Pandemic Influenza Vaccines

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Influenza pandemic vaccines

Take home messages

- Public health vision: equitable and timely access to pandemic vaccine
- Pandemic vaccine production: race against time
- Global production capacity is limited to seasonal vaccine demand; surge capacities are limited
- Estimates are difficult on how much pandemic vaccine is exactly available at which stage of the pandemic but:
  - In the short- and mid-term, vaccines will only be available to a small minority of countries and their population
    - Solutions exist to somewhat shorten (not close) the gap but in the short and mid-term they are unlikely to change in-equitable access
    - Breakthrough unlikely without new vaccines and immunization approaches
Pandemic vaccine availability

History in the US

- **1957**
  - 48 million doses available 6 month after emergence when first wave peaked in the US (was not enough)

- **1968**
  - Epidemic peaked in the US 5 month after emergence of strain
  - Vaccine production began 2 month after strain emerged
  - Only 20 million doses available during peak of epidemic.

Influenza Pandemic Vaccines

Vision

- Timely and equitable access to safe and effective influenza pandemic vaccines

Production capacity
Influenza pandemic vaccines

Seasonal vaccine production

- **Tri-valent**
  - 15 micrograms of HA → 13.5 kilogram
  - Surrogates of protection: seroconversion (HI-T or NT)

- **Egg-based**
  - Cell Culture vaccines coming: Solvay; Baxter; Chiron; Sanofi...

- **Split or subunit**
  - Whole virus only in China; some "residual" licenses in Europe

- **Inactivated**
  - Live-attenuated: Russia and USA

- **Adjuvants:** MF59 (Chiron)
Timely and equitable access to safe and effective influenza pandemic vaccines

- Production and surge capacity
  - Early initiation of vaccine production
    - Delivery
      - As much as possible
      - As quickly as possible
  - Production capacity
    - Safety
    - Immunogenicity
    - Efficacy/Effectiveness
  - Timely availability

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Global Vaccine Production Schedule

-40 -30 -25 -5 February +10 +20 +30 +40 +50 weeks

Order of female chicks
Breading of pullets
First irregular eggs
Egg production
Seed lots
-2 +3
Trivalent vaccine production
+12 Filling
+14 Product ready for shipment
+15 On-line release of AFSSAPS
Registration file
Clinical study
Vaccination
Product launch date

approx 8-9 months to produce 300 mio doses of trivalent vaccine

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Timely availability

Expected scenario today

Pandemic strain emerges

Arrives on all continents

0 1 2 3 4 5 6

Detection of outbreak; isolation; shipment to WHO lab
Development of prototype strain by WHO CCs
Master/production seed; standardizing
Vaccine production
Preclinical and clinical trials; submission of files...

Timely availability
Influenza pandemic vaccines

Timely availability

- Expected scenario today

- Pandemic strain emerges
- Arrives on all continents

Detection of outbreak; isolation; shipment to WHO lab
Development of prototype strain by WHO CCs
Master/production seed, standardizing
Vaccine production
Arrives on all continents
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Timely availability

- Expected scenario today → emerging of variant pandemic virus due to beginning Ag-drift
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- Timely and equitable access to safe and effective influenza pandemic vaccines

**Vision**

- Production and surge capacity
- Early initiation of vaccine production
- Vaccine formulation
- Safety
- Immunogenicity
- Efficacy/Effectiveness
- Delivery
- Amount

**As much as possible**

**As quickly as possible**
Influenza pandemic vaccines

- How much is going to be available: difficult estimate
  - Uncertainty about begin of full scale vaccine production by individual manufacturers
  - Production capacity of seasonal influenza vaccines
    - Localized/few companies
Influenza pandemic vaccines

- Seasonal influenza vaccine consumption and production localized; relatively few companies

Doses distributed/1000:
- 299 to 350 (1)
- 250 to 299 (1)
- 201 to 250 (2)
- 152 to 201 (9)
- 103 to 152 (12)
- 54 to 103 (8)
- 5 to 54 (18)

IVS Task Force, IFPMA 2003
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Amount

- How much is going to be available: difficult estimate
  - Timing of access to emerging pandemic virus?
  - Uncertainty about begin of full scale vaccine production by individual manufacturers
  - Production capacity of seasonal influenza vaccines
    - Localized/few companies → global access when shortage during crisis?
    - Limited to around 300-400 million doses seasonal vaccine (2008 → 580 million)
    - Drivers for increase: up-take (developed/developing countries)
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Amount

- How much is going to be available: difficult estimate
  - Timing of access to emerging pandemic virus?
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    - Limited to around 300-400 million doses seasonal vaccine (2008 → 580 million)
    - Drivers for increase?
  - Surge capacity and yield?
    - Little for egg based production → currently no alternative; Yield low
  - Pandemic vaccine formulation (Ag content)?
    - Dose finding trials needed
      » Ag-sparing necessary because of limited production capacity
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Dose finding - Antigen sparing

- Timely and equitable access to safe and effective influenza pandemic vaccines

Production and surge capacity

- Delivery
  - Early initiation of vaccine production
- Vaccine formulation
- Safety
- Immunogenicity
- Efficacy/Effectiveness

As much as possible
As quickly as possible

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Seasonal vaccine production

- Current status
  - 300 mio
  - 900 mio

→ Smart vaccine composition
  - H5? Reduce antigen content (antigen sparing) + adjuvant
  - 2001: Proof of concept with viruses of highest pandemic potential
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Dose finding – Antigen sparing

- 2005: Several companies began clinical trials; partially funded (directly or indirectly) by national authorities (e.g. Japan, Australia, US)

- 13 companies; 28 different clinical trials
  - 2 Mock-up files with EMEA (H2N2; H9N2); 3 trials finished PII; 2 trials finished Q3/06; 13 trials finished 06
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Dose finding – Antigen sparing

- Summary results from 3 finished trials – several surprises...
  - H5N1 vaccine feasible
    - 90 microgram, subunit, 2 doses, w/o adjuvant
    - 30 microgram, whole virion, one dose, Alum (international verification)
  - Antigen sparing formulation not yet found with H5N1 (CHMP criteria missed)
    - Alum at 7.5 and 15 microgram did not work (subunit, 2 doses)
  - Comparability of results: HI test weaknesses
    - Extrapolation of efficacy of formulation with one subtype/even variant virus to another does not work

Further delays in dose finding studies → more research needed

1. Correlates of protection
2. new adjuvants
3. whole virion
4. immunogenicity and growth of variant viruses

This research will ensure that some at least some vaccine will be available but will NOT open up new sources!
Influenza Pandemic Vaccines

Vision and options to reach it

- Timely and equitable access to safe and effective influenza pandemic vaccines

Strategic options to shorten pandemic vaccine gap

- Develop antigen sparing strategies + improved production processes
- Develop new vaccines and delivery systems
- Increase production capacity according to needs
- Increase surge capacity
- Ensure rapid begin of vaccine production
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Expected scenario

If 15mg: 3.75 million doses per day realistic

Virus detection; isolation; characterization
Vaccine prototype development and testing
Seed virus; standardizing reagents

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