Challenges in Confronting Pandemic Influenza Using Novel Adjuvanted Vaccines
Pandemic Influenza

• Epidemiologic characteristics:
  • High attack rates across broad age ranges
  • Rapid geographic spread
  • Variable mortality (but low as many plagues go)
    • Extremes of age and pregnancy impose high risk
    • Fatal disease predominantly pulmonary
  • Short, explosive outbreaks in populous areas, that may recur in “waves”

• Virologic characteristics:
  • Causative viruses with which a large proportion of the human population then-living has no immunologic experience
  • Persons old enough to have experienced pandemic subtypes earlier in life often spared.
  • Pandemic viruses often (not always) displace older subtypes
Origin of Pandemic Influenza Viruses

- 16 HA subtypes and 9 NA subtypes harbored by aquatic birds
- 3 HA subtypes and 2 NA subtypes have become stably endemic in humans
- Known sources of pandemics include:
  - Direct invasion of an avian virus (1918),
  - Return of an old HA subtype by re-assortment when enough humans are susceptible (1957, 1968, now 2009)
Amplitude of the Pandemic Threat and Control Measures

- Mortality may be massive, but not all pandemics are horrific:
  - 1918 “Spanish” flu – 40 to 50 M deaths
  - 1957 “Asian” flu – 1 to 2 M deaths
  - 1968 “Hong Kong” flu – 1 M deaths
  - 1977 “Lab accident flu” – little excess mortality

- Our array of control measures is now greater:
  - Social distancing and non-pharmaceutical control measures were available in 1918, but better understood now
  - Anti-virals are new on the scene
    - Potential for rapid evolution of resistance
  - Vaccines
Waves of Pandemic Virus Transmission and Disease
UK, 1918-19

Mortality spikes in 30 of 50 largest US cities, influenza in France
Outbreaks at multiple US Army camps
Severe influenza in Haskell County KS

7 months

Tauenberger JK, Morens DM. Emerging Infect Dis 2006;12:15-22
Barry JM. J. Translat Med 2004; 2:3
The Promise of Vaccine for Pandemic Control

No intervention:
- Introduction at 14 US airports (one in every 2500 infected; $R_0 = 1.9$)
- 85 days to peak of epidemic
- ~ 4 M new cases per day at peak
- 43% attack rate

Or:
- Vaccination starts within 2 weeks
- 10 M doses / week
- Only 30% efficacy
- <10% attack rate

Germann et al. PNAS 2006;103:5935-40
The Vaccine Problem

- In 2009, world annual capacity for production of TIV was estimated by WHO at 876 M doses, up from about 350 M in 2006.\(^a\)
  - Assuming a monovalent at the same, single antigen dose as in TIV, that’s roughly 53 M doses per week – once it starts to become available
  - If the virus gives us 7 months from appearance to a major wave of disease as in 1918 (in 2009 it was more like 6), and
  - It takes about 3 months to get the first egg-derived doses out, and 4 months for significant quantities (and in fact it did in 2009), then
  - Vaccine production is sufficient to immunize only a small % of the population at risk in time to intervene in the major peak of the pandemic.
GSK’s Approach to Pandemic Vaccine: 2009

1. Enhance doses available by using an antigen-sparing tocopherol-based oil-in-water adjuvant system, AS03.

2. Using the same adjuvant strategy, seek to enhance cross-reactive immunity, thereby providing a basis for:
   a. Stockpiling in advance of a pandemic, or
   b. Pre-pandemic priming of select populations

Approach 2 remains to be tested; but approach 1 was tested in 2009.
The Threat We Prepared For:

• From 2003 to present, highly pathogenic H5N1 viruses have spread from SE Asia, causing damage to local poultry industries, directly and as a result of control measures.

• Fortunately, these viruses have remained extremely inefficient in human-to-human transmission.

• Since 2003 there have been 498 cases with 294 deaths (case fatality rate 59%) worldwide
  • 30 cases and 12 deaths in 2010, primarily in Egypt and Viet Nam, virtually all associated with direct contact with sick poultry*.

*WHO Avian influenza update 6 May 10
H5N1 Antigens and AS03

- GSK began clinical trials with AS03-adjuvanted H5N1 antigens in 2005.
- Marked antigen-sparing shown:
  - Strong HI responses at 3.8 μg HA exceeded those obtainable with 30 μg without adjuvant
  - Exceeded all reg. criteria for SCR, SPR, and fold-increase in HI titer.
  - Persistent antibody titers at 6 months.
- Essentially identical responses obtained with both GSK antigen manufacturing processes
- Antigen-sparing shown with multiple H5N1 representatives

A/VietNam/1194/04 HI Titers

H5N1/AS03\textsubscript{A} pandemic vaccine has shown a broad and persistent immune response

Two immunisations at day 1 and day 21 with H5N1 A/Vietnam/1194/04 split virus, AS03\textsubscript{A}

H5N1 Antigens and AS03

- Demonstration of both homologous and cross-clade serum neutralizing titers in humans (upper panel), and

- Homologous virus and cross-clade protection against mortality and virus replication in ferrets immunized with adjuvanted, but not unadjuvanted, vaccine (lower panel)

Sources: PLoS One 2008;3(1):e1401
Safety of AS03-adjuvanted H5N1 Vaccines

• > 16,000 subjects in clinical trials to date, some ongoing

• Short-term reactogenicity:
  • Increased frequency of local pain at the injection site relative to TIV or unadjuvanted H5 antigens,
  • Some increase in uncomplicated fever in young children in a limited experience.
  • > 95% compliance with 2nd dose

• Aside from reactogenicity as above, no alteration in overall profile of adverse events, medically-attended adverse events, or serious adverse events relative to TIV or placebo controls.
The Result of the H5N1 Efforts: GSK’s HxNx/AS03 Pandemic Influenza Vaccines

- Monovalent, vaccine strain recommended by WHO
- Std dose is 3.75µg HA administered twice, 21 days apart
- 10-dose Ag vial w/ thimerosal preservative
- 10-dose AS03 adjuvant vial
- Mixed prior to injection

EMEA approved GSK’s Dresden H5N1/AS03 vaccine May 2008 (for interpandemic use)

Also issued a “mock-up” authorization permitting rapid licensure of a similar vaccine w/ a new pandemic strain upon submission of technical & limited clinical data
And then Came Pandemic 2009

- Initial ARI outbreak late Feb.
- 17 April 09: CDC reports illness in 2 children with a novel swine origin virus.
- 23 April 09: ARI syndromes in Mexico, including deaths, with same virus confirmed.
- Subsequent course is explosive, although disease overall mild.
- The virus was not what we had been preparing for (because we had forgotten our history lessons).

Source: WHO H1N1 updates
A/California/07/09 H1N1v

A complex geneology

Gene Segments, Hosts, and Years of Introduction

A lineal descendant of the 1918 virus, without the human drift
Challenges of 2009-10

• A large and compressed clinical trials effort.
• Do the immunogenicity and safety lessons of H5N1 apply to A/California/07/09?
• Is the adjuvant still needed for an H1N1?
• Clarifying the regulatory pathways?
  • Fairly clear in the EU
  • Elsewhere – not so much.
• Can you adequately monitor safety of many million doses given in a matter of weeks to a few months?
  • Will safety prove limiting?
• Ferrets are nice, but will it work in the real world?
GSK Clinical Trials of A/California/7/09 Vaccines

• Complexity of the challenge increased by:
  • Two manufacturing sites with two different antigen manufacturing processes →
    • Pandemrix – Dresden site, Fluarix process
    • Arepanrix – Quebec site, Fluviral (FluLaval) process
  • Varying approaches and requests of multiple regulatory authorities
  • Need to examine adjuvanted and unadjuvanted vaccines to understand if the lessons of H5 carried forward.

• GSK clinical trials of A/California vaccines began approximately 3 months after receipt of the seed virus.

• To date, the GSK Clinical Trial Registry lists results from > 3,600 subjects in 16 trials of A/California/7/09 vaccines, spanning 6 months of age to the elderly.

• Almost 20,000 additional subjects remain on study in continuing RCTs and observational studies sponsored or supported by GSK.
Immunogenicity in Adults: with and without AS03

D-H1N1-007: HI results
after one and two doses in adults 18 years – 60 years
H1N1 3.75 μg HA + AS03A vs. H1N1 15 μg HA alone

All the data of the D-H1N1-007 study can be found on the ‘Clinical Study Register’ Available at: http://www.gsk-clinicalstudyregister.com/files/pdf/27783.pdf
Local Reactogenicity in Adults

D-H1N1-007: local reactogenicity after one and two doses in adults 18 years – 60 years

All the data of the D-H1N1-007 study can be found on the ‘Clinical Study Register’ Available at: http://www.gsk-clinicalstudyregister.com/files/pdf/27783.pdf
Systemic Reactogenicity in Adults

D-H1N1-007: general reactogenicity after one and two doses in adults 18 years – 60 years

Percentage (%)
Immunogenicity in Children, with and without AS03

Q-H1N1-003: HI response after one dose in children 6 months – 6 years

- 3.75 μg + AS03A (N=66) 386
- 1.9 μg + AS03A (N=59) 270
- 15 μg unadjuvanted (N=61) 138
- 7.5 μg unadjuvanted (N=62) 83

Seroconversion rate

www.gsk-clinicalstudyregister.com
Local Reactogenicity in Children

Q-H1N1-003: local reactogenicity after one dose in children 6 months – 6 years

A: 3.75 µg/AS03A
B: 1.9 µg/AS03B
C: 15 µg unadjuvanted
D: 7.5 µg unadjuvanted
Systemic Reactogenicity in Children

Q-H1N1-003: general reactogenicity after one dose in children 6 months – 6 years

*Fever in 30% after second adult dose (3.75 + AS03A), but no increase in half-dose group
Independent Confirmation of Immunogenicity, Safety in Children.

- 1.9 μg of HA + AS03B (half the adult dose) more immunogenic than whole-virion, cell culture-derived vaccine containing 7.5 μg of HA, both in two dose regimen.

- Some increase in local pain relative to unadjuvanted vaccine, but little severe.

- Some increase in fever after dose 2, but less prominent than in GSK’s studies.

Regulatory Pathways

- GSK had productive and efficient interactions with regulatory authorities throughout:
  - Interactions at least weekly throughout second half of 2009
  - Alignment on reagents, rapid e-mail submissions accepted.
- The existence of the EU mock-up authorization for Pandemrix (the product of GSK’s Dresden facility) facilitated European approval on 29 Sept 09.
- Authorization for sale of Arepanrix (the Quebec product) on 21 Oct 09, based on:
  - Prior review by BGTD of H5N1 safety and immunogenicity, and evolving Pandemrix data
  - Weekly follow-up of Arepanrix clinical trials data as they evolved.
- US regulatory guidance focused on unadjuvanted vaccine (although HHS did fund trials of adjuvanted vaccine)
  - IND studies began in October
  - GSK’s strain change supplement for unadjuvanted vaccine accepted 10 November.
- All authorities collaborated with GSK in the iterative revision of labeling as clinical trials data accumulate.
Exposures to GSK H1N1\textsubscript{v} AS03-containing vaccines in mass vaccination (as of 19 May 2010)

- It is our understanding that GSK’s H1N1\textsubscript{v} AS03 vaccines have been administered in 57 countries.
- The total number of doses distributed cumulatively:
  - for Pandemrix (D-Pan), 147 million doses
  - for Arepanrix (Q-Pan), the total number delivered is 148 million doses
- Current estimates are that:
  - at least an estimated 89 million doses have been administered
  - at least 4.3 million doses to children and
  - at least 430,000 doses in pregnant women have been administered

\textsuperscript{1} GSK's estimate compiled with data from local affiliates
the figures presented here have been estimated based on GSK data on file, and data provided by national health authorities
Pharmacovigilance Reports: Arepanrix

- Public Health Agency of Canada Vaccine Surveillance Report of 27 April 2010*
  - 25.1 M doses of 3 H1N1 vaccines distributed, great majority Arepanrix
  - 25.9 adverse events, including 1.1 serious adverse events per 100K doses distributed.
  - Overall rate of AEs increased relative to prior seasonal campaigns, but not serious AEs (avg. 1 per 100K doses distributed in prior seasons).
  - Rate of anaphylaxis = 0.53 per 100K doses distributed; “does not exceed the normal range observed after receiving any vaccine.”
  - “Concerns about GBS have not emerged.”
  - “No safety concerns regarding H1N1 vaccines given to pregnant women have been identified….”
  - Preliminary analyses of independent pediatric data from PHAC Influenza Research Network trial do not show increased reactogenicity, including fever, after a second dose.

* http://www.phac.aspc.gc.ca/alert-alerte/h1n1/vacc/addeve-eng.php
Pharmacovigilance Reports: Pandemrix

• EMA 18th pandemic pharmacovigilance update – 20 May 2010*
  • At least 131.7 M doses distributed in EEA, ≥ 30.6 M persons vaccinated
  • 10,963 reports: 8.32 per 100 K doses distributed
  • “The benefit-risk balance of the centrally authorized pandemic vaccines and anti-virals for the current H1N1 influenza pandemic continues to be positive.”
  • Prior updates analyzed, and found no evidence for excess incidence or vaccine causation of:
    • Anaphylaxis
    • GBS or other demyelinating disorders
    • ITP or autoimmune thrombocytopenia
  • Conclusions unchanged at most recent update.

*EMA/326582/2010
Is There Evidence that It Worked?

- At this point, there are no RCT data concerning efficacy.
- GSK has ongoing RCTs in adults and children to assess relative efficacy of adjuvanted and unadjuvanted vaccines.
- Multiple effectiveness studies, using various methods, are now in analysis. Wichmann, *et al* report the first of these:

* Eurosurveillance 2010; 15(18) pii=19561
Challenges of 2009-10

• Do the immunogenicity and safety lessons of H5N1 apply to A/California/07/09?
  • The lessons of H5N1 were helpful.
  • Only 1 dose needed, but AS03 remains 4 to 8-fold dose-sparing. Responses strong in young children, adults and elders (not shown).
  • Reactogenicity is increased, but tolerable
    • Fever may be a concern in a two-dose regimen in children -TBD
    • No other salient findings in RCTs to date.

• An unprecedented clinical trials effort.
  • Well, yes.

• Is the adjuvant still needed for an H1N1?
  • It is clearly possible to immunize with 15 μg or even 7.5 μg of plain A/California/7/09 HA, but
  • Antibody titers (and CD4+ T cell responses) are greater and more rapid with adjuvant.
  • Using AS03 has allowed GSK to distribute an >250 million doses of adjuvanted pandemic H1N1 vaccine.
Challenges of 2009-10

• Clarifying the regulatory pathways?
  • The European Core Dossier (mock-up file) approach worked pretty well; a pre-existing plan clearly helped.
  • Canadian regulators likewise leveraged prior review of a “rolling NDS” for H5N1 pandemic vaccine
  • All regulators worked hard with sponsors to find paths forward, to adjust labeling on the fly as data became available, and to address product issues in real time.

• Can you adequately monitor safety of many million doses given in a matter of weeks to a few months?
  • Yes, using a (large) dedicated team
  • Pharmacovigilance results to date show no limiting safety issues with AS03-adjuvanted pandemic vaccines.

• Ferrets are nice, but will it work in the real world?
  • Preliminary results say yes – much more to come.
Other Lessons:

• We were too late, but not by much, and not everywhere.
• What were the other lessons to take away for next time?
  • Continued enhancements in surveillance are key.
  • SRID reagents remain on the critical path – new methods of quantitation could save a month.
  • Once antigen production is ramped up, fill and finish was a bottleneck.
  • Matching supply to demand through dozens of rapidly evolving contracts with numerous governments was inefficient.