

Global Action Plan to Increase Supply of Pandemic Influenza Vaccines



**World Health
Organization**

What is the Question

- | *How does the world produce enough pandemic influenza vaccine for the entire population on the planet?*
- The threat is global, strategies must be global
- Hence we are in this together, neither the private sector nor the public sector can do this alone
- Civil society and Community involvement is critical



How?

- | Identify activities with members states, especially vaccine producing countries, to determine the most feasible and efficient ways to expand production for a safe and effective vaccine once a pandemic starts.
 - Ø The WHA 56.19 noted: *that better use of vaccines for seasonal epidemics will help ensure that manufacturing capacity meets demands in a future pandemic....*



Method

- | WHO Consultation May 2006
- | Develop a Global vaccine action plan for pandemic influenza vaccines
 - National Immunization Program Managers
 - National Regulatory Authorities
 - Vaccine Manufacturers
 - Research Community



Why a Global Plan?

- | In order to strengthen pandemic-influenza preparedness and response, WHA 58.5 requested to WHO secretariat to seek solutions *with international and national partners, including the private sector*, to reduce the potential global shortage of influenza vaccines for both epidemics and pandemics, including vaccination strategies that economize on the use of antigens, and development and licensing of antigen-sparing vaccine formulations.



Objectives

- | The global action plan identifies approaches and strategies to increasing supply of influenza pandemic vaccines in order to reduce the anticipated gap between potential vaccine demand and supply during an influenza pandemic.
- | It is not just a WHO plan. It requires for its implementation the participation of key partners and stakeholders from governments, the research community, development banks, charitable foundations and the pharmaceutical industry.



Objective

Produce enough pandemic vaccine to immunize the world's population (6.7 billion people)

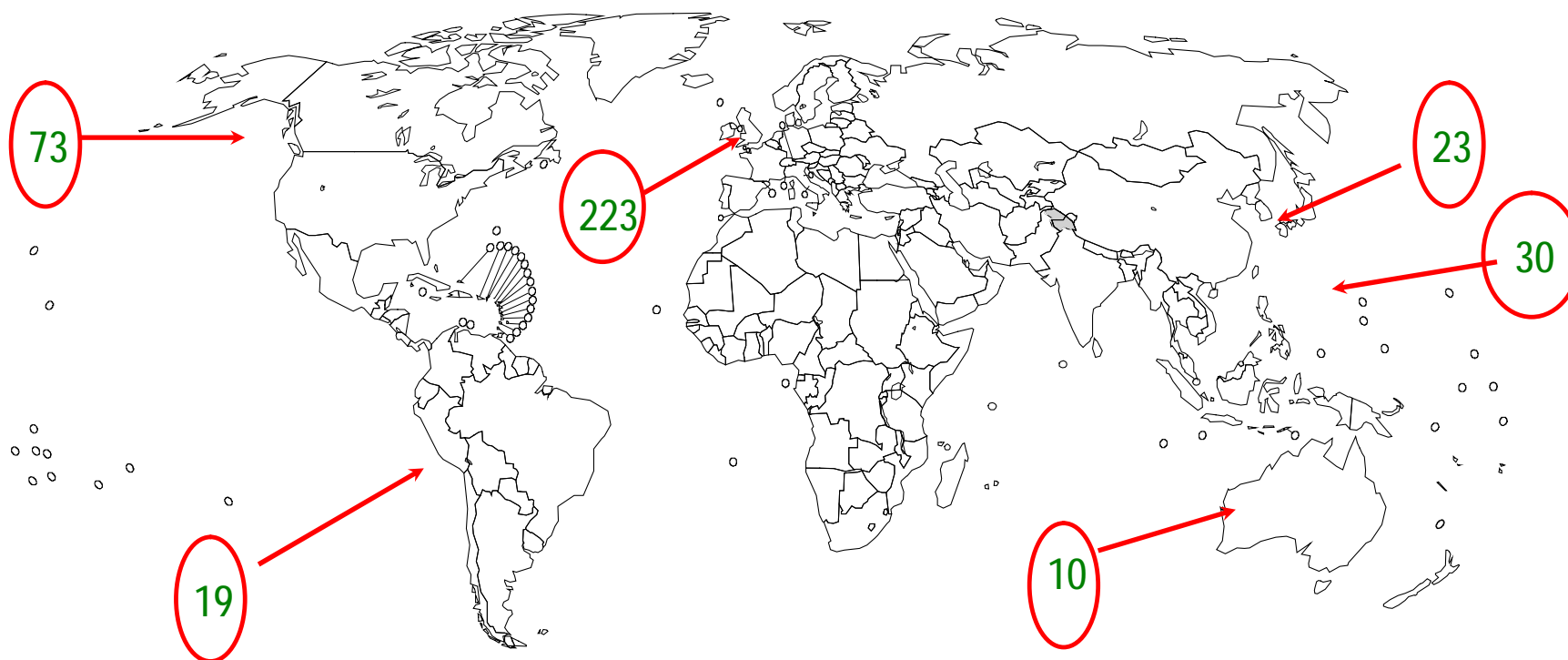


Present situation, current challenges: influenza vaccine production
(inactivated trivalent vaccine containing 15 µg of HA per dose)

- | Current capacity estimate : 350 million doses
- | Optimize current output (example 3 shifts /24 hours): 500 million doses
- | Planned expansion production capacity in the next 2-3 years (280 millions) : 780 million doses
- | Production capacity switches to *monovalent pandemic influenza* (2009 projection) : 2340 million doses of pandemic vaccine



Estimated number of seasonal trivalent influenza vaccine doses (in millions) produced by manufacturers, by geographic region, based on available data., March - 2007



Sources: data collected by site visit, reports, or by manufacturer

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Three major Approaches to increase pandemic influenza vaccine supply

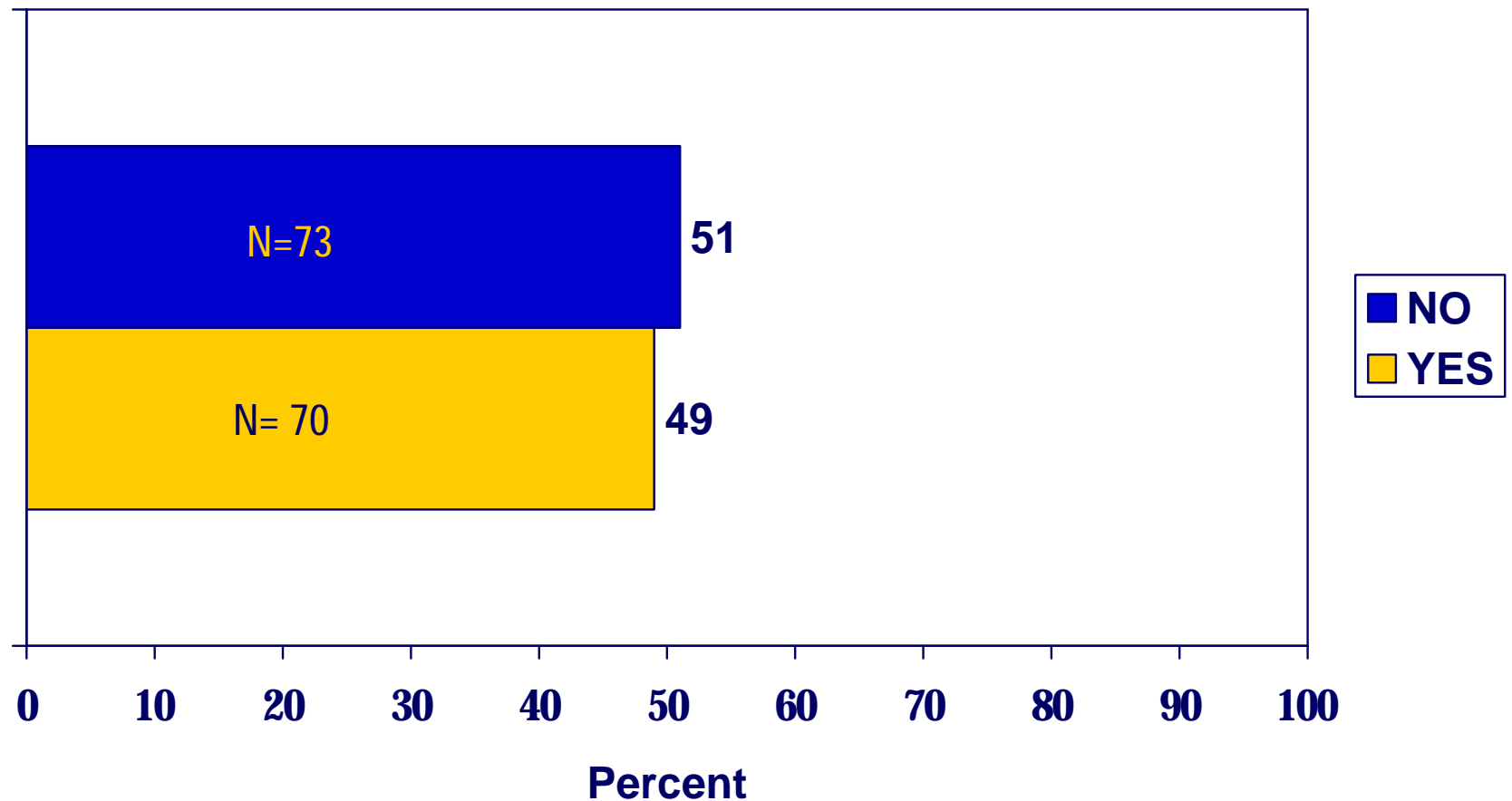
- I. Increase use of seasonal influenza vaccine
- II. Increase production capacity for pandemic vaccines, independent of seasonal vaccine use
- III. Research and develop new technologies



I. Increase use of seasonal influenza vaccine



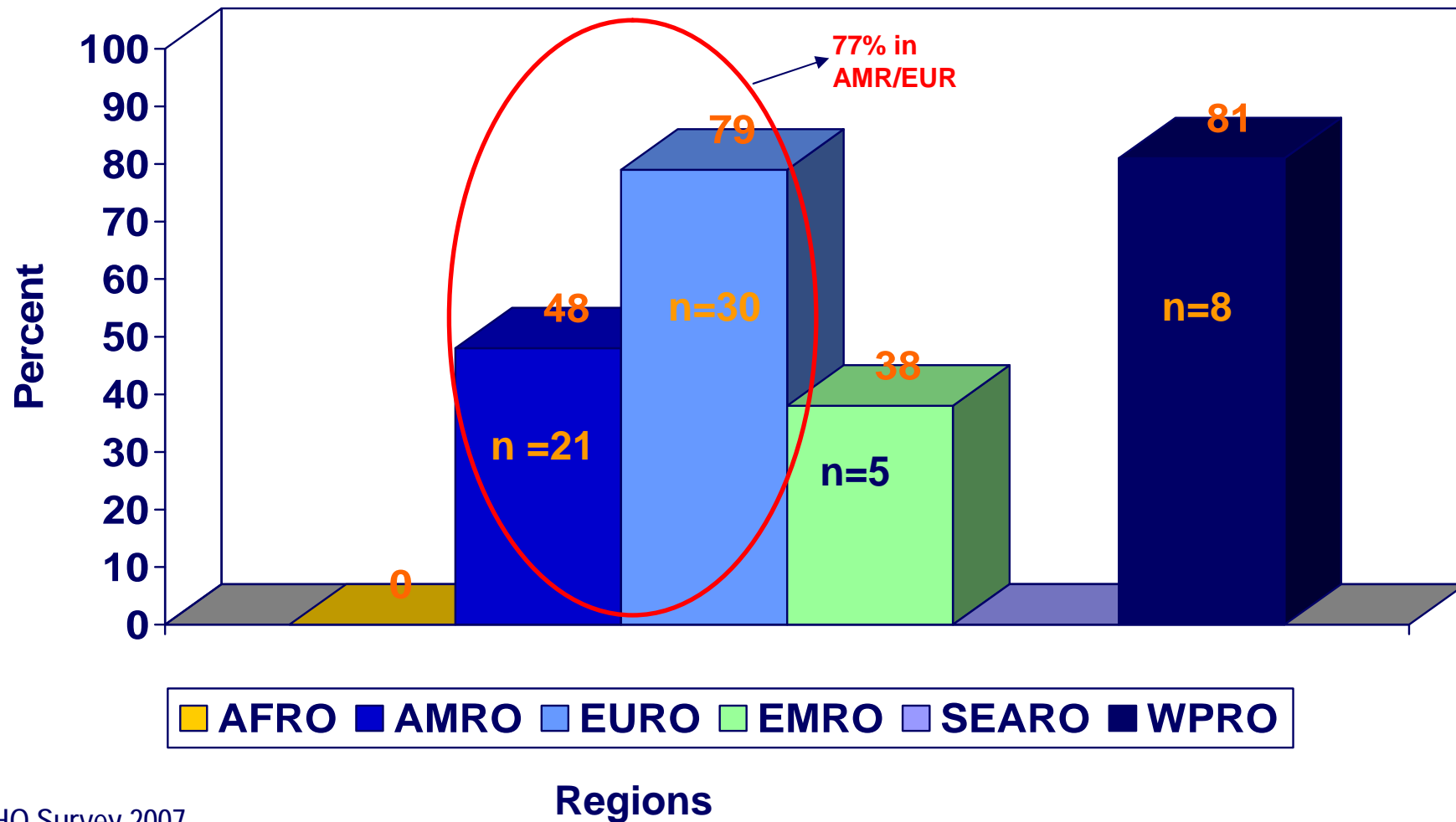
Percent of countries using a seasonal influenza vaccine (n=143)



Source: WHO Survey 2007



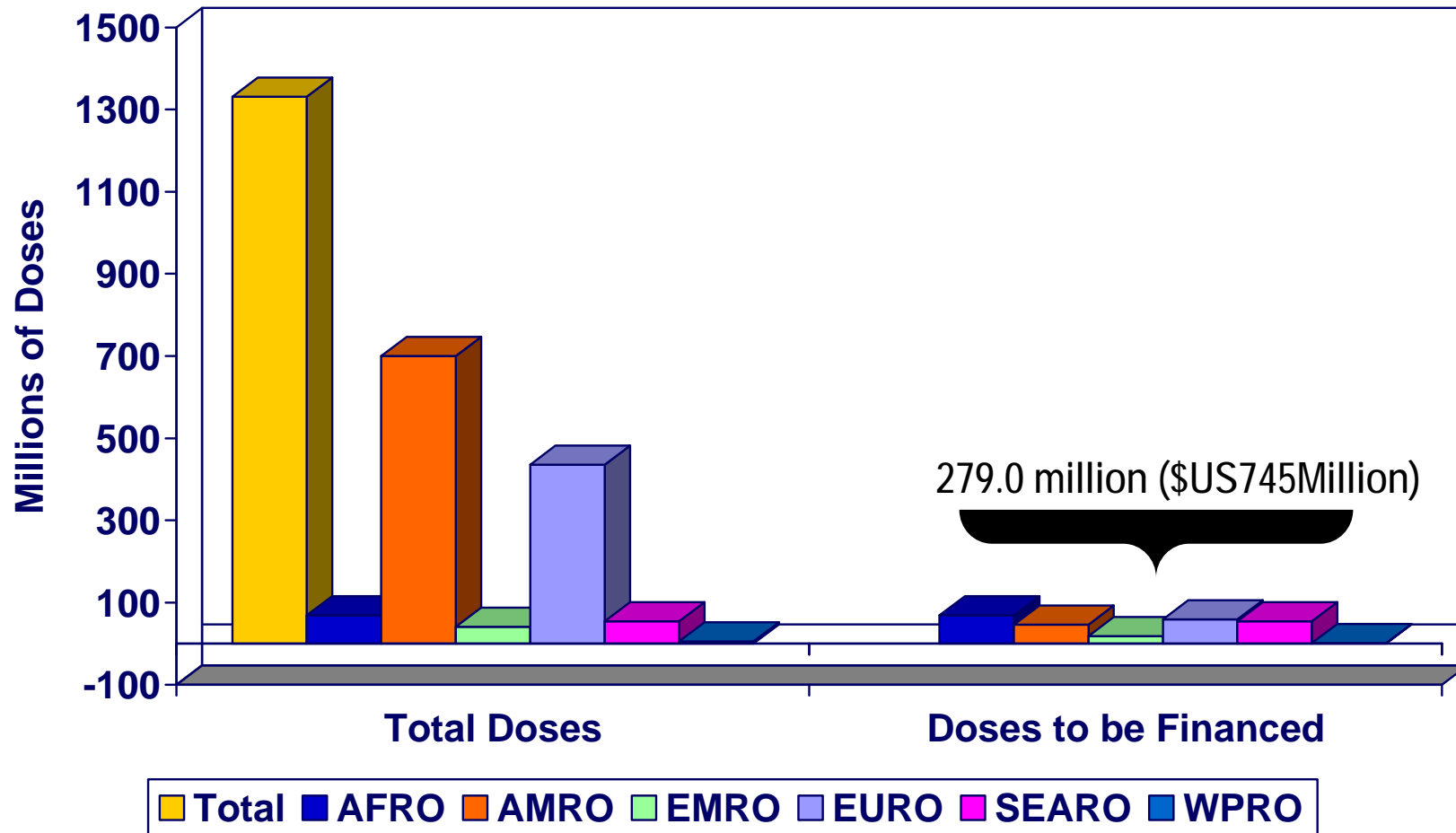
Percent of countries by Region that answered 'Yes' , to using a seasonal influenza vaccine



Source: WHO Survey 2007



Would your country purchase possible doses of a pandemic influenza vaccine doses and would your country require financing of the doses that could be purchased, by WHO Region



Source: WHO Survey 2007



Supporting Developing Country Access to Influenza Vaccines (1)

- | Under the umbrella of the GAP, WHO, UNICEF and GAVI are considering how the international community could work together to increase access to influenza vaccine for both seasonal and possible pandemic use. Potential investments will be proposed to the GAVI Board to:
 - Support introduction of seasonal influenza vaccine
 - Financial support, similar to other vaccines supported by GAVI
 - Promote vaccine production in selected countries
 - Improve national capacity to deliver a pandemic vaccine



Supporting Developing Country Access to Influenza Vaccines (2)

- I Creation of a virtual stockpile of a pandemic vaccine and a revolving stockpile of injection equipment:
 - Consideration for a stockpile of influenza prototype pandemic vaccine for use in developing countries.
 - Evaluation of the need for a revolving stockpile of safe injection equipment
 - o AD syringes

- I Establishment of a Advance Purchase Commitment (APC) mechanism for a pandemic vaccine
 - Would need financial support from GAVI or other donors; would specify demand for a predetermined number of doses at a guaranteed price



Supporting Developing Country Access to Influenza Vaccines (3)

- | Creation of a Revolving Fund for bulk purchasing of seasonal influenza vaccines:
 - Consolidation of vaccine requirements from all participating countries
 - One low price for all countries
 - WHO pre-qualified vaccine
 - Pre-determined delivery schedule to support smooth program operations
 - Facilitate the placement of influenza pandemic vaccine orders



Possible challenges to rapid access to a pandemic influenza vaccine

- | Licensing requirements in countries differ
- | Regulatory pathways affect vaccine approval
- | Post marketing surveillance systems in place are not uniform and in many countries are very weak

Ø Harmonization:

- Ø Agreed shared regulatory processes among groups of countries or even within a Region
- Ø Common licence application procedures, formats, and dossiers
- Ø Acceptance of same clinical trial data for evaluating safety and efficacy
- Ø Share high costs for achieving harmonization
- Ø Model to manage seasonal influenza vaccines

F Biggest winner: vaccine recipients

- Ø equivocal high quality safe vaccines everywhere



Supporting developing countries strengthen regulatory pathways for approval of influenza vaccines.

- | WHO will work with developing countries to:
 - provide standardized reagents
 - develop pharmacovigilance guidelines
 - promote regulatory convergence for the licensing of pandemic vaccines
 - work with manufacturers to strengthen their capacity for overseeing bio-safety measures



Some preliminary observations on challenges to access (1)

- | Low income and middle income countries will require financial assistance to buy the required vaccine to mitigate a pandemic.
- | Most resource-constrained countries do not include seasonal influenza in their national immunization schedule and do not have disease surveillance in place for assessing seasonal influenza burden.
- | Recent information from several assessments indicate that most low and middle income countries do not yet have the capacity to deliver an influenza vaccine within 7 days throughout a country. But this may true for many of the wealthier countries as well.



Some preliminary observations on challenges to access (2)

To improve and maintain the capacity to rapidly deliver a pandemic influenza vaccine for an event that maybe years away will require that countries provide the following support, especially if influenza vaccine production technology permits large quantities of vaccine to be produced in very short timeframes:

- | Government leadership under a interagency task force,
- | A pre-agreed pandemic influenza vaccine distribution plan,
- | Funding, and where necessary assure external multilateral support, and
- | Periodic simulations



II. Increase production capacity for pandemic influenza vaccines



WHO's efforts to assist in the transfer of appropriate technologies for development and evaluation of influenza vaccines in developing countries

I Transfer of technology for influenza vaccine production to developing country manufacturers

- WHO's role is one of facilitation between the owner of the technology and the developing country manufacturer.
- Nevertheless the final business decision to be agreed to remains between the two parties.



Establishment of in-country production capacity for influenza vaccines in developing countries (1)

- | Implement one of the priority activities identified in the GAP – *increase production capacity for pandemic influenza vaccines, both in industrialized and in developing countries*
- | Initial financial support has been provided by the USA and Japanese governments for a project to request project proposal:
 - Eligible technologies: inactivated (whole virus or split) and live attenuated vaccines, produced in eggs or on cell culture



Establishment of in-country production capacity for influenza vaccines in developing countries (2)

- | Request for Letters of Intent, November 2006
- | Selection of projects to be further developed in full proposals, December 2006
- | Full proposals received and evaluated, February 2007
- | Up to six proposals in final stages of negotiation

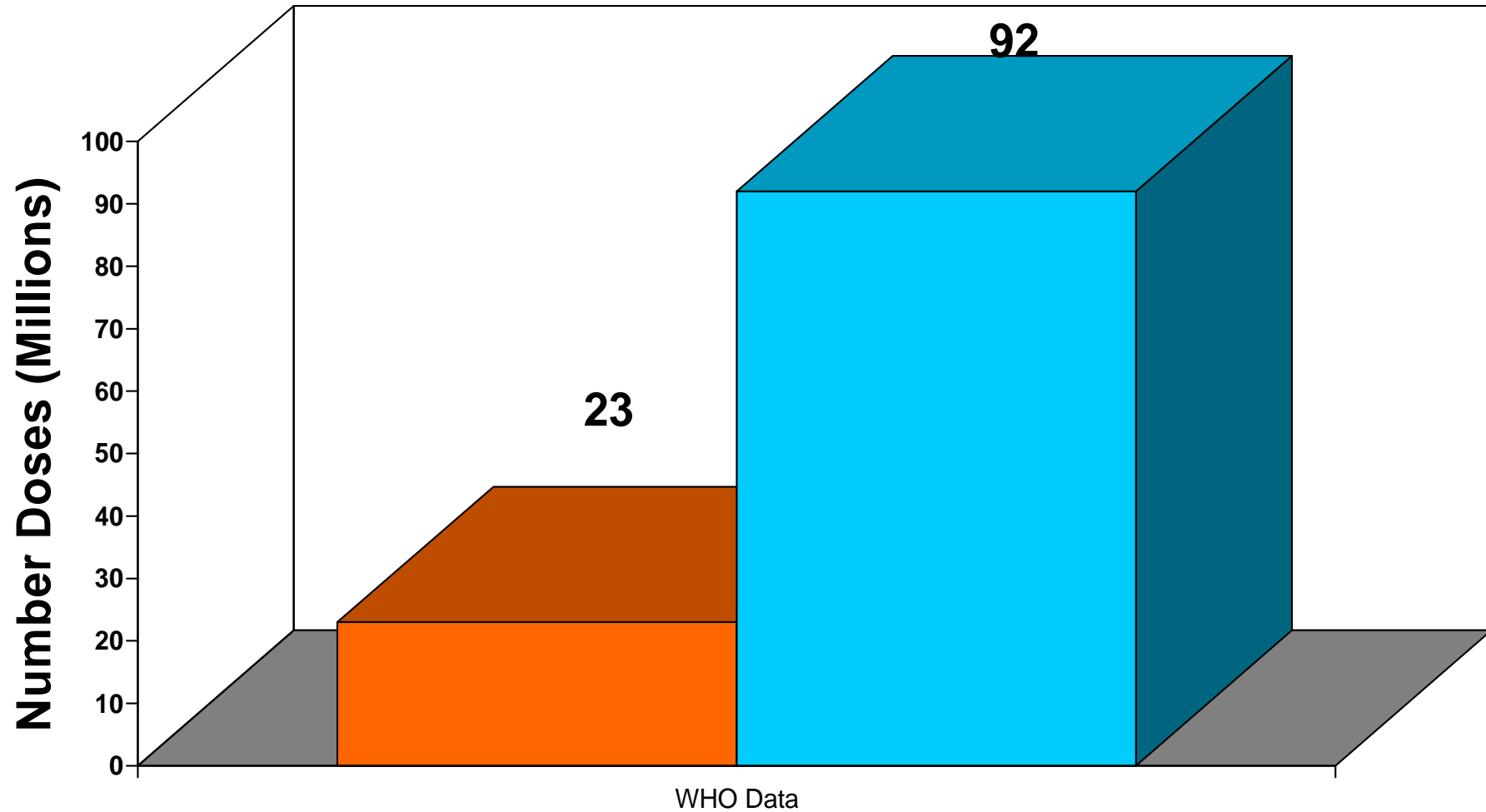


Potential outcome of the ongoing efforts of production capacity building in developing country

- | If the six projects are successful, they could - with a time horizon of 5 years - lead to an additional yearly production of at least of 40-50 million trivalent seasonal vaccine doses or 120-150 million monovalent pandemic doses in developing countries.
 - The type of seasonal vaccine will be either:
 - Inactivated
 - LAIV
 - Funding to create this additional capacity will come from national, other external donors and WHO



Results from WHO Assessment in one country, December 2006: Estimated Potential Increases in Total Seasonal Influenza Vaccine (in doses) as a result of tentative improvements and investments in six visited *Facilities*



■ Current Installed ■ Investments & Improvements



Industrial country vaccine manufacturers efforts to increase their capacity to produce influenza vaccine

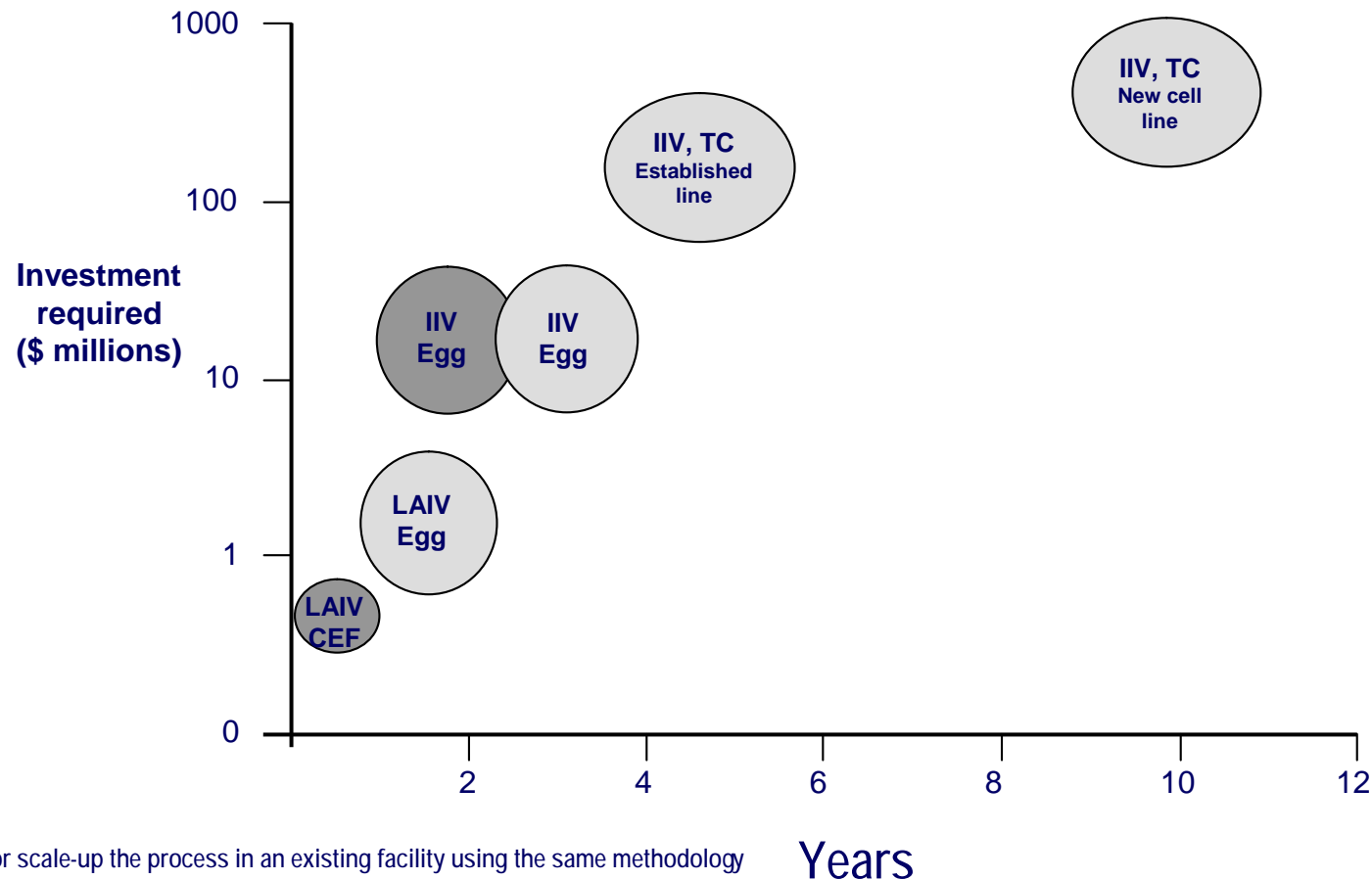
- | Developing new adjuvants to reduce HA contents of their vaccine and thus stretch their capacity to produce more doses.
- | Creation of alliance with developing country manufacturers for creating new production facilities: Novovax and Bharat Biotech - recombinant DNA vaccine
- | Bulk Fill and Finish Facilities
- | Possible Tech transfer agreements
- | Research efforts for testing new vaccines - H5N1



III. Research and develop new technologies



Indicative Timeline required to establish seasonal vaccine production (years)



Dark shading – adapt or scale-up the process in an existing facility using the same methodology

Light shading – set up process from scratch in an existing vaccine campus

Area of circle represents relative scale of production



Available Manufacturing Technologies

Available technological options

Egg-based process



Cell culture process



Transient expression of Haemagglutinin



Rino Rappuoli (2006, April 10) Schematic Diagram of available technological options. Presented at Potential Engineering Approach to a Pandemic.

<http://www.vaccine2006.org/program.html>

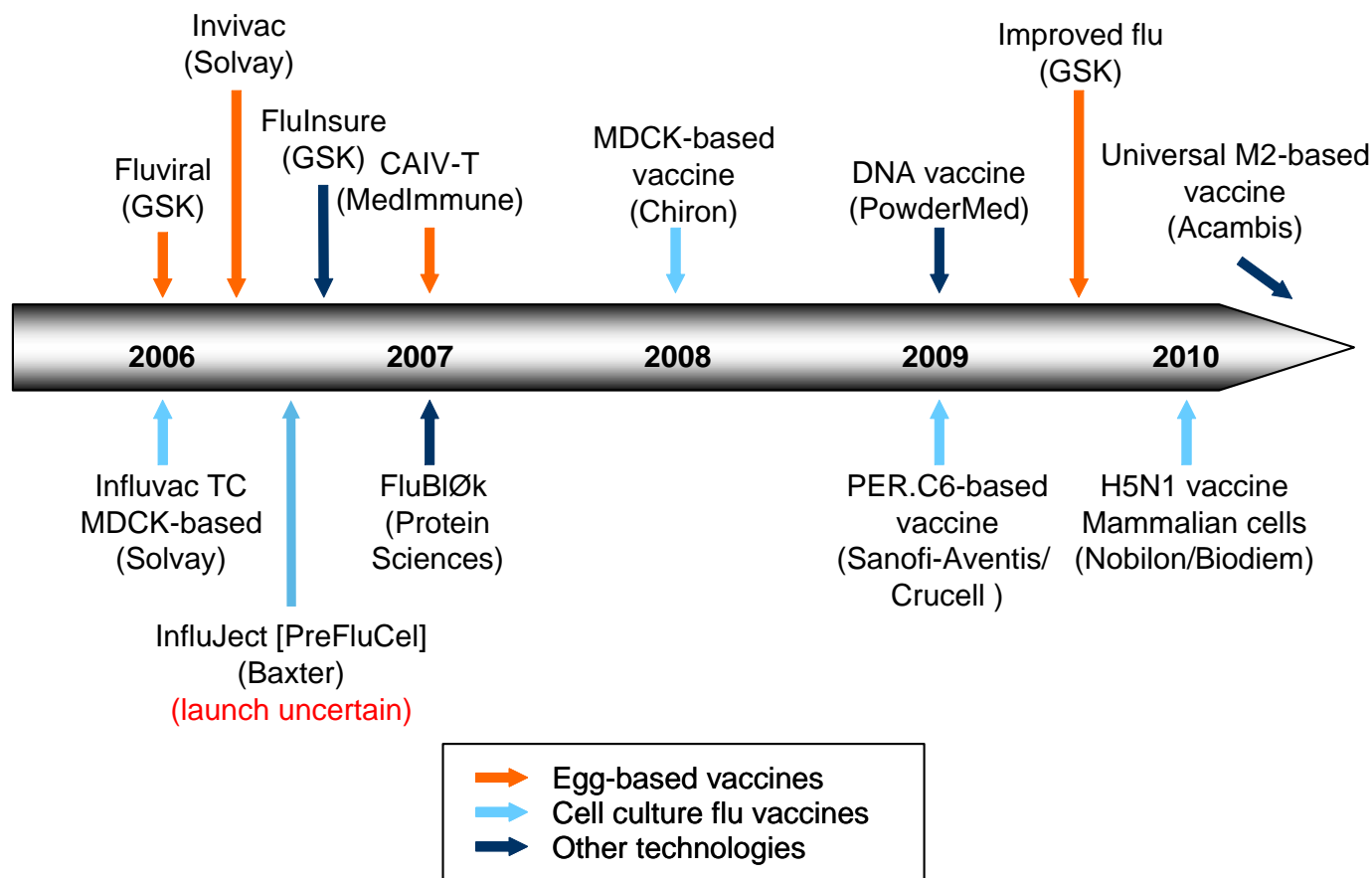
Source: Novartis Vaccines and Diagnostics



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- | The presentation of the following products and or processes for producing an influenza vaccine is for informational purposes only and does not constitute an endorsement by WHO for any of them.



Indicative timeline for new generation of influenza vaccines in the pipeline



Source: Data Monitor report 2005

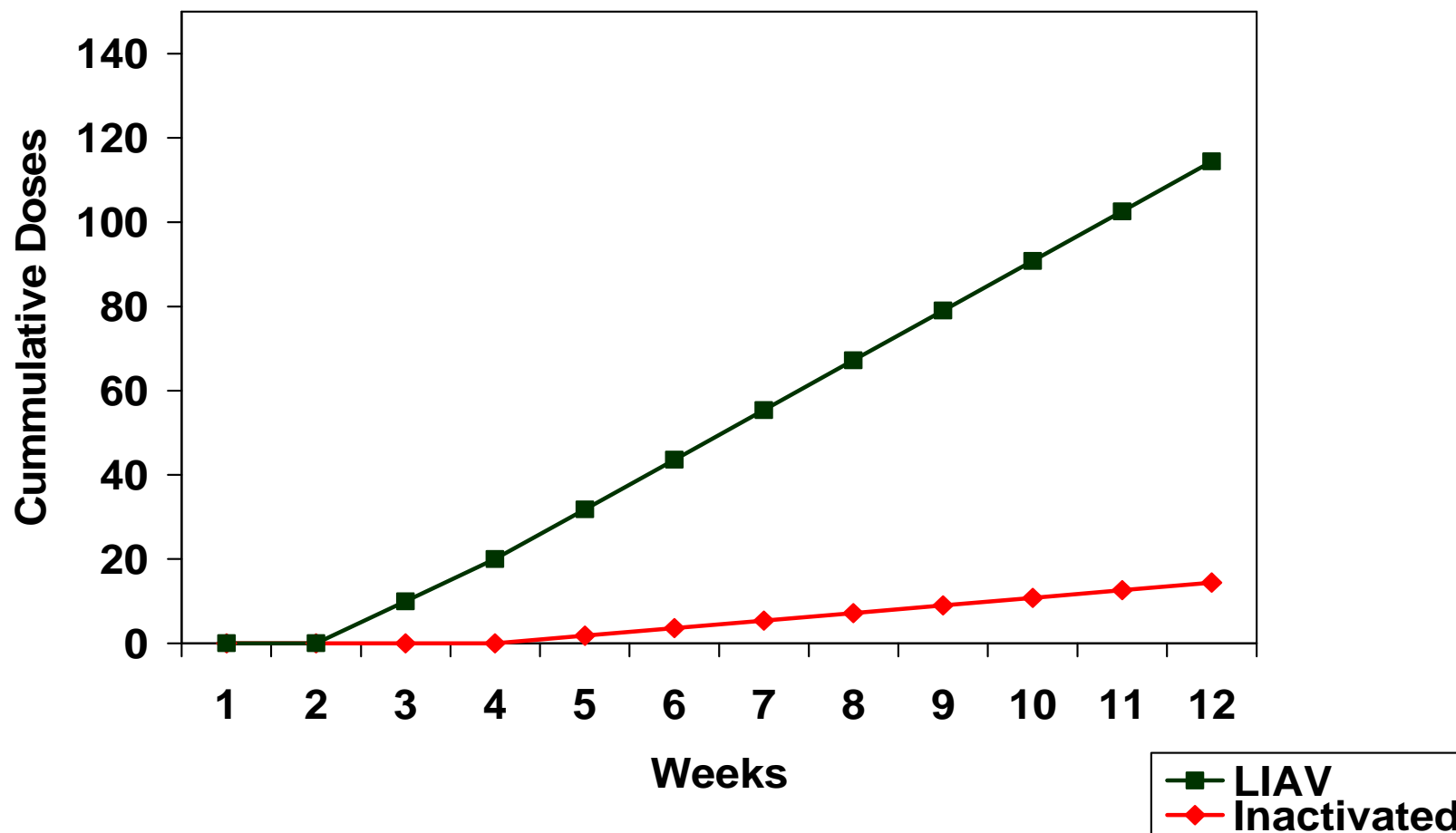


Live Attenuated Influenza Vaccines (LAIV)

- | Classic reassortment methodology: HA, NA are from circulating strains, the additional six genes are from proprietary backbone strains ("donor strains")
- | Temperature sensitive (ts) donor strains: limited growth at 37-39 centigrade
- | Cold adapted (ca) donor strains. Selected to grow well at reduced temperature such as in upper respiratory tract
- | Attenuation (att)
- | Licensed backbone viruses:
 - A/Leningrad/134/57(H2N2) and B/USSR/60/69: ca, att
 - A/Ann Arbor/6/60 and B/Ann Arbor/1/66: ca, ts, att
- | So far only egg-based products are licensed



Comparison of Estimated Output in doses of IIV and LAIV pandemic vaccine



In a facility with 20 million doses of seasonal influenza capacity for a normal production season



FluBIØk™ - Next Generation Vaccine for Influenza

"Making products where speed, cost and safety matters"

- | Trivalent recombinant HA (rHA) antigen vaccine
 - Produced *in vitro* via insect cell culture technology
 - Cloned from WHO/CDC recommended strains
 - Easier to produce, no eggs, no live viruses, no bio-containment required, no preservatives
- | Note: has not received national regulatory approval in any country to date.



Source  Protein Sciences
CORPORATION



Illustration : Rapid Production of a vaccine against Potential Pandemic Flu – Hong Kong “Bird Flu”



- Time required for development and production
 - Ø Six weeks from gene to product
 - Safety during production
 - Ø No need to grow or handle a live influenza virus
 - Ø Use of a well defined cell line versus egg production
 - Expected surge capacity:
 - Ø 1M doses of 135µg per 10,000L in 5-day production cycle
- F** feasible to produce billions of doses in a matter of weeks

Summary Comments (1)

- | WHO is working to fulfil the mandate given by the WHA:
 - Closing the 'gap' between the current production capacity and what may be required in the event of a pandemic by:
 - Working with partners to create new production capacity in developing countries, including provision of technical assistance to improve manufacturing efficiencies in countries with ongoing influenza vaccine production

- | WHO is collaborating with the IFPMA Influenza task force and other influenza manufacturers



Summary Comments (2)

- | WHO is working with regulatory agencies to evaluate how to harmonize regulatory procedures in order to standardize processes and rapidly approve the use of a pandemic influenza vaccine
- | WHO is exploring opportunities:
 - o to financially support access to a pandemic vaccine for developing countries
 - o On the feasibility to put into place new mechanism such as Bulk Procurement using a Revolving Fund to obtain more favourable prices for seasonal influenza vaccines
- | WHO is facilitating discussion between vaccine manufacturers from industrialized and developing countries for possible technology transfer agreements



Conclusion

- | Underlying the swift development and production of a pandemic vaccine is the rapidity with which any country identifies an emerging pandemic strain during an outbreak and shares the isolates with WHO
- | The success of the GAP hinges on everyone's cooperation and support. We can transform the present threat of avian influenza into a solid productive cooperation.

Thank You

