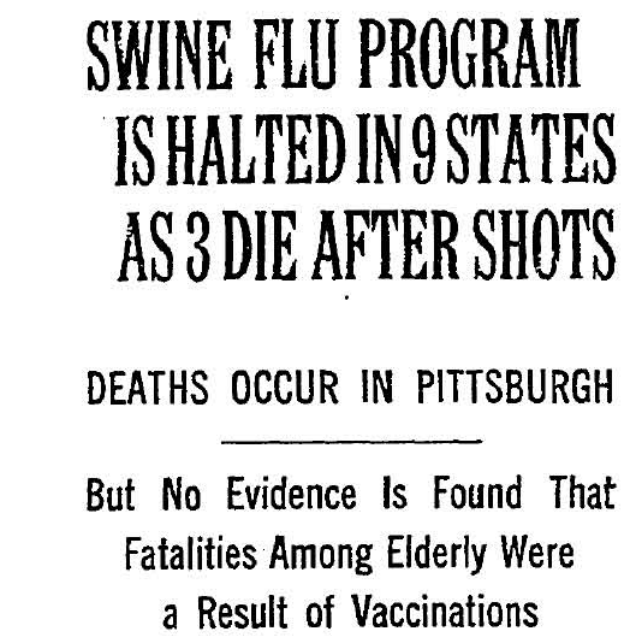
- **10/11: 3 elderly people die suddenly after immunization at a clinic in Pittsburgh: coroner Cyril Wecht *"bad vaccine definitely a possibility"***
- **10/14: NY Post: *"Scene at Pennsylvania Death Clinic".***



Death of 3 Curbs Swine Flu Program

Heart Attacks Fell Elderly in Pa.; Full Inquiry Set

By Victor Cohn
Washington Post Staff Writer



SWINE FLU PROGRAM IS HALTED IN 9 STATES AS 3 DIE AFTER SHOTS

DEATHS OCCUR IN PITTSBURGH

But No Evidence Is Found That Fatalities Among Elderly Were a Result of Vaccinations

The Final Blow: GBS

- 11/21: First GBS case, then clusters, no good background rates
- Mid-December – 40 million immunized, lower than expectations, clusters of GBS – ? 2-8 fold increase, (ultimately perhaps 10-fold in 2-3 week window)

4 Fatalities Among 51 Paralyzed After Vaccination

By Victor Cohn
Washington Post Staff Writer

The government ordered a halt of at least a month in the nation's troubled swine flu vaccination program yesterday because of 51 cases of paralysis—four fatal—in persons who got the shots.

The 51 were residents of 14 states, including Virginia and Maryland, surveyed by health officers so far. Study in other states is continuing.

The 51 came down with a rare paralytic disease called Guillain-Barre syndrome—also known as "French polio" because it was discovered by French scientists and is often confused with polio. The disorder is also called "ascending paralysis" because it tends to creep up the body. It sometimes reaches the lungs, where it can be fatal.

The temporary suspension of the flu shots was ordered by Dr. Theodore Cooper, assistant secretary of health, education and welfare, after two days of emergency meetings at the federal Center for Disease Control in Atlanta. The CDC said 34.9 million Americans had received swine flu shots through Dec. 4.

Cooper called the suspension "a prudent step" in a situation where "we have not proven any association" between the shots and the paralysis, "but we are not able with available data to rule out" any relationship.

All the vaccinated persons who got the paralytic disease did so sometime between one and three weeks after being vaccinated, he said.

Though both Cooper and CDC officials emphasized that no link between the disease and the shots has been proved, more than half the 94 known Guillain-Barre cases in the 14 states had been vaccinated. This is the kind of association that alarms health officers until they can learn more.

In answer to reporters' questions at a news conference yesterday afternoon, Cooper denied that the vaccine program's latest problem would kill

See FLU, A26, Col. 1

No flu but GBS = The End

- 12/16: Campaign stopped
- Ultimate legal claims $3.5 billion, awards ~ $ 90 million

Observations: Policy and Politics

- Good people doing the right thing for public health but –
- Tendency for herd mentality and for once a policy is arrived at, coalescence around it
  - Failure to weigh contrary data/hypotheses e.g. lack of additional cases over time, low virulence in most cases (most infections apparently asymptomatic, ~1/>500 death rate)
- Alternate options too easily rejected Communication of risk as all or none – loss of trust
- High level political involvement can help or hurt – use wisely or not at all
- Full diversity of opinion not always encouraged or heard
- Dissidents – always will be, important to bring out dissent earlier rather than later

Safety Reporting and Analysis

- **The detection of GBS was actually another serendipity**
  - **The reporting physician in MN had heard a audiotape saying flu vaccine does not cause GBS, he thought it said it did and reported his case**
- **Still unclear extent of increase and why not observed in military**
- **No clear association with a specific vaccine**
- **First use of CDC computing in field epidemiology investigation**

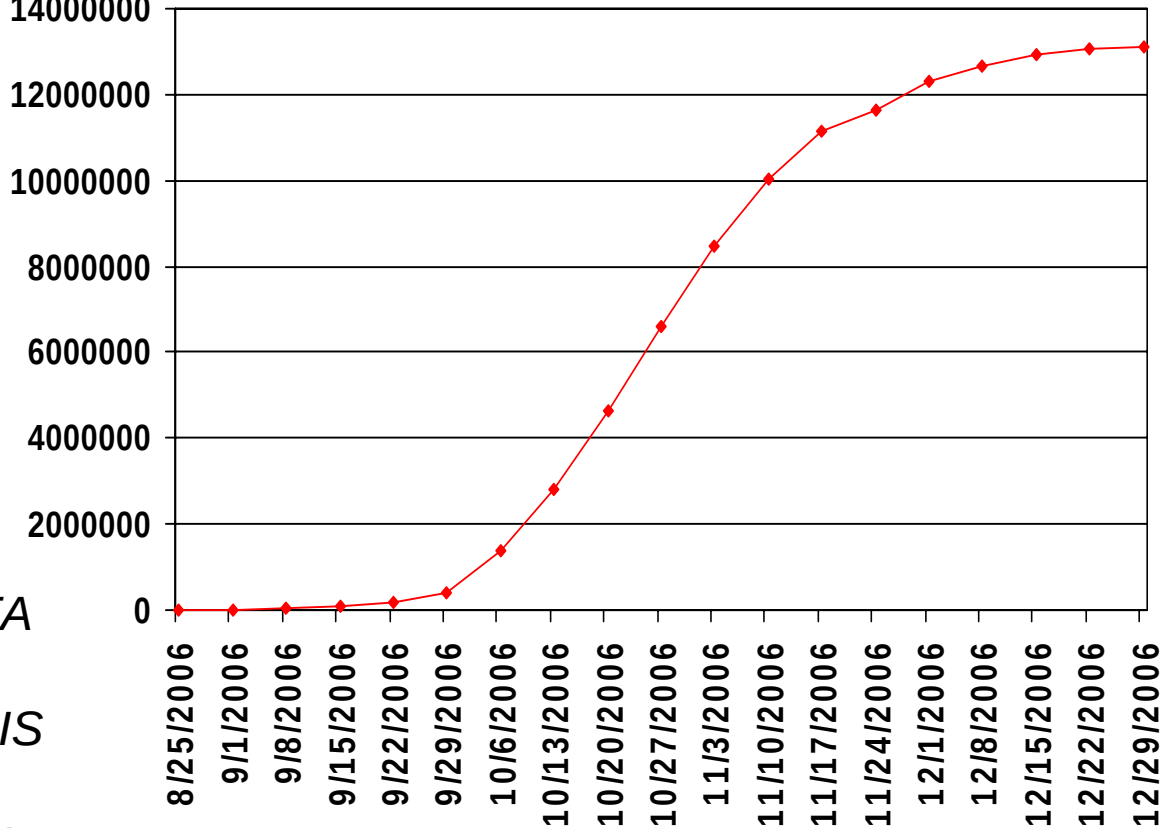
Communication

- In general experts communicated in balanced manner but policy did not always follow
- Difficulty and failure to explain/understand epidemiology and coincidence/causality issues
- Certainty of pandemic and of severe disease amplified as issue rose from scientists to President – where were controls?
- Once decision made, media interest, emphasis dissent and early AEs.
- Many interpreted flu campaign as politically motivated

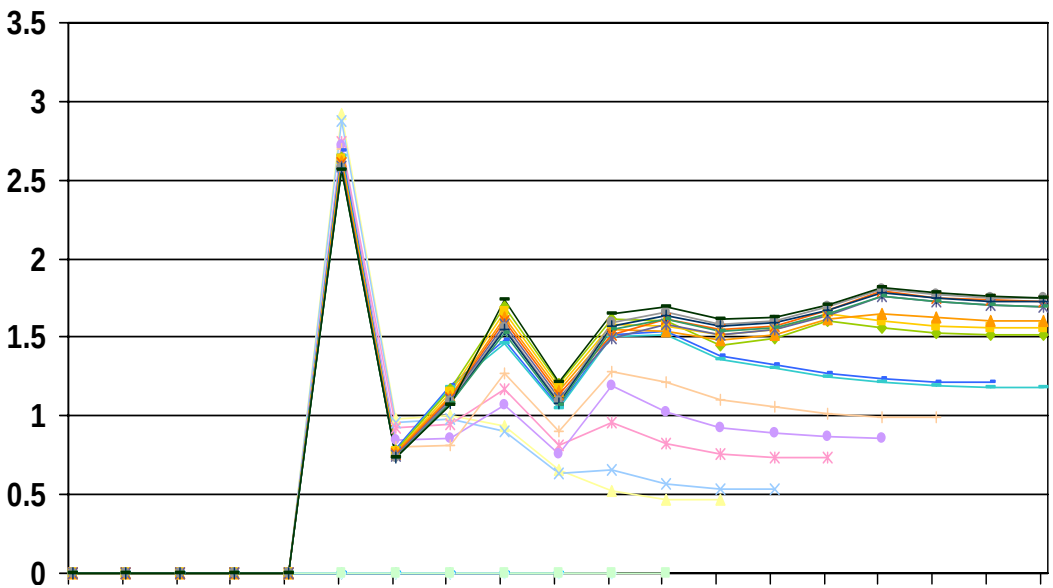
Five Major Lessons

- Lesson 1: Expect the unexpected, including from vaccine(s) and their manufacturing
- Lesson 2: Actions and short-cuts that may be appropriate/needed in an emerging crisis or actual emergency may not be appropriate prior to one
- Lesson 3: Unexpected adverse events will occur, whether coincidental or vaccine related – need background rates and surveillance systems in place
- Lesson 4: Clear communication re: all uncertainties of benefits/risks critical
  - *Includes balanced communication of uncertain risk of pandemic and uncertainties about safety*
- Lesson 5: Success is possible

FDA/CBER DATA USING CMS – RAPID ANALYSIS OF GBS AND SEASONAL FLU VACCINE - 2006



DOSES



GBS rates

Novel Vaccines: Theoretical Concerns

- Adjuvants - potent and potentially antigen nonspecific immune stimulation
  - Generally increased reactogenicity
    - Unclear if any risk of correlation with rare SAEs
  - Is there a potential for increased autoimmunity?
  - Is there a potential for effects on developing immune systems?
  - *No current evidence of these problems with compounds being most actively considered, one with broad experience in elderly*
  - *Unclear if whole cell and recombinant vaccines may raise such issues – not to date – but same general issue of limited experience/database size*

Detecting Rare Adverse Events: some simple math

- Even impractically large trials will often fail to confirm small increases in events which may be significant when applied to a large population
- Examples:
  - Confirming an increase in an event from ~1/10,000 to 2/10,000 would need ~ 314,000 subjects yet this difference could result in >300 SAEs in a birth cohort of > 3 million
  - Magnify that population to that of a country or region of 60 million and there could be 6000 such events
    - ***Low compared to a 1 % death rate from a pandemic, or 600,000 in 60 million – but what if no pandemic, or a lower death rate?***

Rare Serious Events; cont.

- This problem could be even more challenging if an adverse event is more common, poorly defined or not temporally related.
  - e.g. 768 baseline deaths/100,000 age <1. To detect an increase in to 798/100,000 (or >1200 attributable deaths/US birth cohort); might need 2.6 million subjects
- Temporal clustering expected in most vaccine related AEs, which can be quite helpful in increasing power and allowing other analytic approaches
- Difficulties greater post-approval if no control group and often limited baseline rates for most events in most geographic areas
- And, as mentioned, with mass vaccination - event clusters will occur

Prepandemic targeted roll-out approaches?

- Should we consider stepwise targeted approaches with potential health benefits while developing broader vaccine experience and safety and effectiveness data, especially for novel products?
  - One approach could be to initially vaccinate in strata based on potential exposure risk (thus vaccinating first those more likely to ever have a potential benefit), accumulating data as the number immunized increases

Pre-pandemic Immunization: Potential Tiered Goals

- Protect critical infrastructure
- Protect critical infrastructure and health care providers/workers (or where avian flu, potentially exposed individuals – also could reduce risk of viral adaptation)
- Protect general public

Targeting and stepwise data acquisition? Theoretical approach in area of avian flu

- Presume experience at time of approval (e.g. indicated in pandemic and/or for at risk individuals) ~ 5×10^3
  - » A risk of $1/10^2$ or more unlikely to have been missed
- Step 1: Consider offer to ~ 5×10^4 at potential exposure risk, e.g. poultry workers/handlers of backyard poultry in area(s) of outbreaks, laboratorians, possible next tier.
  - » Ideally - field RCT - Perform simple monitoring (e.g. cell phone or PH worker at 1, 12 months) for unexpected major SAEs – need infrastructure and $
- Step 2: Broaden to 5×10^5 in tier and/or next tier(s)
  - » E.g. public health, critical infrastructure, HCWs in/traveling to areas
- Step 3: If no signal, consider broaden use e.g. to all in or potentially traveling/deployed to areas of avian infection
- Step 4: With ~10^6 experience, if H5 threat continues, consider voluntary population-wide availability

Targeting and stepwise data acquisition in non-endemic area (e.g. US)?

- Similar to previous but no tier of individuals with current ongoing risk of exposure to virus from poultry
- Step 1: RCT with ~ 5 x 10^4 volunteers – critical infrastructure, first responders, front line HCWs, travelers w/significant potential for poultry contact in endemic area
- Step 2: Broaden experience to 5 x 10^5 - e.g. could include interested US public health, safety, HCWs, additional individuals working/traveling in affected areas
- Step 3: If no signals, and H5 still endemic in multiple regions, consider broadened use on voluntary basis
- Step 4: With ~10^6 experience (likely needed to detect 1976 order increase in GBS), and if H5 threat continues, or future threat, consider voluntary population-wide availability separate or related to seasonal immunization

Risk based pandemic preparedness –a scientific and capacity building process?

- Such approaches not only may help protect individuals and populations but would provide data for more accurate risk/benefit assessment in considering broad prepandemic use. In addition, such approaches could support and test national and regional infrastructures and capacity needed for pandemic preparedness (e.g. manufacturing, delivery, AE surveillance).
- In thinking about any vaccine use – also consider and reconsider in light of emerging epidemiologic data and data about strains, especially as predictive science improves
- New technologies and tools are likely to provide additional vaccine and non-vaccine approaches

Communications

- For any pandemic vaccines, and any use strategy, clear communication re: benefits/risks critical
  - Includes balanced communication of uncertain risk of pandemic (or of exposure) - vaccine benefit depends on it
  - Includes uncertainties re: vaccine safety and effectiveness
  - Recognize different audiences, cultures
  - National and individual respect and autonomy
  - Continuous reassessment of outcomes and strategy
- Safety concerns and expectations important and can affect, even derail, vaccination plans

Confidence in vaccines, governments, industry and public health systems will be on line

Your votes and input

- *Scenario 1*: novel adjuvanted vaccines are safe and immunogenic in trials including ~$10^{3\text{-}4}$ individuals. H5 threat continues globally as at present. Would you recommend, in the US:

  1 – no further immunization at this time

  2 – immunization of volunteers in groups such as critical infrastructure and HCWs, or travelers to areas with avian flu: a) as part of large field trial(s) or b) freely

  3- availability of vaccine to all adults interested a) as part of trial(s) or b) freely

- *Scenario 2*: as in scenario 1 but if safety data available on ~ 50,000 exposed individuals
- *Scenario 3*: same for other new H5 vaccines without novel adjuvants?

Your votes and input

- Related Question: In the current H5 situation, or similar future situations (e.g. pandemic threat strain circulating pathogenic to humans but not yet spreading in human populations), would you ever *recommend* routine immunization of the US population for pandemic risk strains?

  1 - never, unless there were clear evidence of more than sporadic human to human transmission

  2- once there is reliable safety experience with a closely related vaccine in large numbers of volunteers (e.g. ~10^6), I would recommend pandemic strain vaccine as:

    a) an added immunization for those interested or

    b) if feasible, incorporated into seasonal influenza vaccine

Thank you!

- The availability of cross-protective and/or priming H5 vaccines raise the potential for early or prepandemic use to blunt or prevent a pandemic
- These advances also may improve seasonal vaccines
- Safety of and confidence in vaccines are critical as ever
  - Transparency needed re: uncertainties in risk and benefit
  - Tiered, monitored approaches to use could help provide substantial additional experience and form basis for more widespread use

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