



Development of Influenza Pandemic Vaccines: The Industry Perspective

L. Hessel, A. Palache, A. Colegate

Influenza Vaccine Supply International Task Force

WHO Global Vaccine Research Forum

Montreux, 9 June 2004



- The 1918 pandemic killed 50-100 million people, 2.5% to 5% of the world's population
- A 1918-like pandemic today could kill 150-300 million people
- In the early 1980s, an avian influenza virus killed ~20% of the seal population along the North Atlantic coast
- Avian (H5N1) influenza in humans killed 33% (1997) to > 50% (2004) of those infected



- Burden of disease
 - attack rates are especially high in children and working adults
 - > 50% of deaths occur in persons < 65 years in age
- Influenza vaccination
 - clinically effective and cost-effective in all age groups
- Target population for pandemic vaccination
 - all age groups

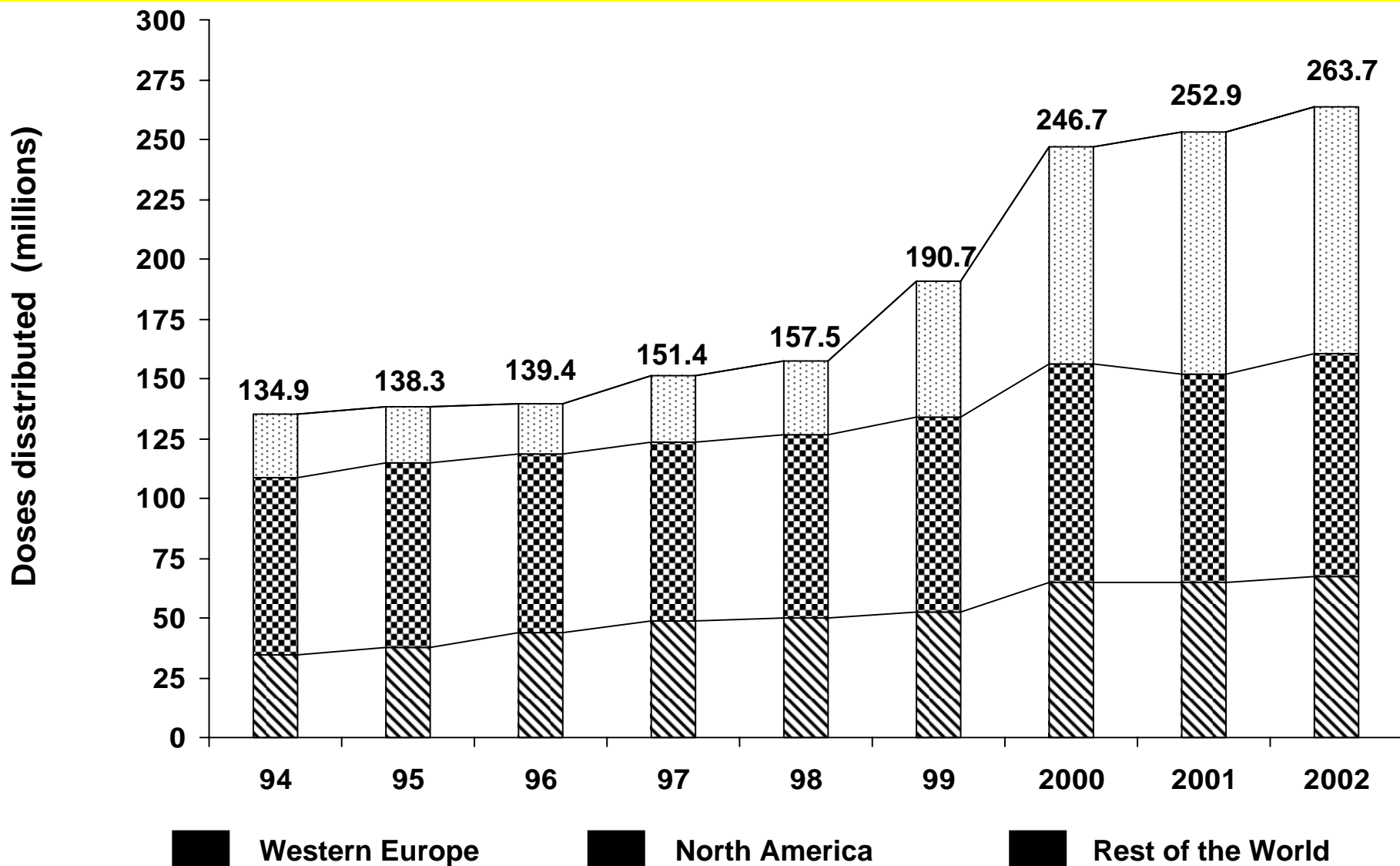


- Vaccines are the single most important intervention for preventing influenza-associated morbidity and mortality during both seasonal epidemics and pandemics
- An influenza pandemic is one of the few disease events in which all populations will be fully susceptible to infection
- Current manufacturing capacity is sufficient to cover less than 5% of the world's population
- Global vaccine supplies will almost certainly remain inadequate throughout the first wave of infection. Their availability for subsequent waves should be greatly beneficial



Country Cluster	Total Doses Distributed		
	2000	2001	2002
Western Europe	62,653,982	68,376,595	73,084,243
Central & Eastern Europe	28,919,036	31,594,057	30,401,188
Western Pacific	25,933,440	35,032,477	38,783,459
Southeast Asia	61,648	47,644	46,057
Eastern Mediterranean	1,256,385	1,193,639	1,304,930
North Africa	320,000	710,000	511,000
Latin America (NH)	1,875,689	2,755,083	3,328,910
Canada	11,900,000	10,600,000	9,700,000
United States	68,000,000	78,345,000	82,705,000
Total (NH)	200,920,150	228,654,495	239,864,837
Southern Hemisphere	not available	29,894,187	28,824,368
Global total	-----	258,548,682	268,689,205

For the three years 2000, 2001 and 2002, vaccine distribution data for Central and Eastern Europe include doses produced in Russia (16,400,000; 19,300,000; and 18,100,000) and Hungary (1,120,000; 1,300,000; and 1,300,000). For the Western Pacific, the data include doses produced in Japan (12,491,426; 17,439,978; and 20,801,526). All doses produced in these countries were distributed domestically.





- **Total Production (trivalent) vaccine: 292 million doses**
 - 207 million (71%): Canada, USA, Western Europe, Australasia, Japan
 - 85 million (29%) Rest of World (Argentina, Brazil, Chile, Uruguay, Hungary, Poland, Russia, S.Korea)
- **Influenza Vaccine Producing Countries:**
 - Australia, Canada, USA, Japan, France, Germany, Italy, Netherlands, England
 - 12% of world population; 95% global vaccine production
- **Production capacity European countries: 190 million doses (65%)**
 - 78.5 million doses used outside USA, Western Europe, Canada, Australasia, Japan
 - 97% of these doses are produced in Europe
- **ISSUE:** Most countries of the world depend on European Vaccine Manufacturers for (pandemic) influenza vaccine supply



World Health Assembly Resolution on Influenza, May 2003

- Urges Member States to give "particular attention to the need to ensure adequate supplies of vaccine ... as outlined in the Global agenda on influenza ..."
- Requests the Director-General to search "for solutions to reduce the Global shortage of, and inequitable access to influenza vaccines ... and to make them more affordable, both for epidemic and global pandemic situations."



- Available global trivalent vaccine production capacity (2003):
300 million trivalent (15 mcgr HA/ Strain)
- Pandemic vaccination scenario's (monovalent vaccine):
 - 1* 15 mcgr HA / dose: 900 million
 - 2* 15 mcgr HA / dose: 450 million
 - 1* 45 mcgrHA / dose: 300 million
 - (2* 45 mcgrHA /dose: 150 million)
 - 2* 5 mcgrHA / dose: 1.35 billion



- Aim to develop pandemic vaccines with optimal balance between protective efficacy and vaccine supply (WHO, 2004)
 - High vaccine dose strategy compromises pandemic vaccine supply
 - Low-vaccine dose (adjuvanted) strategy optimizes pandemic vaccine supply
- Research to find optimal vaccination strategy is key for pandemic preparedness
- Increase inter-pandemic influenza vaccine usage to optimize pandemic vaccine supply (WHO, 2002, 2004)



Industrial constraints and risks

- Need to anticipate & to invest
- Technological challenges
- Regulatory constraints
- Production timelines
- Interference with production of interpandemic vaccines
- Risk of producing vaccines that would not be used
- Liability ...

Economic incentives / Technical support / Risk - sharing agreements



Key Issues

- **Clinical development and regulatory process**
 - Need for a consolidated approach (USA, EU, ROW)
 - Technical support (scientific and regulatory)
 - Financial incentives (R&D)
- **Intellectual property rights for reverse genetics**
 - OK for clinical development
 - Potential issues regarding the production of pandemic vaccines
- **GMO classification of the pandemic vaccine strain (EU)**
- **« prototype » vs. « actual » pandemic vaccines**



Two guidance documents issued by EMEA in April 2004

- Note for guidance on dossier structure and content of marketing authorisation for pandemic influenza vaccines

Scientific guidance

- Guideline on submission of marketing authorisation applications for pandemic influenza vaccines via the centralised procedure

Procedural guidance



- Principle of a « mock-up » prototype vaccine:
 - Clinical data from interpandemic vaccine cannot be extrapolated to pandemic situation
 - A variation from an interpandemic vaccine into a pandemic vaccine (1-strain, likely different antigen content and adjuvanted, possibly preserved and different dosing schedule) not scientifically justifiable
 - A « mock-up » prototype vaccine is developed during inter-pandemic period that include viral antigen(s) to which humans are immunologically naïve (e.g. H5N1)
 - The « mock-up » vaccine, using the production process and final formulation of the future pandemic is submitted for registration



- **Core pandemic “mock-up” vaccine dossier**
 - Quality, Safety and Efficacy data for “mock-up” generated
 - The « mock-up » vaccine registration file, using the production process and final formulation of the future pandemic vaccine is be submitted and authorised during the interpandemic period (centralised procedure)
- **Pandemic variation**
 - Includes only quality data related to the pandemic influenza strain
 - Commitment to gather clinical information during pandemic
 - Fast track approval (Art. 8 of Regulation (EC) 1085/2003)



- A step-wise approach

1. Selection of the formulation(s): dose-range, schedule(s)

2. Study in healthy adults and elderly: immunogenicity criteria

3. Additional studies:

- Booster 6- 12 months (dossier submission without those results)

- Specific to each vaccine

- Children

4. Post-marketing surveillance



1. Dose-range/formulation/schedule (research for optimal vaccination strategy)

- various dosages (at least 3)
- with / without adjuvant
- Age 18-40; naive
- + 30 per group
- 2 doses 3 weeks apart
- optimal balance immunogenicity / maximal supply needed when selecting formulation



2. Safety and immunogenicity in healthy adults and elderly (core-registration dossier)

- Using selected dose/schedule
- at least 300 (1% frequency, AE), + 18y, naïve
- 18-59 and elderly analysed separately
- booster dose at 6 and 12 months



Safety:

- 6 months follow-up (dose 2)
- Where emergency: dossier submission before month 6

Immunogenicity criteria:

- CPMP criteria
- Nt: no correlation with protection established
- SRH/HAI, Nt: per dose / formulation group, per age
- Primary immunogenicity = day 42
- Secondary immunogenicity = day 21, month 6 and 12



-
- Pandemic preparedness is not only important but also urgent
 - Pandemic vaccine development is urgent and should be strategically focused
 - Pandemic vaccination strategies should strive for an optimal balance between protective efficacy and vaccine supply capabilities
 - Vaccine industry is committed to develop pandemic vaccines
 - Dose / formulation finding studies and registration studies for pandemic vaccines by industry must be financially and technically supported by the public sector
 - Administrative issues such as Intellectual P
 - roperties, national GMO regulations, global registration requirements and vaccine injury compensation should be resolved by international collaboration and coordination



-
- The European EMEA guidelines for licensing pandemic vaccine provide clear and concrete direction for vaccine manufacturers who want to develop pandemic vaccines and might serve as an example for other regulatory agencies
 - Many countries of the world will rely on European manufactured pandemic vaccine, at least in the short term future