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Human H5N1 and Pandemic Vaccines Practicalities of Production: A perspective from Industry

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Pandemic Influenza Working Group

European Vaccine Manufacturers

4th Joint EC/ECDC/WHO Workshop on pandemic influenza preparedness

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Presentation outline

- **Challenge and commitment of the vaccine industry in flu pandemic preparedness**
- **Practicalities of Influenza vaccine production (seasonal and pandemic)**
- **How to secure pandemic vaccine production**
- **Impact of R&D efforts and increase in production capacity on (pre-) pandemic vaccine supply**
- **Key priorities for industry and the international community**

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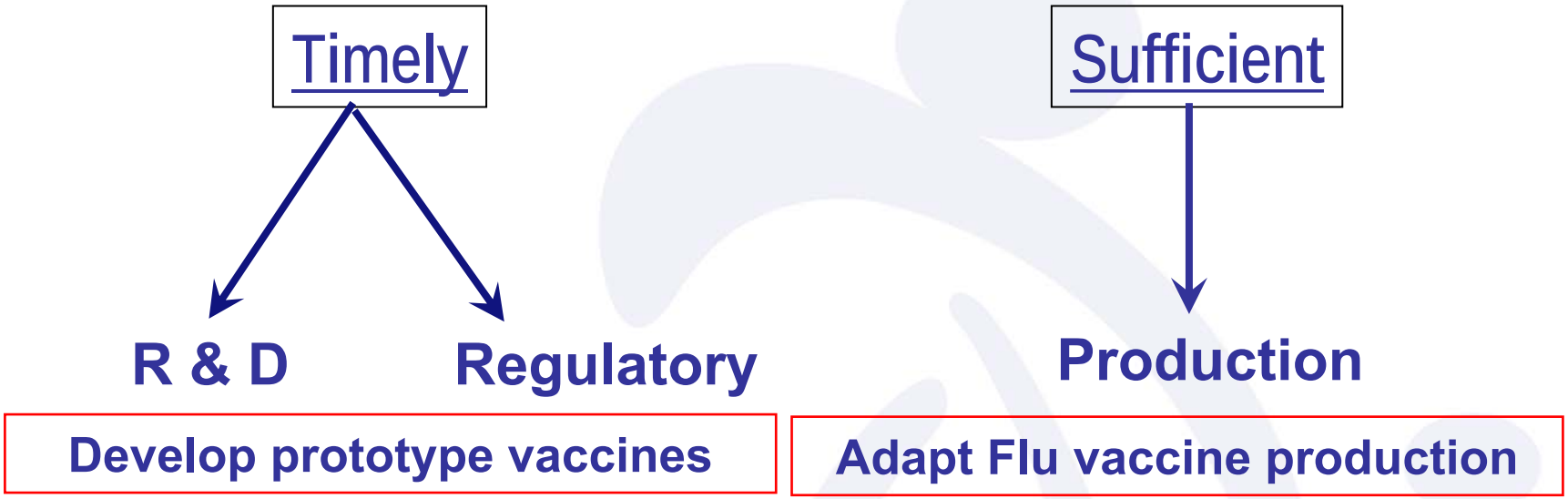
The challenge of pandemic preparedness

Deliver as much pandemic vaccine as quickly as possible after the pandemic has been declared



A shared responsibility between industry, national and international health authorities, academia…

and a real political willingness

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The vaccine industry is committed to pandemic preparedness

- Collaborate with governments and intergovernmental bodies to address preparedness issues (inc. allocation of pandemic vaccines and liability)
- Propose/support measures to increase global access to vaccines for humans
- Adapting and expanding manufacturing capacity in line with demand
- Ensure maximum production of pandemic vaccine in shortest timeframe
- Evaluating alternative/complementary vaccination strategies
- Develop and license safe and immunogenic pre-pandemic vaccines

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Flu Pandemic Preparedness: Two Options

Two major challenges for effective vaccine

- *How to get enough vaccine doses?*
- *How to induce protection as early as possible?*

World-wide H5N1 Pandemic

Vaccine Manufacturing during pandemic

Pandemic Vaccine

Manufacturing before pandemic and stockpile

Pre-Pandemic Vaccine

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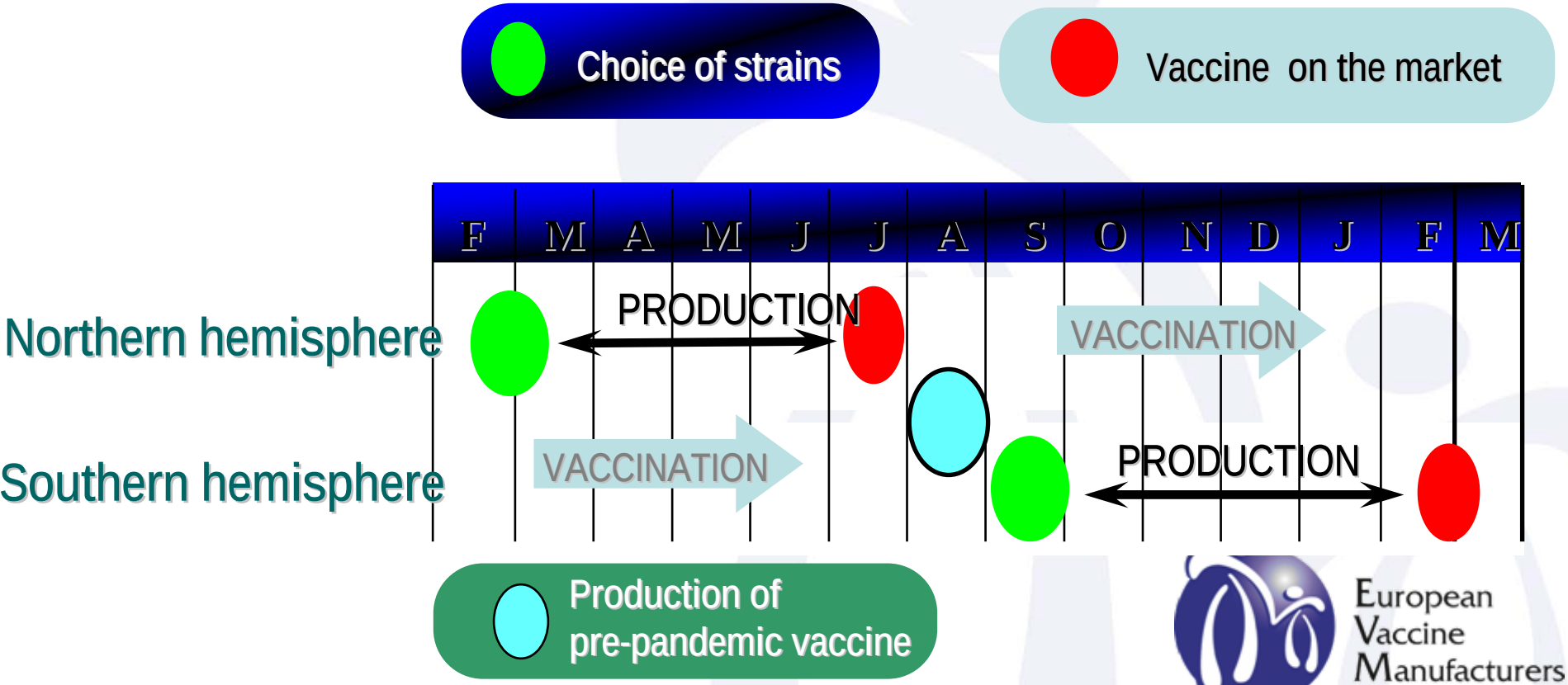
Practicalities of seasonal influenza vaccine production

Each year: 2 new vaccines within a 6-month timeframe



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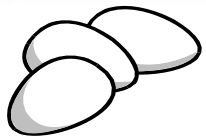
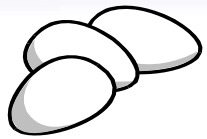
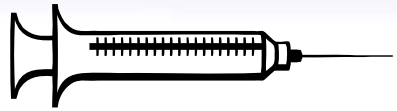
Global seasonal Influenza Vaccine Production timelines



Egg supply organisation

Egg supply for production

Seed lots

Monovalent batches

Filling

Blending

Pharmaceutical File

MA

Ref Member State Release

Clinical Trial

Vaccine Delivery

D0 - 6 months

D0

WHO meeting D0 = mid Feb

Reagent availability Mid May

July/August

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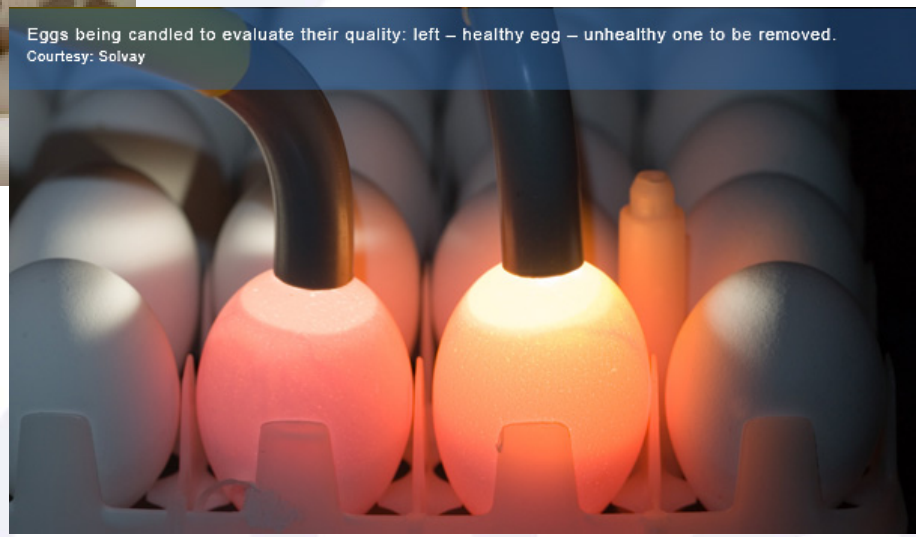
Egg-based Influenza Vaccine Production*


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


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


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

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* www.ifpma.org/influenza

Egg-based Influenza Vaccine Production

* www.ifpma.org/influenza

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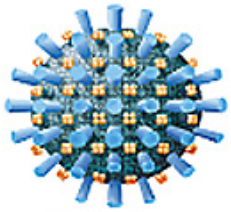
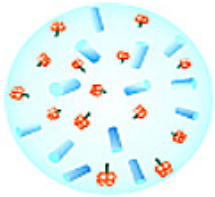
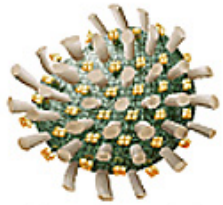
Cell-based Influenza Vaccine Production


Whole virus


Split virus


Subunit
(surface antigen)

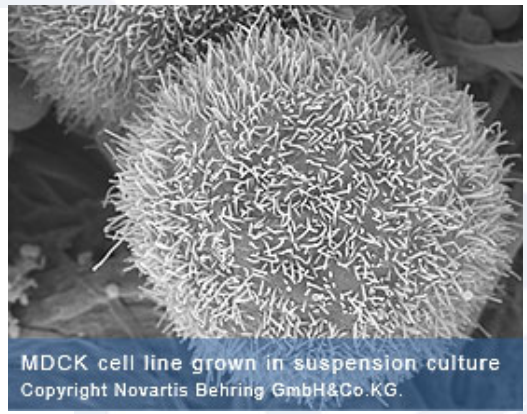

Live attenuated

Fermenter 4
Virus Production

Fermenter 3
Cell propagation
High Cell Density

Fermenter 2
Cell Propagation

Fermenter 1
Cell Propagation



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* www.ifpma.org/influenza

Pandemic vaccine development

Use as much as possible current know-how to switch in a timely manner facilities to pandemic vaccine production

Vaccines

Inactivated vaccine

WVV

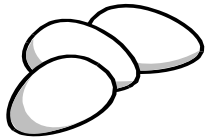
Split vaccine

Subunit vaccine

Live attenuated vaccine

Production substrates

Conventional eggs



SPF eggs

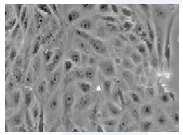
Cells

MDCK

VERO

PerC6

EBx



Formulation

Adjuvant

Extemporaneous

Ready to use formulations

Presentation

Multidose presentation

Vials

Simplified packaging documentation

Counterfeiting issues

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Mock-up/Pandemic and Pre-pandemic Vaccines: EU licensing status

MOCK-UP/PANDEMIC

Company	Strains	Regulatory status
GSK	H9N2 & H2N2	Submitted EMEA Dec. 05
Daronrix	H5N1 (whole +alum)	EU Marketing Authorisation (March 07)
Pandemrix	H5N1 (split + AS03)	Accepted by EMEA for review (Jan. 07)
Novartis	H9N2 & H5N3 (SA+MF59)	Submitted EMEA Jan 06
Focetria (Panfluad)	H5N1 (SA+MF59)	EU Marketing Authorisation May 07
sanofi pasteur	H5N1 (split+alum)	Submitted EMEA May 07

PRE-PANDEMIC

Company	Strains	Regulatory status
Novartis Aflunov	H5N1 (SA+MF59)	Submitted EMEA (Nov. 06) Review ongoing. Assessments reports finalised
GSK Pre-Pandemrix	H5N1 (split + AS03)	Accepted by EMEA for review (Jan. 07)

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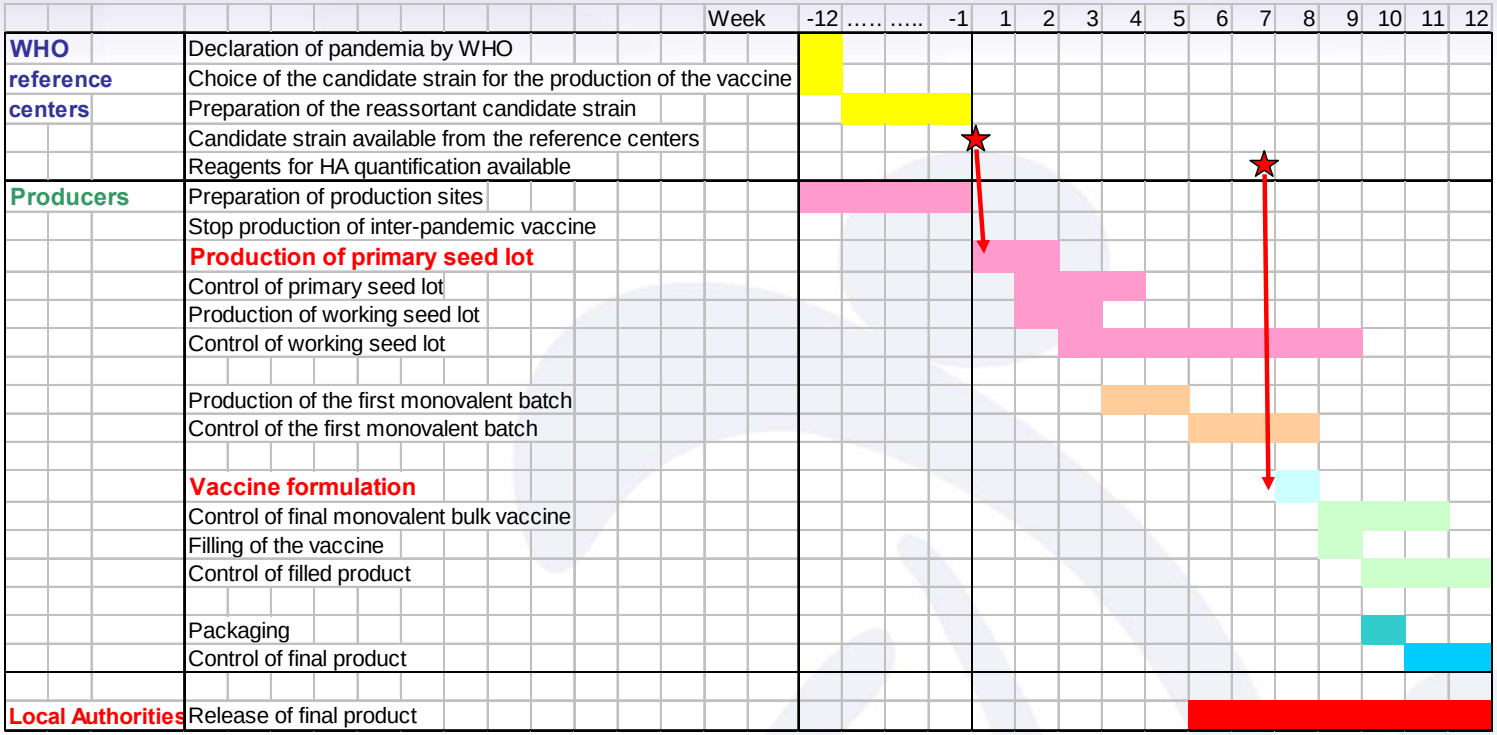
Timelines for pandemic vaccine production*



- **6 months overall timeline from pandemic declaration to first supplies of pandemic vaccine**
- **12 weeks between the arrival of the strain and the availability of the first doses, if reagents are available**
- **Reagents need to be available 7 weeks after arrival of the strain**

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* Timelines for pre-pandemic vaccine development are the same than those of seasonal flu vaccines

Factors influencing timelines and capability for pandemic vaccine production

- **Availability timing of vaccine candidate strains & specific reagents +++**
- **RG strain manipulation permit* (GMO and biosafety, regulation, MTA ,…)**
- **Ability to convert easily production facility to pandemic vaccine production (validation by local authorities)**
- **Simplified data packaging documentation (flexible & universal availability of the vaccine)**
- **Streamline dose release process (collaboration with ONCLs)**

*** More critical for pre-pandemic vaccines**

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How to to secure pandemic vaccine production (1)

- **Procedures for avian RG vaccine candidate production (WHO biosafety group lead)**
- **Adaptation of facilities and practices to produce avian strains in total compliance with appropriate bio-safety standards**
- **Produce different candidate strains at industrial scale to :**
  - **Understand the impact of such strains on current production processes and flows**
  - **Anticipate pandemic vaccine availability (simulation plans)**
- **Validate large scale production step (including F&P) to ensure delivery of a safe and consistent product**

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How to secure pandemic vaccine production (2)

- **Anticipate any potential disruption in the pandemic production due to crisis situation: Business continuity planning***
- **Secure production capability**
  - **Year-round egg supply with geographic diversity and security stocks**
  - **Critical raw materials (vials, stoppers and packaging documentation)**
  - **Human resource plans in crisis situation**
  - **Protection of sites, workers and products**
- **Production simulations to assess capability for pandemic vaccine (and other priority vaccines) production and supply**

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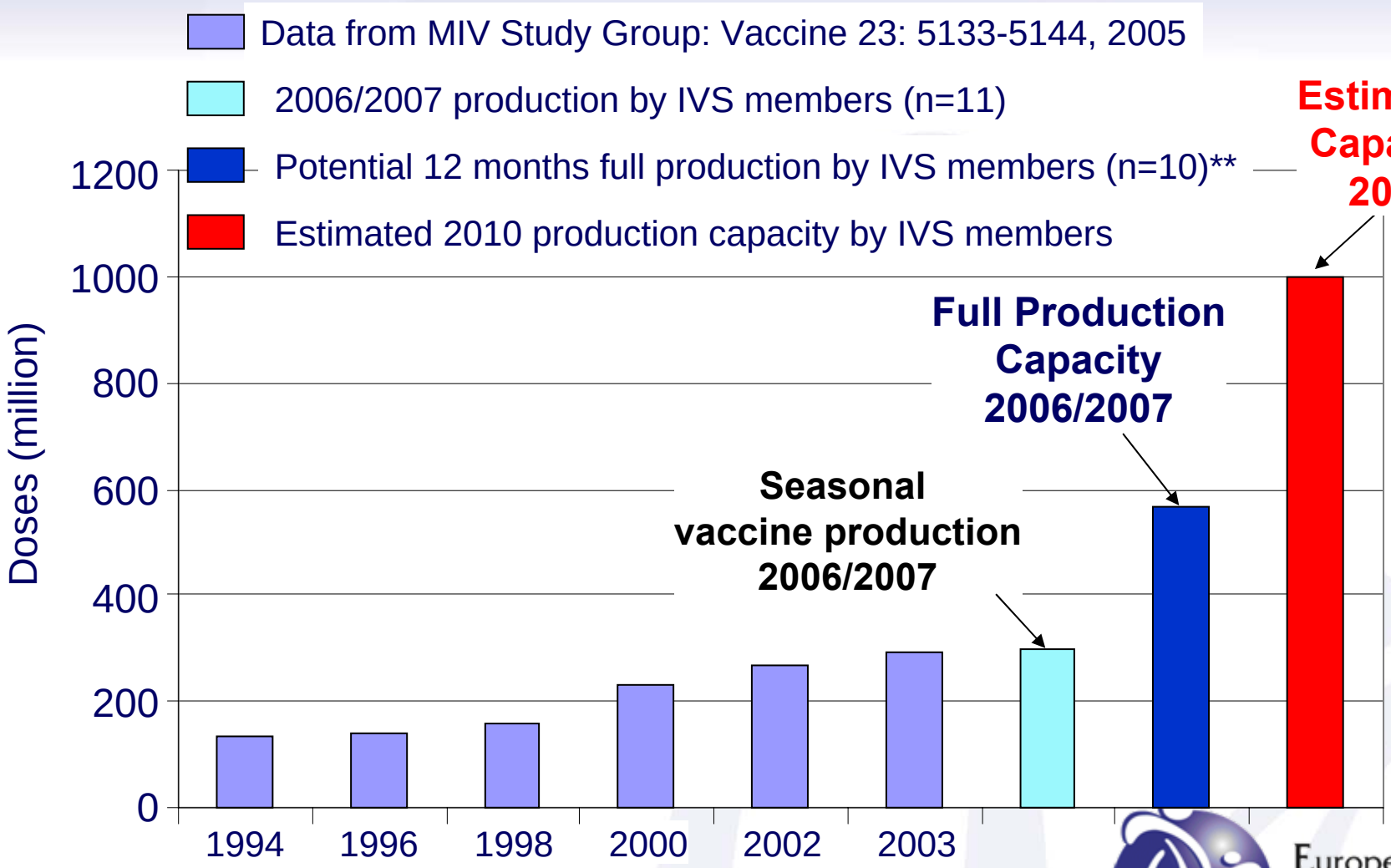
* http://www.ifpma.org/Influenza/index.aspx?48

Seasonal influenza vaccine production and estimated capacity*



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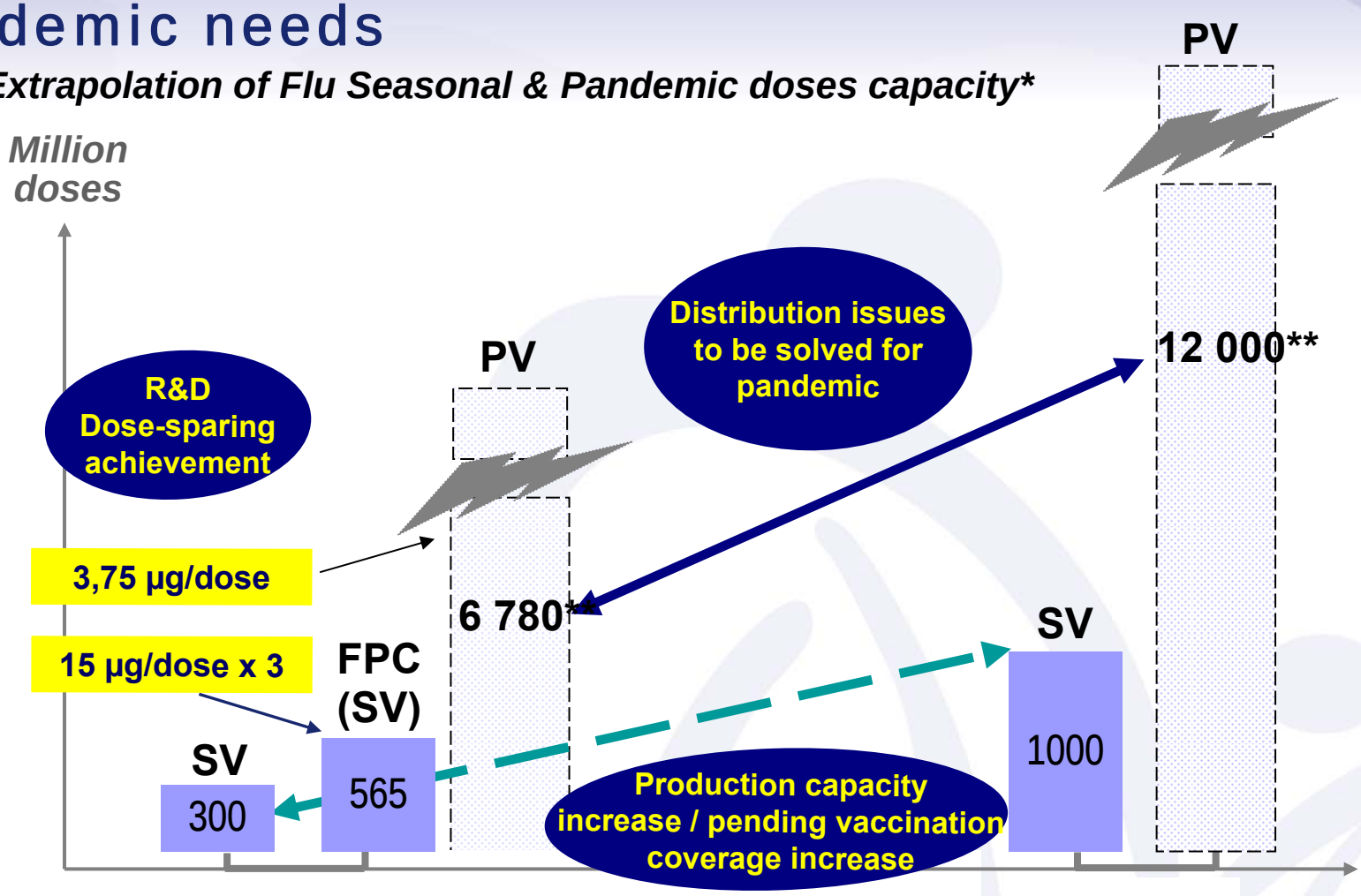
*** IFPMA / IVS internal survey, April 2007**

**** 12 months continuous production, 7 days a week, 24 hours a day**

The impact of dose-sparing strategies and extrapolated capacity of Flu Seasonal on global pandemic needs

Extrapolation of Flu Seasonal & Pandemic doses capacity*



SV: Seasonal Vaccine

PV: Pandemic Vaccine

FPC: Full Production Capacity

* IVS survey April 2007

** Assuming same growth properties as seasonal vaccines

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The potential impact of dose-sparing stategies and capacity of Flu Seasonal on global Flu pandemic needs

- **Successful antigen-sparing strategies and adjuvant technology achieved by major manufacturers could potentially solve the pandemic supply issue and make pre-pandemic strategies a reality.**

- **Production capacity might no longer be an issue – but the 6 month production lead time is (and needs to be covered by pre-pandemic vaccines)**

- **Three priorities**
  1. **Stockpiling of pre-pandemic vaccine**
  2. **Procurement and distribution of pandemic vaccines**
  3. **Implementation of seasonal flu vaccination policies**

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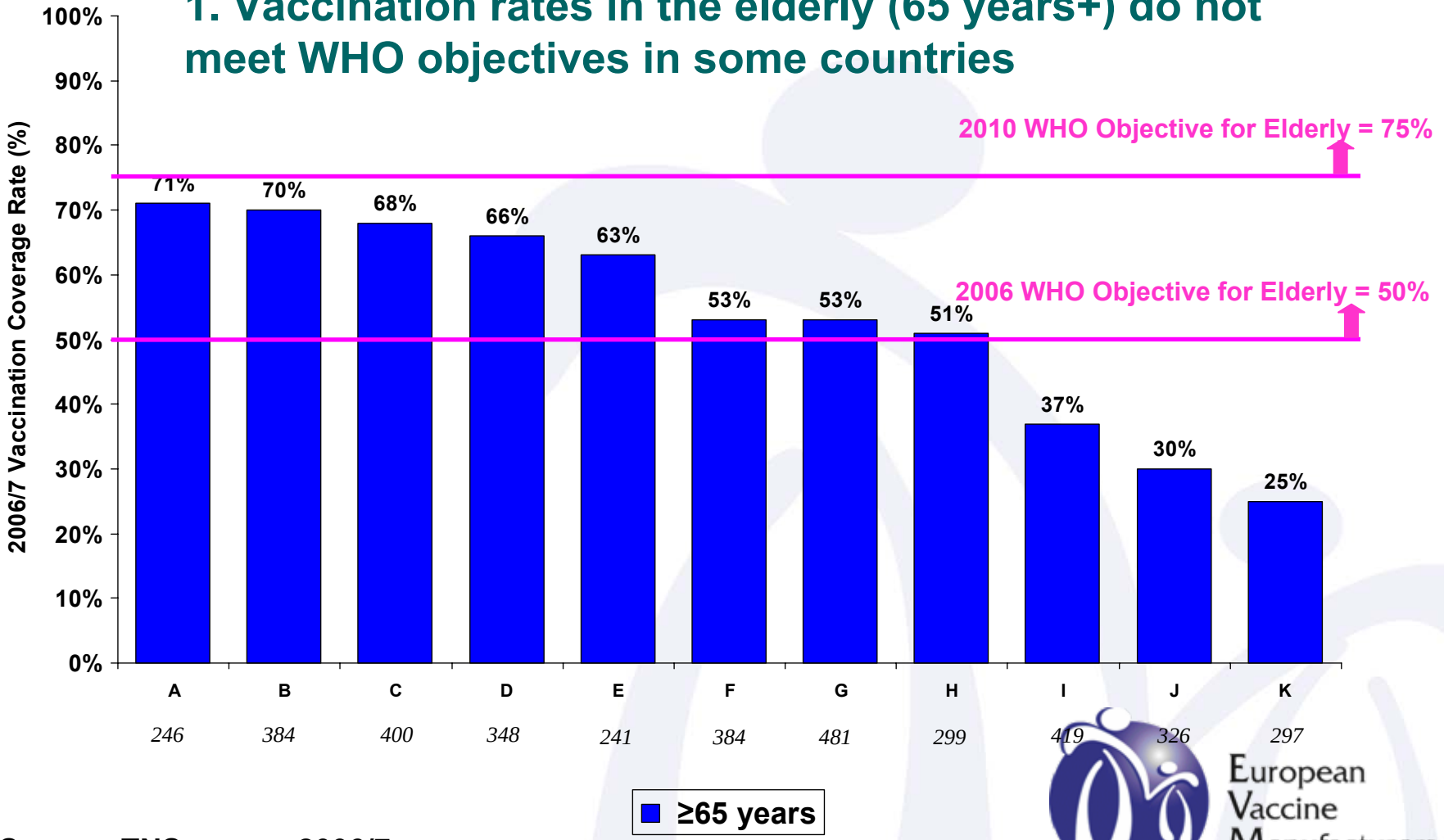
Implementation of seasonal flu vaccination policies: Flu vaccination uptake in 11 EU countries*

1. Vaccination rates in the elderly (65 years+) do not meet WHO objectives in some countries



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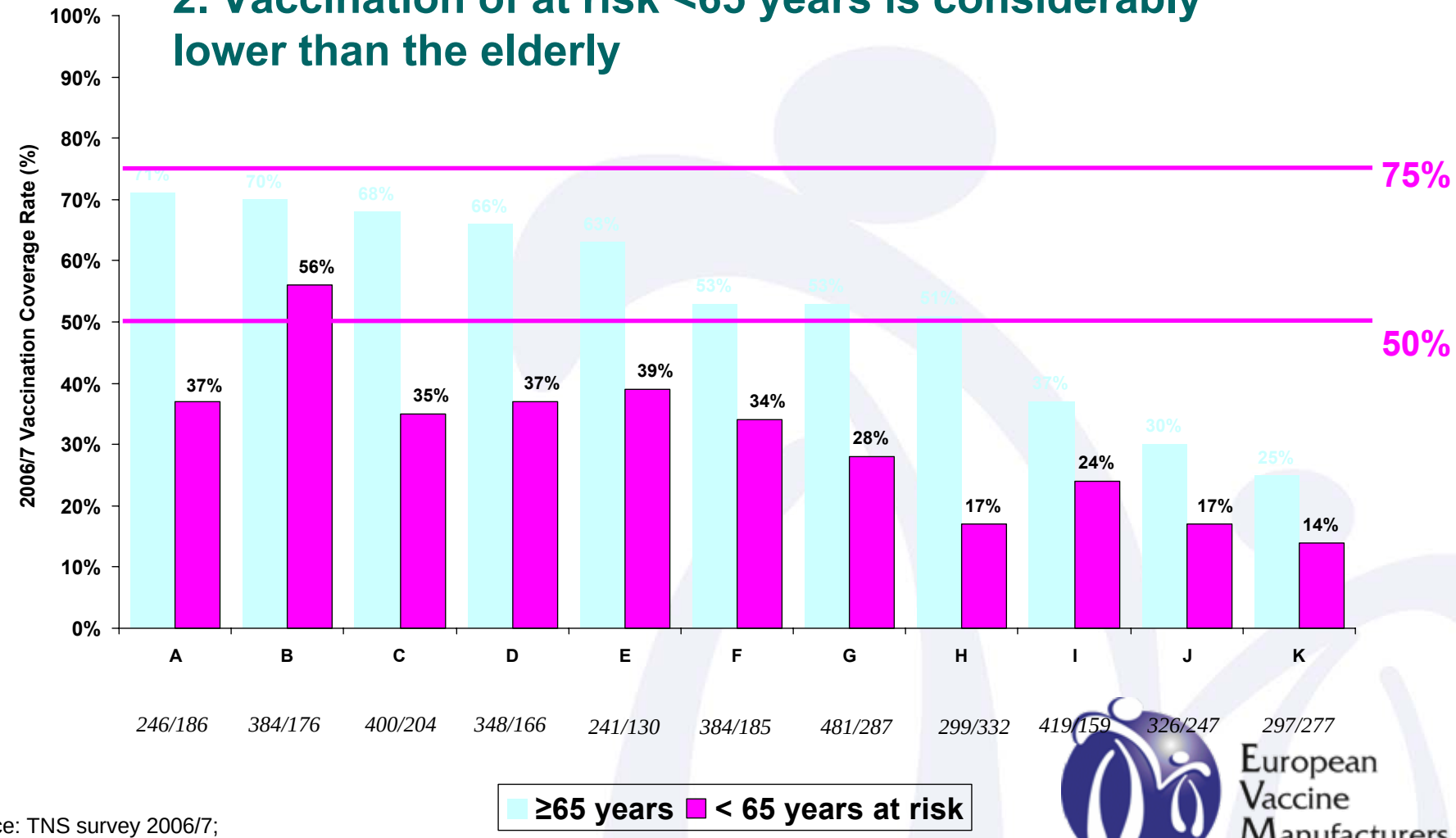
*** Source: TNS survey 2006/7**
Data in file

Implementation of seasonal flu vaccination policies: Flu vaccination uptake in 11 EU countries*

2. Vaccination of at risk <65 years is considerably lower than the elderly



* Source: TNS survey 2006/7; Data in file

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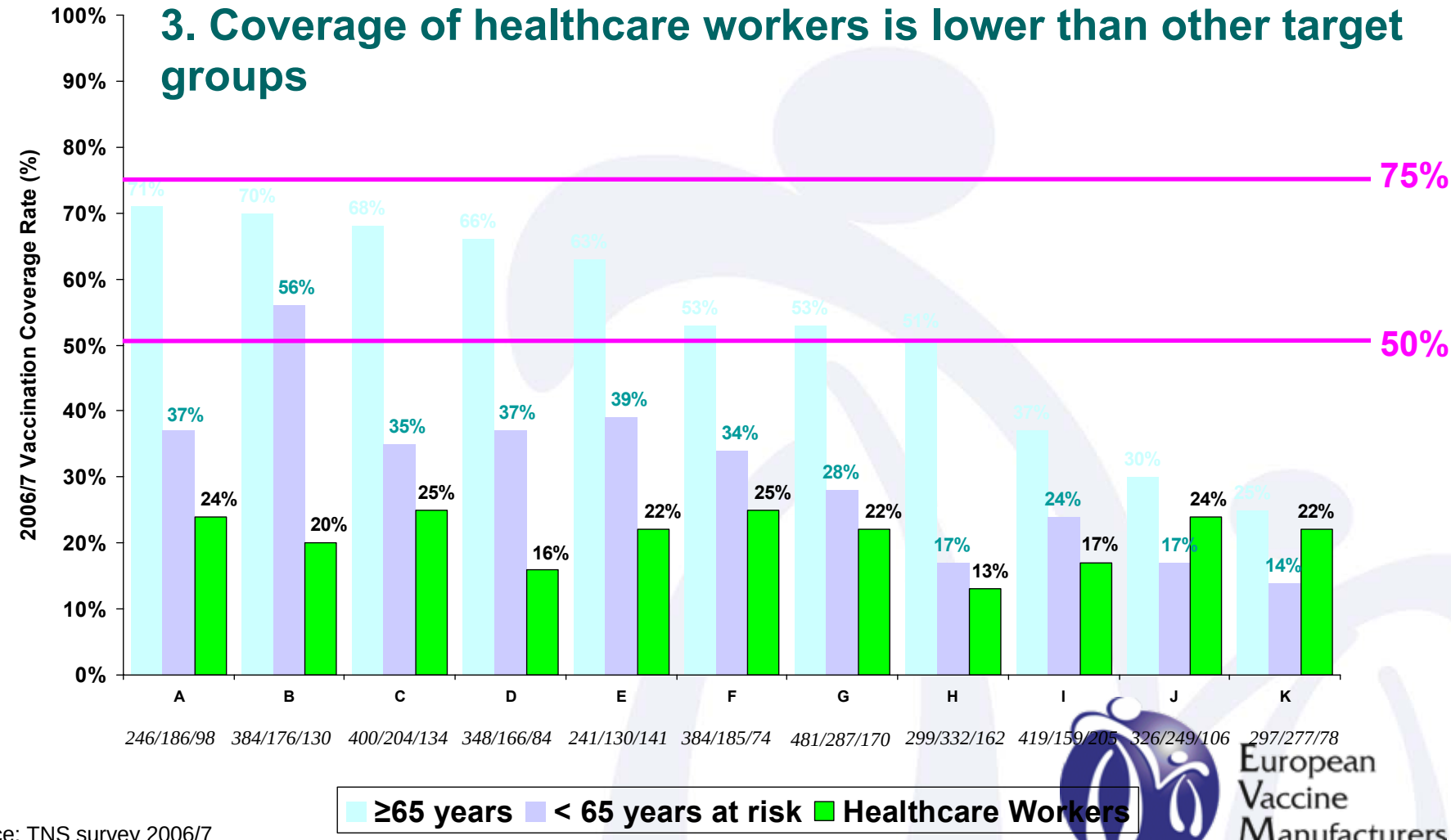
Implementation of seasonal flu vaccination policies: Flu vaccination uptake in 11 EU countries*



* Source: TNS survey 2006/7
Data in file

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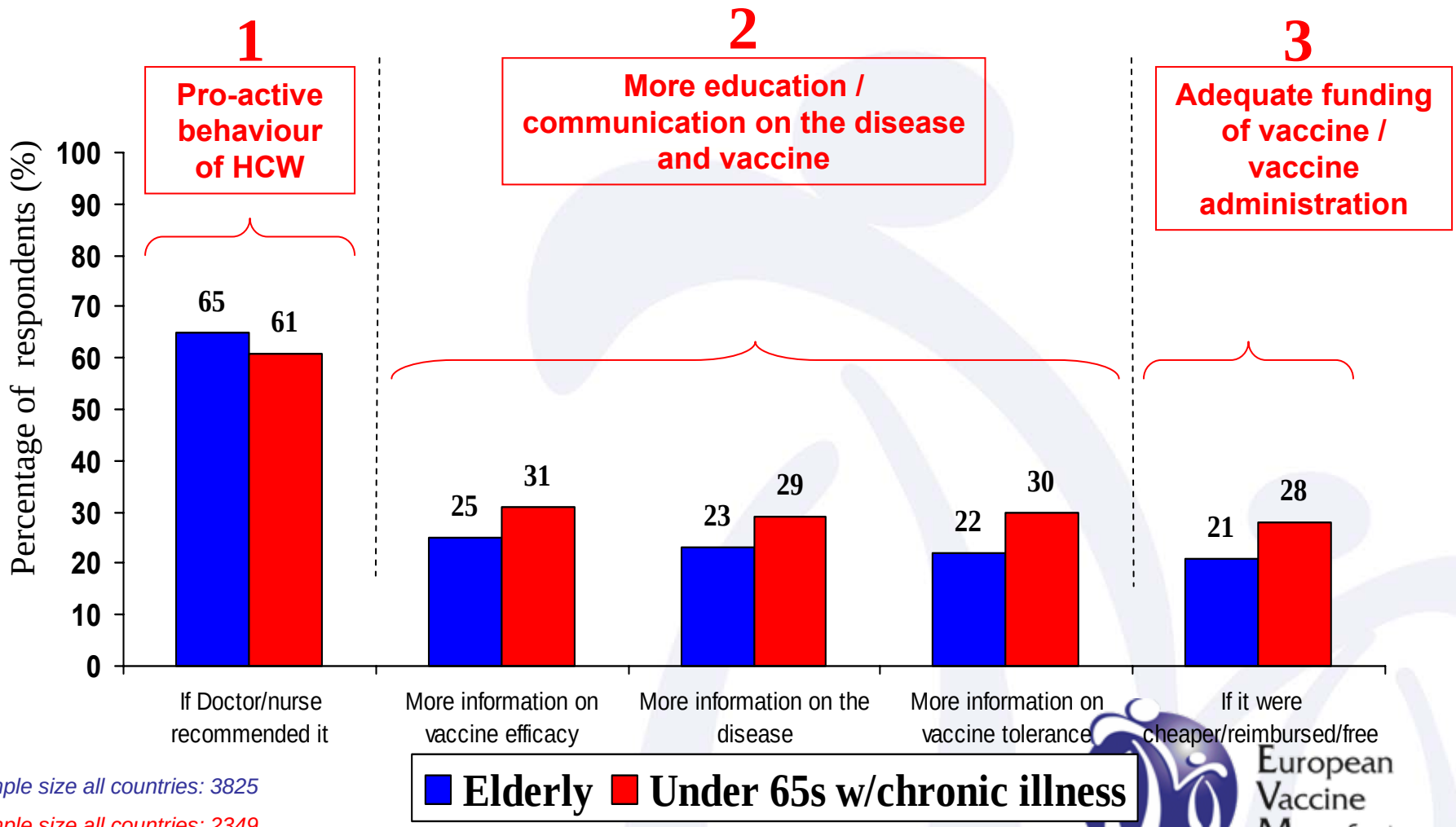
Implementation of seasonal flu vaccination policies: Three key drivers would improve vaccination uptake*



Sample size all countries: 3825

Sample size all countries: 2349

Source: TNS survey 2006/7. Data in file

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Key priorities and challenges for the industry

- **Complete development and licensing process**
  - Define optimal formulations
  - Develop appropriate and standardised immunological tools and animal challenge models
- **Address technical issues of the supply and logistics**
  - filling and packaging (multidose vials)
  - Stability, storage, supply chain …
- **Establish new vaccination strategies (pre-pandemic)**
  - Vaccination schedules
  - Duration of the protection
  - Cross-reactivity/protection with new mutated strains
  - Booster with homologous and heterologous strains

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Key priorities and challenges for Member States and International organisations

- **Define allocation and procurement processes for all countries**
- **Consider a policy for use of H5N1 stockpile and pandemic vaccines**
- **Develop and/or strengthen critical health systems and infrastructure for vaccine delivery** (inc. injection material)
- **Ensure implementation of seasonal influenza vaccination policies (inc. forecast and evaluation)**
- **Support industry efforts**

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The way forward:

Working in partnership

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The potential impact of dose-sparing stategies and capacity of Flu Seasonal on global Flu pandemic needs

- **Optimistic view**
  - **Successful antigen-sparing strategies achieved by major manufacturers could potentially solve the pandemic supply issue**

    Antigen production capacity might no more be an issue
- **Realistic view**
  - **Simple mathematical model to be consolidated (many remaining technical issues)**
  - **This will only be achieved if seasonal flu vaccine demand fits projected increase in seasonal flu production capacities**

Two priorities

1. **Implementation of seasonal flu vaccination policies**
2. **Procurement and distribution of vaccines**

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