Current Status of

Development and Evaluation of

Vero Cell-Derived Vaccines

Otfried Kistner

The First WHO Integrated Meeting on development and clinical trials of influenza vaccines that induce broadly protective and long-lasting immune responses

January 24 - 26, 2013, Hong Kong SAR, China

Disclaimer

The following information and data has been presented at the "The First WHO Integrated Meeting on development and clinical trials of influenza vaccines that induce broadly protective and long-lasting immune responses"

in Hong Kong SAR, China on January 24 - 26, 2013

and reflects Baxter's then available knowledge.

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Overview

- Vero Cell Technology Platform
- Pandemic Vaccine Program: H5N1, H1N1pdm09, H9N2
- Seasonal Vaccine PREFLUCEL
- Summary & Conclusions
- References

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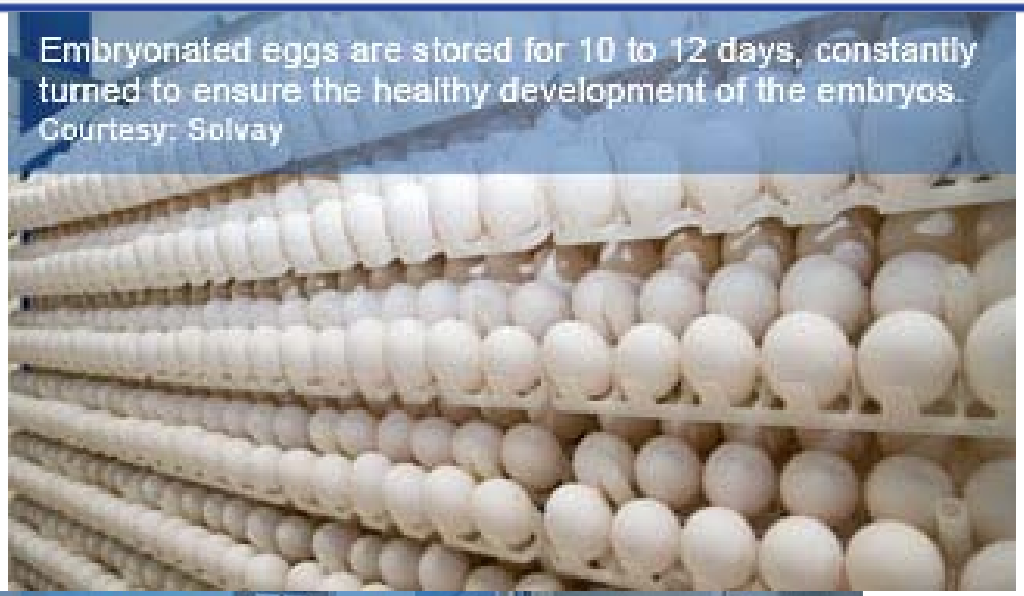
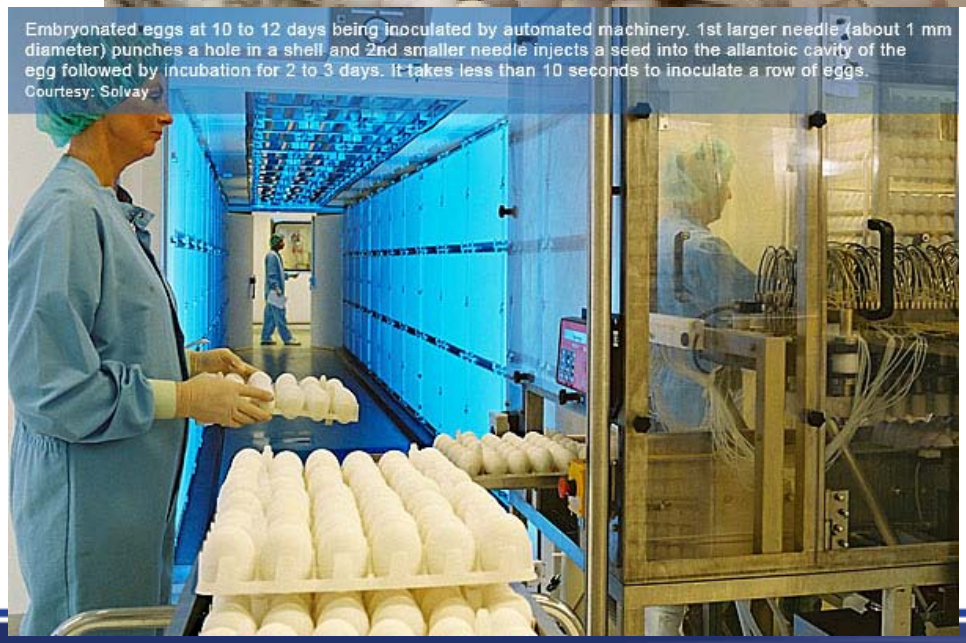
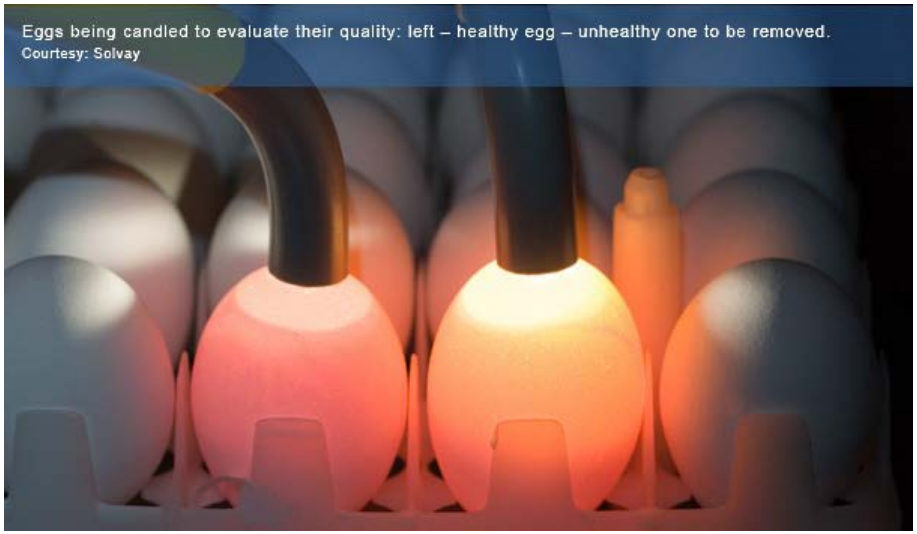
Conventional Influenza Vaccine Production in Embryonated Hens' Eggs

Baxter


Embryonated eggs are stored for 10 to 12 days, constantly turned to ensure the healthy development of the embryos.
Courtesy: Solvay

IFPMA
Influenza Vaccine Supply
International Task Force


Embryonated eggs at 10 to 12 days being inoculated by automated machinery. 1st larger needle (about 1 mm diameter) punches a hole in a shell and 2nd smaller needle injects a seed into the allantoic cavity of the egg followed by incubation for 2 to 3 days. It takes less than 10 seconds to inoculate a row of eggs.
Courtesy: Solvay


Eggs being candled to evaluate their quality: left – healthy egg – unhealthy one to be removed.
Courtesy: Solvay

Memorandum from a WHO Meeting (1995)

Baxter

Memoranda / Memorandums

Cell culture as a substrate for the production of influenza vaccines: Memorandum from a WHO meeting*

Influenza has been a significant public health problem worldwide, with three pandemics during the past century. Immunization is the most effective measure to control an influenza pandemic. Since rapid production of large amounts of influenza vaccine depends on the availability of fertile hens' eggs to grow the viruses, there is an urgent need for the development of alternative cell culture systems, which would allow rapid scale-up of production in the event of a pandemic. This WHO meeting discussed the results of studies from several laboratories on the cultivation of influenza viruses in stable cell lines, and made recommendations for further work.

Bulletin of the World Health Organization, 1995, **73** (4): 431–435

Baxter‘s Serum Protein Free Vero Cell-Technology

- **Vero cells are an optimal basis for the production of vaccines:**
  - **accepted by Regulatory Authorities in more than 60 countries worldwide**
  - **used for the production of licensed vaccines for nearly 30 years, mainly polio and rabies; more recently Rota as well**
- **Baxter has a fully characterized Vero Cell line:**
  - **Baxter‘s Vero cell vaccines are licensed in the EU as well as in the US, Australia, New Zealand, Singapore, and Brazil**
- **Use of a serum protein free medium**
- **Potential for production of vaccines against a wide variety of viral diseases**
- **Suitable for production of all types of viral vaccines:**
  - **inactivated whole virus**
  - **split**
  - **subunit**
  - **live-attenuated**

Barrett et al. Expert Rev. Vaccines 2009; 8: 607-618. Vero cell platform in vaccine production: moving towards cell culture-based viral vaccines

Baxter‘s Vero Cell Based Vaccine Production Facility in Bohumil, Czech Republic: Fermentation

Summary – Baxter's Vero Cell Technology for Influenza Vaccines

- Fully characterized continuous cell line
- Serum protein free medium
- Well-established, highly standardized, robust and closed manufacturing process:
- GMP production of more than 80 millions of doses of influenza vaccines with a total of

  17 different seasonal (H1N1, H3N2, B) as well as pandemic (-like) H5N1, H1N1, and H9N2

  WHO-recommended vaccine strains since 2003
- Allows for shorter and more flexible production cycle compared to traditional egg-based influenza vaccines
- Enables use of the original virus instead of reassortants

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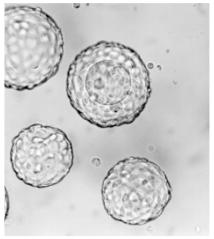
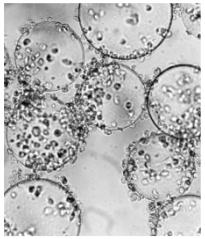
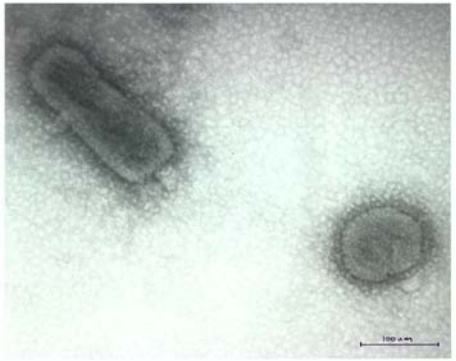
Baxter's Pandemic Influenza Vaccine Program

- **State-of-the-Art Vero Cell Culture Technology: Independence from hen's eggs**
- **Use of wild-type virus, not reverse genetics**
- **Use of whole virus, not split or subunit vaccine**
- **Not adjuvanted**
- **Proven for Production of**
  - **H5N1 A/Vietnam/1203/2004**
  - **H5N1 A/Indonesia/05/2005**
  - **H1N1pdm09 A/California/7/2009**
  - **H9N2 A/chicken/Hongkong/G9/97 (RG)**







2009 H1N1 Pandemic Influenza – Course of Events with Respect to Pandemic Wave in a Representative European Country

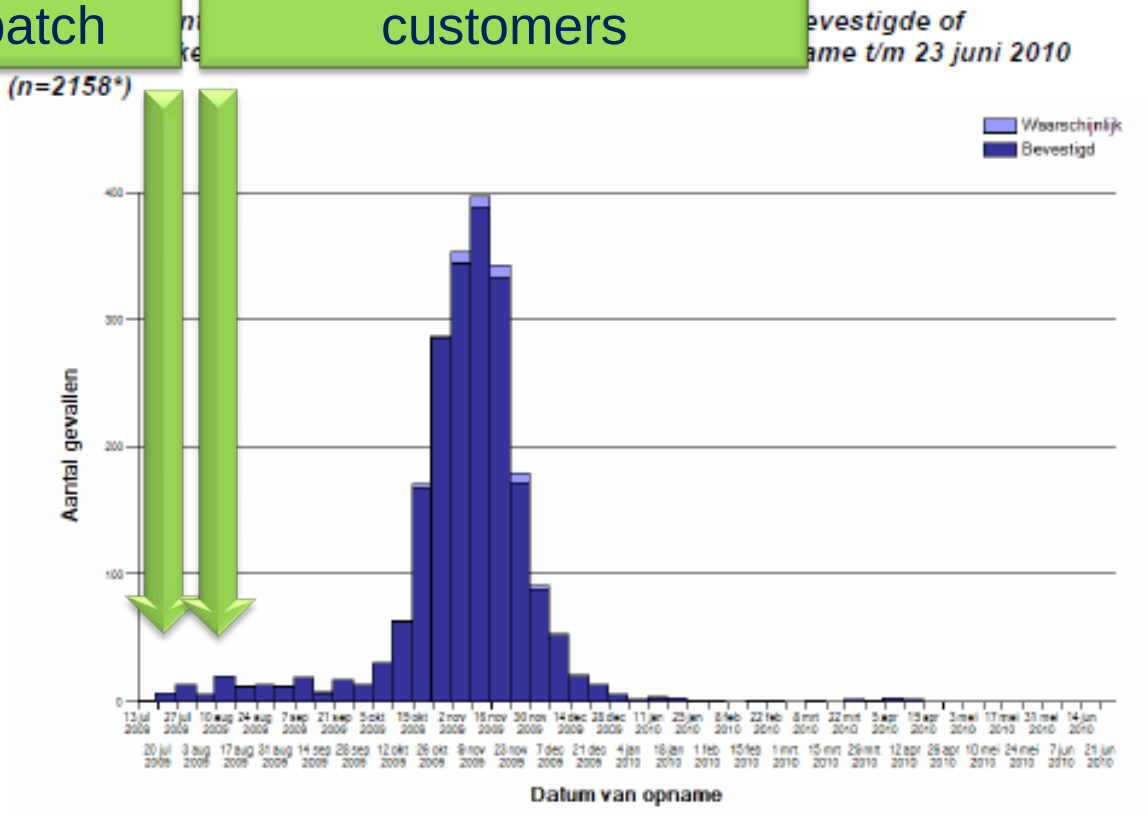
Baxter

24 July 2009
Internal release of first batch

12 Aug 2009
First Baxter shipment to customers

24 April 2009
First Report on „Swine Flu“

4 May 2009
Baxter receives the virus from US CDC



http://www.rivm.nl/cib/binaries/H1N1overzicht_24062010_tcm92-72132.pdf

H5N1 & H9N2 Clinical Development Program

- **EU Mock-up Licensure (A/Vietnam/1203/2004) → License**
  - 4 Phase I/II/III studies including
    - dose finding
    - heterologous booster with Indonesia (clade 2.1) 12 – 17 month after primary immunization with Vietnam 1203 (clade 1)
    - study in younger (18-59 years) and elderly (60+ years) adults with 6, 12-15 and 24 month booster
    - supportive study with Indonesia
- **EU Pre-Pandemic Licensure (A/Vietnam/1203/2004) → License**
  - 3 Phase I/II/III studies including
    - ped's, adults, elderly, and risk groups
    - supportive Single Prime Boost study
- **Japan H5N1 Vaccine Licensure (A/Indonesia/05/2005)**
  - Phase II/III study in adults
- **US Studies**
  - 3 Phase I/II studies in adults with Vietnam 1203, RG Indonesia, RG H9N2

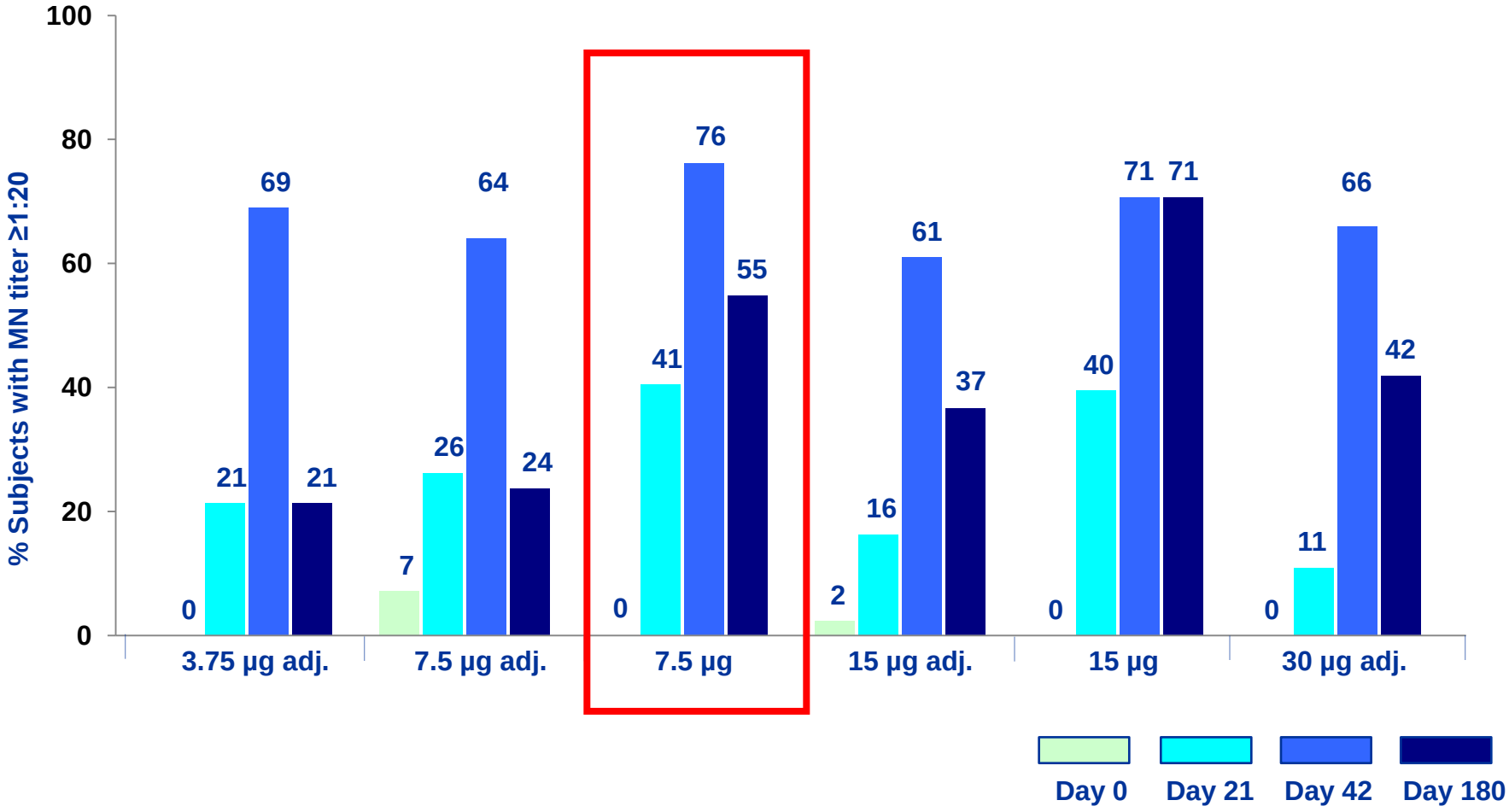
N > 6700 Subjects

Phase I/II Study with Baxter's H5N1 Vaccine
"A Dose-Escalation Study of a Mock Up Pandemic Influenza Vaccine"

Baxter

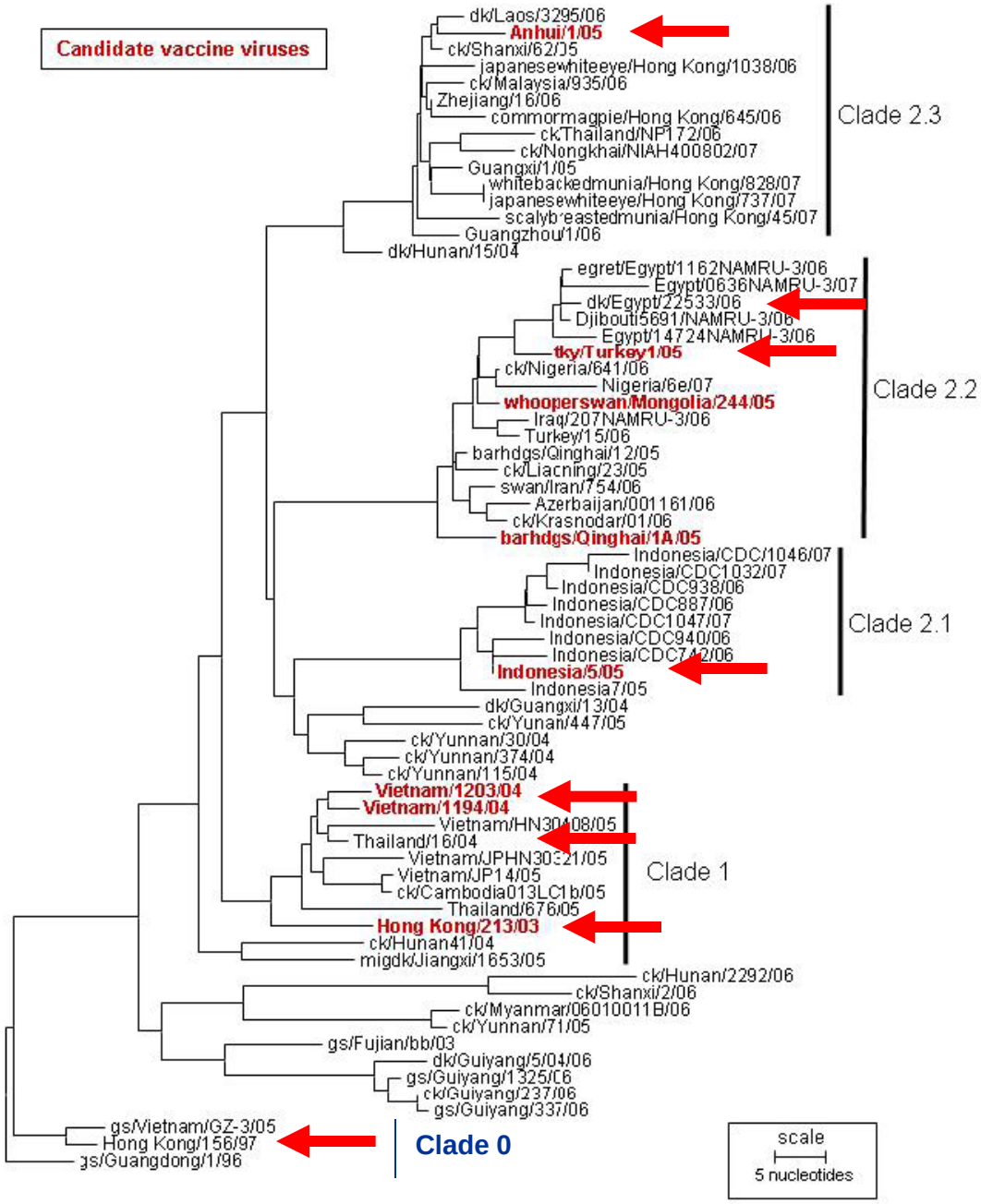
- **Primary Objective**
  - To identify the immunogenicity and safety of different doses of adjuvanted and non-adjuvanted mock-up pandemic influenza vaccine
- **Subjects**
  - 270 subjects aged 18 to 45 years, healthy volunteers
- **Vaccination**
  - 2 vaccinations on day 0 and day 21 (A/Vietnam/1203/2004 vaccine)
- **Six arm study (45 subjects / arm)**
  - 3.75, 7.5, 15 and 30 µg with aluminum adjuvant
  - 7.5 and 15 µg non-adjuvanted
- **Study sites**
  - Austria and Singapore

H5N1 Seroprotection Phase I/II Dose-Escalation Study
Seroprotection Rate (MN) against A/Vietnam/1203/2004



Ehrlich et al. N Engl J Med 2008; 358:24. A clinical trial of a whole-virus H5N1 vaccine derived from cell culture

Evolution of the H5N1 Haemagglutinin Gene



Phase II Booster Study – Study Design
Follow Up of Phase I/II Dose-Escalation Study

Baxter

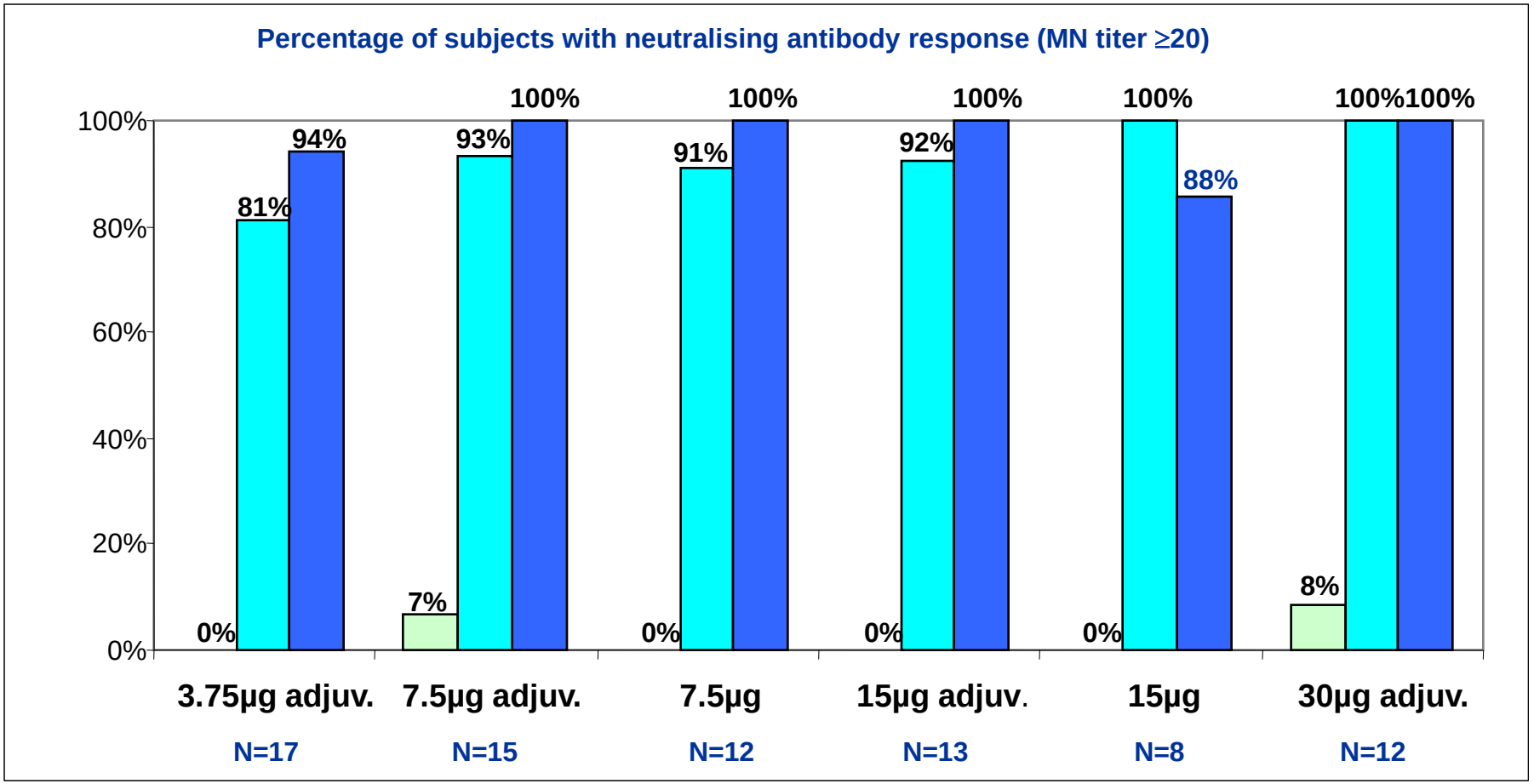
- **Primary Objective**
  - Assess immunogenicity and safety of a heterologous booster 12 to 17 months after two-dose priming vaccination
  - Assess antibody persistence 180 days after a heterologous booster vaccination
- **Subjects**

  77 (out of 141 eligible) subjects
- **Vaccination**

  Booster vaccination with 7.5 μg HA A/Indonesia/05/2005 at 12-17 months after first vaccination in Phase I/II (A/Vietnam/1203/2004)
- **Study site**

  Austria

Phase II Study – 12 to 17 Months Booster with Indonesia Vaccine Seroprotection Rate (MN) against Indonesia

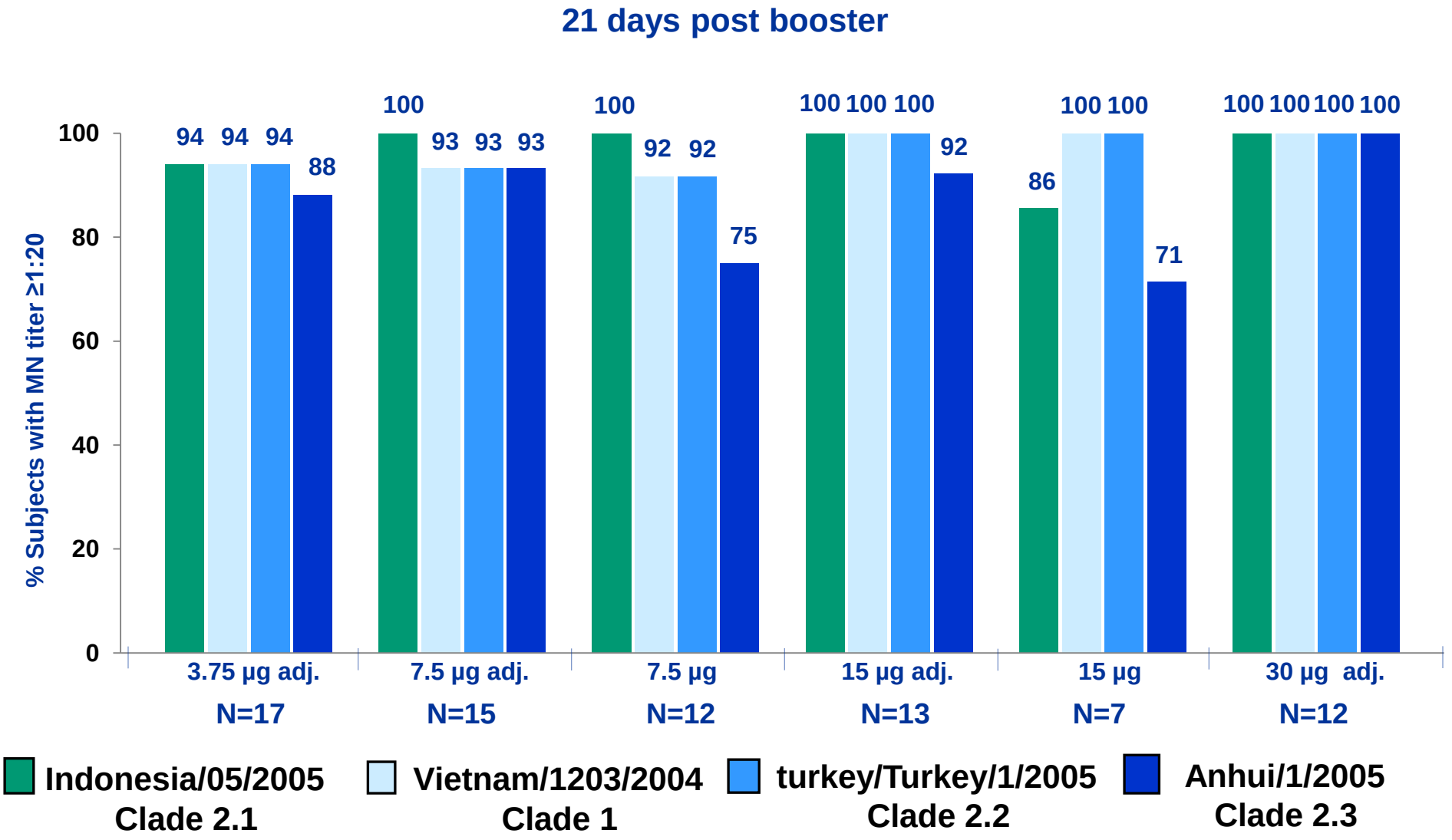


Ehrlich et al. J Infect Dis 2009; 200: 1113-1118. A cell culture (Vero) Derived H5N1 Whole Virus Vaccine Induces Cross-Reactive Memory Responses

Day 0 Day 7 Day 21

Phase II Study – 12 to 17 Months Booster with Indonesia Vaccine Heterologous Seropotection (MN) against Different Clades

Baxter



Ehrlich et al. J Infect Dis 2009; 200: 1113-1118. A cell culture (Vero) Derived H5N1 Whole Virus Vaccine Induces Cross-Reactive Memory Responses

Baxter‘s H5N1 Clinical Development Program – Conclusions Safety

- **Baxter's Vero cell derived whole virus H5N1 vaccines against A/Vietnam/1203/2004 and A/Indonesia/05/2005 demonstrate excellent tolerability profile that is highly consistent across all clinical studies**
- **Safety profiles in healthy populations and risk groups (elderly adults, chronically ill, immunocompromised) are comparable**
- **The vaccine was safe and well tolerated in all three pediatric age strata i.e. 6 – 35 months, 3 – 8 years, and 9 – 17 years**
- **Sytemic and local reaction rates were low and predominantly mild and transient**

Baxter‘s H5N1 Clinical Development Program – Conclusions Immunogenicity

- Vaccine doses as low as 3.75 µg or 7.5 µg are highly immunogenic following two dose immunization, as shown in the MN and the SRH test
- Non-adjuvanted formulations are more immunogenic than the adjuvanted ones
- Vaccine induced substantial immune responses in immunocompromised and chronically ill individuals
- Vaccine shows cross-neutralization against widely divergent H5N1 strains
- Vaccine is capable of inducing long-lasting cross-clade immunological memory response that can be effectively boosted up to 24 months following priming
- Similarly strong booster response is achieved following either a two dose or single dose priming schedule
- Vaccine induced same level of cross-clade reactive CD4+ T-cell and memory B-cell responses adults (18–59 years) and elderly (≥60 years)
- Vaccine induces effectively Neuraminidase-inhibiting (NAI) antibodies

Ehrlich et al. N Engl J Med 2008; 358: 2573 -2584. A clinical trial of a whole-virus H5N1 vaccine derived from cell culture
Crowe et al. Vaccine 2011, 29: 166-173. Evaluation of the cellular immune responses induced by a non-adjuvanted inactivated whole virus A/H5N1/VN/1203 pandemic influenza vaccine in humans
Fritz, et al. A Vero Cell-Derived Whole-Virus H5N1 Vaccine Effectively Induces Neuraminidase-Inhibiting AntibodiesJ. Infec. Dis. 2012, 205: 28-34

Baxter's H5N1 Clinical Studies – Conclusions Heterologous Prime Boost

- **A single heterologous boost with the clade 2.1 vaccine Indonesia 12 – 17 months after the primary immunization with the clade 1 vaccine Vietnam 1203 resulted in the rapid induction of very high titers against the initial vaccine and the booster strain**
- **Seroneutralization rates between 90% and 100% against the priming vaccine and the booster vaccine were already obtained 7 days after the booster vaccination**
- **This heterologous prime-boost effect with the Indonesia vaccine after the primary immunization with the Vietnam 1203 vaccine has been confirmed in a Phase III study in two different age groups, in younger (18 – 59 years) and older (60+ years) adults**
- **The rapid induction of a protective immune response was not only achieved against the clade 1 strain Vietnam 1203 and the clade 2.1 strain Indonesia, but also against representative viruses of clade 2.2 (turkey/Turkey) and 2.3 (Anhui) not being covered by the vaccination strategy; indicative of cross-protective memory**

Ehrlich et al. J Infect Dis 2009; 200: 1113-1118. A cell culture (Vero) derived H5N1 whole virus vaccine Induces cross-reactive memory responses

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Clinical Studies with Seasonal Vero Influenza Vaccines (Inactivated Split TIV‘s)

Baxter

4 Studies (Phase I/II/III) in seasons 2006/2007 – 2008/2009

- **Safety and immunogenicity in all age groups from 18 years and risk groups**
- **Efficacy in young and healthy adults from 18 – 49 years**
- **15.045 subjects**

Vero Vaccine	**9001**
Egg Vaccine	**599**
Placebo	**5461**

Conclusions – Efficacy

Primary Endpoint of Vaccine Efficacy Met

- **Overall vaccine efficacy against matching strains is 78.5% (CI 60.8 – 88.2%)**
- **Overall vaccine efficacy against matching and non-matching influenza strains is 71.5%**
- **Protective Efficacy against all circulating viruses proven over the whole influenza season 2008/2009**

Reduction of Disease Symptoms

- **The vaccination significantly reduces the duration and severity of disease symptoms in those individuals in which infection is not prevented**

Barrett et al. Immunogenicity of a Vero cell culture-derived trivalent influenza vaccine: a multicentre, double blind, randomised, placebo-controlled trial. Lancet 2011; 377:751-759
Ehrlich et al. A Cell Culture-Derived Influenza Vaccine Provides Consistent Protection Against Infection and Reduces the Duration and Severity of Disease in Infected Individuals. Clinical Infectious Diseases 2012, 54: 946-954

Conclusions – Immunogenicity

- **Consistent Immunogenicity**

  with regard to achieving all 9 of 9 CHMP criteria for rate of seroprotection, rate of seroconversion and GM-fold increase confirming data from 3 Phase III Studies with more than 8000 younger and elderly adults, i.e. 27 out of 27 criteria

- **Correlate of protection**

  Vaccine efficacy correlates with an HI titer of ≥ 15, no added benefit at HI titer > 30

Barrett et al. Immunogenicity of a Vero cell culture-derived trivalent influenza vaccine: a multicentre, double blind, randomised, placebo-controlled trial. Lancet 2011; 377:751-759
Ehrlich et al. Clinical development of a Vero cell culture-derived seasonal influenza vaccine. Vaccine 2012, **30:** 4377-4386

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Overall Summary – Pandemic Influenza Vaccines

Baxter

- **The combination of**

  - **Preclinical Data**

    - H5N1 protection studies in mouse and ferret challenge studies (lethal model)
    - H5N1 passive transfer studies using sera from human studies (lethal model)
    - H1N1 protection studies in mice and ferrets (non-lethal models)
    - H1N1 passive transfer studies with human sera in transgenic mice (lethal model)
    - H9N2 protection studies in mice (non-lethal model)

  - **Clinical Data**

    - H5N1 immunisation (priming and booster studies) – humoral and cellular data
    - H1N1 primary immunisation studies
    - H1N1 efficacy studies
    - H9N2 primary immunisation studies

Indicate that Vero cell derived whole virus pandemic vaccines are highly protective

Overall Conclusions – Baxter‘s Vero Cell Influenza Vaccines

- 12 weeks between receipt of a pandemic virus and availability of internally and externally released vaccine lots
- No adjuvant required – whole virus structure may work as an adjuvant itself
- Cross- Protection against all relevant H5N1 clades which cause frequent human infections by heterologous Prime-Boost vaccinations
- Pandemic (-like) H5N1 and H1N1 vaccines are safe and immunogenic in all age groups from 6 months of age onwards
- Seasonal vaccine has shown high efficacy against matching and non-matching strains over the whole influenza season 2008/2009
- EMA / FDA accepted protective HI titer of 1:40 confirmed with a Vero-derived seasonal influenza vaccine (Preflucel)

Baxter's Licensed Influenza Vaccines

Pandemic Influenza Vaccine H5N1 Baxter

Pandemic Mock-Up Vaccine

H5N1 licensed in EU, CH, Australia, NZ, Singapore

Pandemic (Mock-Up) Vaccine

H1N1pdm09 licensed in EU, Australia, NZ, Brazil

Pre-pandemic H5N1 Vaccine (A/Vietnam/1203/2004)

Licensed in EU

Seasonal Influenza Vaccine

- **Licensed in 15 European countries and Brazil**
- **Submitted for licensure in several Asian-Pacific and Latin-American countries**

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Vero Cell Technology & Vero-Derived Seasonal Influenza Vaccines

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J Infect Dis 2009; 200: 1113-1118

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Evaluation of the cellular immune responses induced by a non-adjuvanted inactivated whole virus A/H5N1/VN/1203 Pandemic Influenza vaccine in humans
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Vaccine 2012 30: 6127-6135

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