"Prospects for timely and effective vaccines for the next pandemic - Impediments".

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Health Systems and Innovation & Essential Medicines Programme

World Health Organization

"Prospects for timely and effective vaccines for the next pandemic - Impediments".

- **Vaccine will likely not be available for 24 weeks**
  - Stockpiles may not be useful
- Issues on the 'Switch' from seasonal to pandemic production
  - Decisions and Bottlenecks
  - CVV development, Biocontainment, Clinical, regulatory, delivery etc
  - Vaccine virus selection
  - Advice to WHO decision makers
- GAP progress after 10 years
- New vaccine platforms, improvements on current vaccines
- Nagoya protocol
- PIP

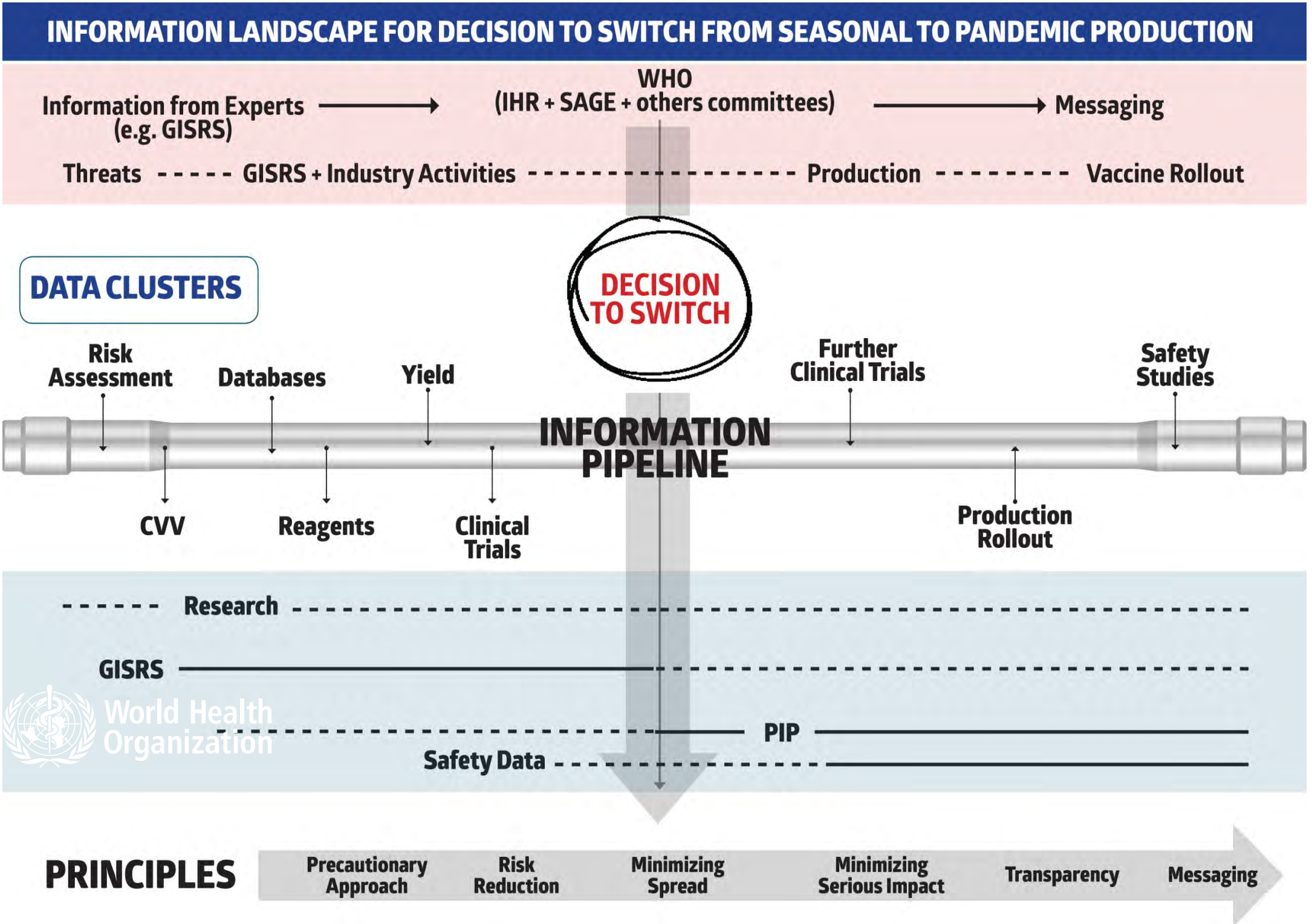
‘Switch’ meetings in 2015 2016 2017

Challenges and timelines in producing a pandemic vaccine

- AIM: Develop global strategy and operational mechanism for pandemic vaccine response at the start of a pandemic when seasonal influenza vaccine may still be needed in many parts of the world

- Timelines very tight - depend on interaction between many players
  - GISRS, WHO CC, WHO ERLs, GISAID/data platforms
  - Candidate Vaccine Virus (CVV) reassorting laboratories,
  - Vaccine manufacturers,
  - Regulatory agencies,
  - Governments
  - Clinical trial experts
  - Vaccine program managers

INFORMATION LANDSCAPE FOR DECISION TO SWITCH FROM SEASONAL TO PANDEMIC PRODUCTION



Mapping the pandemic vaccine production process

- Draft Operational Framework for Pandemic Vaccine Response – who?
- Timeline of pandemic vaccine production – when?
- Process for WHO pandemic vaccine response to pandemics – how?

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Practical considerations

- There are threats and bottlenecks in the manufacturing process which can cause a domino effect & affect both seasonal and pandemic vaccine production and availability.

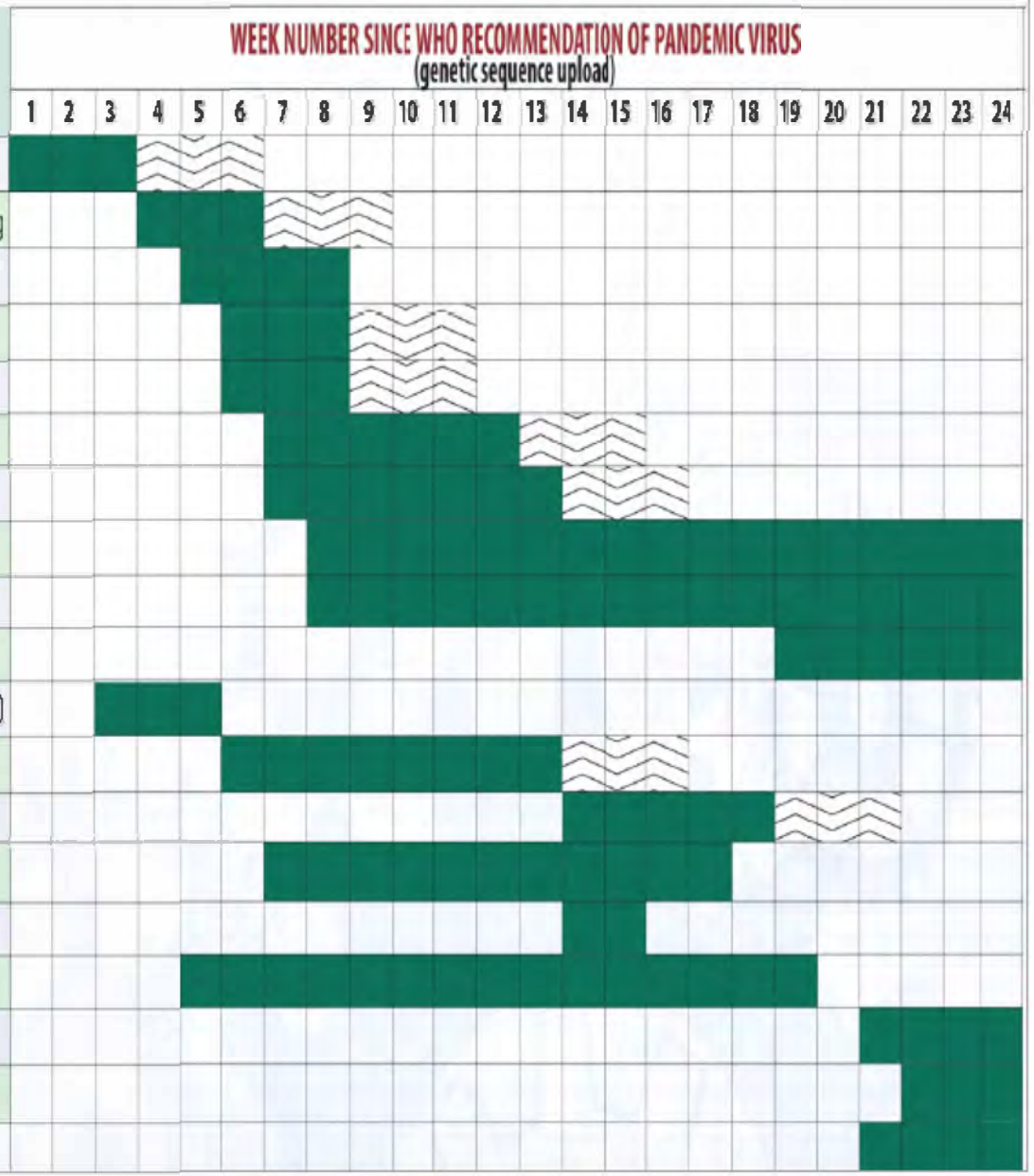
Identification of bottlenecks

Activity	Number of bottlenecks
CVV production/availability	6
Biocontainment for wt pandemic virus and CVV	4
Yield and manufacture of CVVs	4
Clinical trials for the first pandemic vaccine	5
Timing of SRID reagents for vaccine potency test	1
Regulatory harmonization	1
Risk assessment	1
Fill and finish capacity	1

TIMELINE OF PANDEMIC VACCINE PRODUCTION

"The when"

	ENTITIES	ACTIVITIES	ACTIONS
1	Reassorting Labs	Reassortant development	Development of CVVs for distribution
2	WHO CCs and Reassorting Labs	Reassortant evaluation	CVVs characterization including safety and shipping
3			Biosafety/GMO approval
4	Manufacturers	Reassortant assessment	CVVs Yield and growth characteristics
5		Developrrent	Clinical lot production
6		Clinical trials	Recruitment and Execution
7			Serology
8			ADR monitoring
9		Vaccine Production	Antigen production
10			Vaccine Formulation/Packaging/Distribution
11	ERLs	Reagents	Preparation of purified HA (for sheep immunisation)
12			Procuction of reagents
13			Calibrations and supply of reagents
14	Regulatory Authorities	Regulation	Strain variation in mock dossier
15			Emergency use approval
16			Registration process
17		Lot release	SRID and Endotoxin tests, cold chain review
18		Pharmacovigilence	AEFI monitoring
19	Program managers	Vaccine Distribution	Vaccine available for deployment



Bottlenecks

CVV production/availability

Bottleneck	Data needed	Solutions
Lack of suitable BSL3/GMP laboratories for early small scale work	• Review number of suitable labs available	• Dedicated publically-funded pilot BSL3/GMP labs
Not enough labs producing CVVs especially from highly pathogenic viruses	• None identified	• WHO to identify and establish more pandemic CVV labs
Not enough high containment labs for making LAIV CVVs	• Review number of suitable labs available	• Dedicated publically-funded pilot BSL3/GMP labs
Slow decision on CVV status for Nagoya Protocol or SMTA2	• Prepare a review of the type of CVVs to be produced and their use	• WHO to obtain clarification
Uncertainty about manufacturers' obligations to share synthetic seed viruses and shipping requirements	• None identified	• Manufacturers to start dialogue with WHO
Delays in shipping	• None identified	• Manufacturers to obtain import permits (including GMO CVV) in advance; obtain agreement(s) with courier(s)

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Bottlenecks
Yield and manufacturing of CVVs

Bottleneck	Data needed	Solutions
Identification of the type of safety tests needed; availability of wt virus comparator; the need for ferret safety tests	• wt virus risk assessment • Criteria for attenuation and biosafety and utility of safety tests	• WHO to review guidance on safety testing of CVVs
Continued need for chicken pathogenicity tests of CVVs derived from hp viruses	• Historical review of chicken test data • Review in vitro test data	• WHO/WHO CCs request that either USDA remove requirement for chicken pathogenicity test or remove hp influenza viruses from Select Agent status
Slow decision on biosafety and USDA Select Agent status; biosafety status could be country-specific	• Information on pathogenicity • Sequence especially HA/NA gene segments and including both egg and cell isolates	• All CVV labs aiming to work with hp viruses should register with USDA in advance • WHO to lead and coordinate biosafety assessment and to speed up assessment • WHO to provide feedback on IFPMA 'white paper' on CVV biocontainment • Better coordination of CVV labs • Better communication between CVV labs and manufacturers • CVV labs to standardized lab release documents for CVVs • Future use of synthetic HA/NA CVVs
Uncertainty about biosafety status of synthetic CVVs especially with USDA Select Agent status	• Information on pathogenicity • Sequence especially HA/NA gene segments and including both egg and cell isolates	• Manufacturers to clarify status with human and agricultural safety authorities • WHO to coordinate

Bottlenecks
Clinical trials for the first pandemic vaccines

Bottleneck	Data needed	Solutions
Delay in availability of clinical trial vaccine lots, specifically related to vaccine potency assays	• Data from SRID and alternative potency assays	**WHO and ERLs to review and recommend alternative potency assays**
Delay due to GMO issues	• Certificate of analysis	• None identified
Delay due to country-specific vaccine lot release	• Lot release data	• WHO to coordinate pandemic vaccine lot release globally
Delay in clinical trial protocol review	• None identified	• Harmonize clinical trial procedures
Delay in serology assays	• Robustness and reproducibility of assays	• Improvement, standardization and acceptance of assays

Bottlenecks
Timing of SRID reagents for vaccine potency testing

Bottleneck	Data needed	Solutions
Delays in reagent supply will delay vaccine lot release and vaccine supply	• Availability of antigen and antiserum for use in reagent production • Biosafety status of antigen • Which CVV is being used? • Suitability of existing reagents i.e. are new ones really needed? ○ Is use of heterologous reagents realistic?	• Reagent supply needs better coordination and harmonization • **Alternative validated potency tests** • **Early start of antiserum production (before CVV availability)** • **Allow use of heterologous reagent** • **Consider making panel of reagents at risk**

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Bottlenecks
Regulatory harmonization

Bottleneck	Data needed	Solutions

Lack of mutual recognition of regulatory procedures leading to delays in vaccine supply	• Review regulatory requirements in different countries
	• Identify a basic set of criteria for seasonal and pandemic vaccine Prequalification
	• What requirements are there for donated vaccines in an emergency
	• Do country NRAs meet published criteria for functionality
	• Robustness of pandemic vaccine capability in countries
	• Review of data on vaccine effectiveness
	• Explore labelling requirements for emergency use of pandemic vaccine
	• Review pandemic vaccine lot release requirement in different countries
		• Cross communication between regulatory authorities
		• WHO to introduce Prequalification for seasonal and pandemic influenza vaccines
		• Continue to support regional regulatory harmonization in low and middle income countries
		• Establish or strengthen NRA's:
		  ○ Regulatory systems
		  ○ Marketing Authorization
		• Agreement on criteria for assessment of vaccine effectiveness
		• Harmonization of labels and package inserts for pandemic vaccines
		• Harmonization of pandemic vaccine lot release

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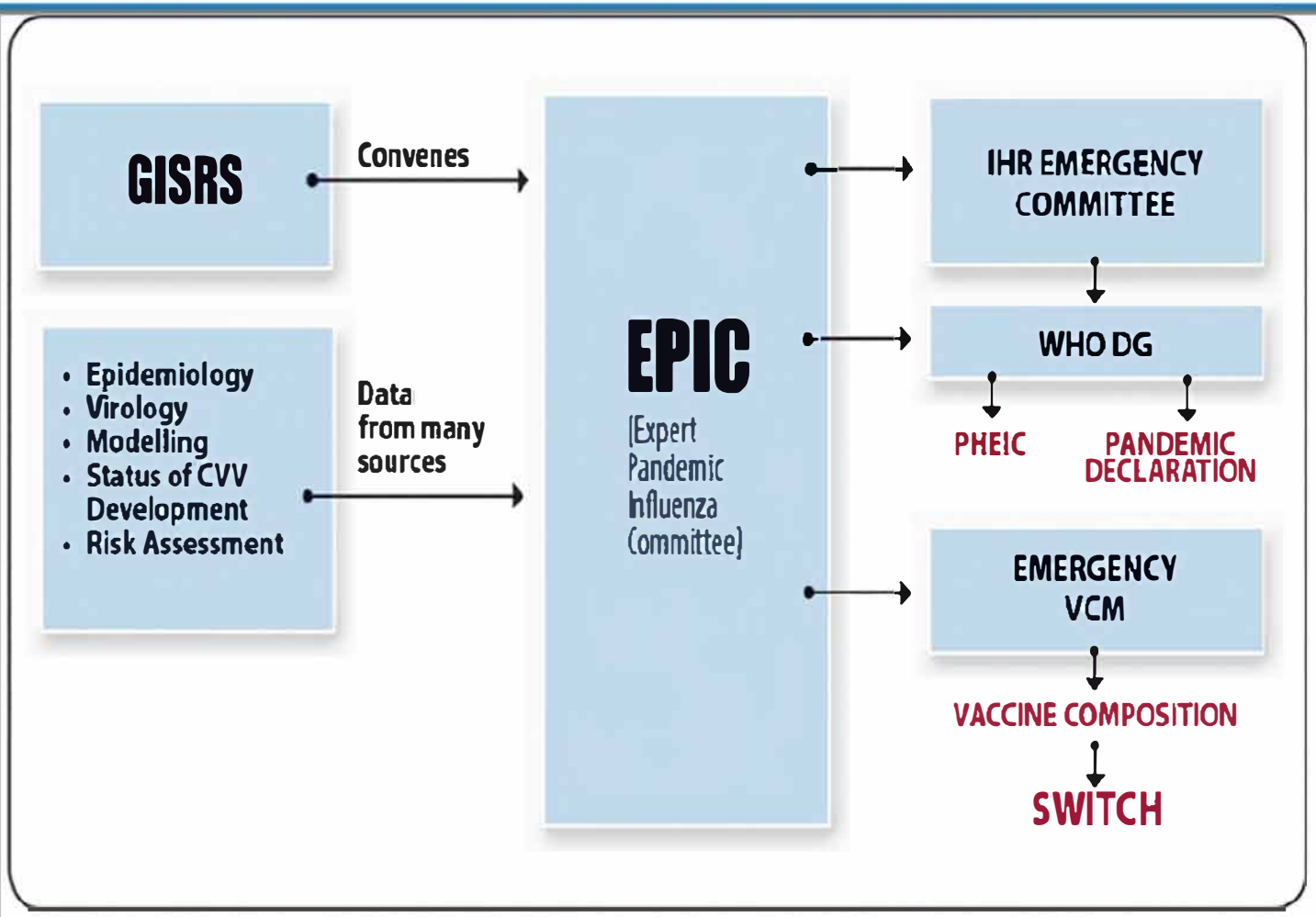
Principles to guide Decision Making

- Any decision will be made on incomplete data.
  - Amount and quality of later data likely to be different
- If no switch is recommended, need flexibility to review the recommendation as new data arises,
- The declaration of a pandemic does not automatically trigger a switch to pandemic vaccine production
  - Time of year, geography, severity of pandemic and seasonal infections, availability of CVVs all affect decision
- The WHO recommendation should maximise global health and be guided by expert opinion

Process for WHO pandemic vaccine response – "The How"



The Role of **EPIC** in declaration of a **PHEIC** and a Pandemic and in initiating vaccine switch

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Key messages – Switch meetings

- Recommendation of the formation of an Expert Pandemic Influenza Committee (EPIC), which would provide advice to WHO decision makers.
- A set of principles for EPIC to follow to ensure a clear, transparent and integrated approach to the process of declaring a PHEIC or pandemic.
- Proposal of a process to activate the vaccine Switch by means of a WHO Emergency Vaccine Composition Meeting (VCM). The Emergency VCM would recommend the composition of a pandemic vaccine, which would in turn activate and globally harmonize the Switch process.
- Suggestions for solutions to the technical bottlenecks that would interfere with making a timely Switch and making pandemic vaccine available quickly.
  - leading entities to work on solutions, including creation of Implementation Groups
  - Suggestion that many of the technical bottlenecks could be solved by use of a publicly funded, small-scale GMP pilot lot vaccine production facility
- The perspective of Low and Middle Income countries was included in the outcome of the Consultation.

Key messages – Switch meetings

- Recommendation to explore the feasibility of establishing a publicly funded small scale GMP pilot lot vaccine production facility.
- The facility could be used in the early stages of pandemic vaccine development by assessing CVV yield; assessing biosafety; producing pilot lots of vaccine for evaluation of process yield and for clinical evaluation; supplying antigen for potency reagents; and establishing diagnostic capacity.

Working Group Meeting on the Revision of the WHO TRS941

May 9 -10 2017

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2007
The TRS 941

- The TRS 941 document is critical guidance to CVV and GISRS laboratories, national regulators and all manufacturers, as well as other international organizations such as the OIE, national agencies.
- There is a need to keep the TRS 941 guidance up to date.

2009

- Manufacturers' were delayed in starting vaccine manufacturing for H1N1pdm09 vaccine until the biocontainment level was determined by WHO
- Concerns developed that vaccine will again be delayed if another pandemic virus emerges soon.
- *These issues have led manufacturers and regulators to seek revision, clarification and updating of the current TRS 941 document.*
- Ideally there would also be regulatory harmonisation and agreement on BSL level according to risk assessment criteria so that any delay in manufacturing would be avoided.

2012
IFPMA 'White Paper'

- IFPMA produced a detailed 'white paper' in 2012
- *Biocontainment Requirements for Influenza Vaccine Manufacturing Facilities*
- Details alterations to the TRS 941 from a manufacturing perspective.
- *A key issue in this document is the call to allow manufacturers to proceed with pandemic vaccine production prior to completion of safety testing during a pandemic alert period, provided agreed BSL safety conditions can be met.*

Global Action Plan (GAP) for Influenza Vaccines (2006-2016)

Concerning situation in 2006: Small production capacity & concentrated in a few HICs

10 year strategy to reduce anticipated global shortage & inequitable access to vaccines in the event of an influenza pandemic

Goal: Capacity to produce enough vaccine to immunize 70% of the global population with 2 doses of vaccine = ~10 billion doses

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Progress Toward GAP Goal

Situation in 2006

- Enough capacity to produce 1.5 billion doses of pandemic vaccine
- Production was based entirely in HICs

Situation today

- Enough capacity to produce 6.4 billion doses of pandemic vaccine
- Production has expanded to include LMICs
- But, still falls short of global needs (10 billion doses) & challenges to maintaining this capacity

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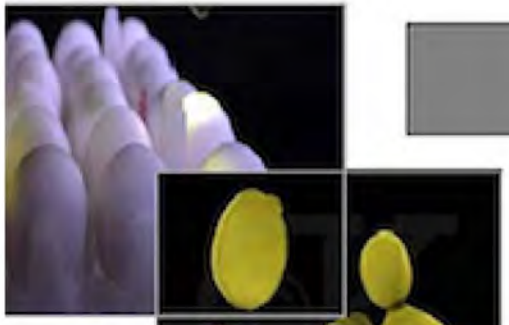
GAP progress under Objective 3
Promote R&D of influenza vaccines

- Some novel vaccines licensed, but overall little R&D progress
  - *Recombinant baculovirus (Flublok), LAIV, Quadrivalent, adjuvanted seasonal (infants); high dose ID (elderly)*
- Still far from a "universal" flu vaccine
- WHO has published ‘Preferred Product Characteristics (PPC) for Next Generation Influenza Vaccines’

Review of Production Technologies

- Changing landscape technology
- Only way to ensure long term aim of vaccine availability for all
  - ie a variety of Tech needed at this stage
  - **Need for new high performance Platform Technologies**
- Current Technology (Eggs and cell culture)
  - Long established (safe) production processes
  - Suffer from unpredictable yields and growth properties
  - Poorly responsive to surge capacity for a pandemic outbreak

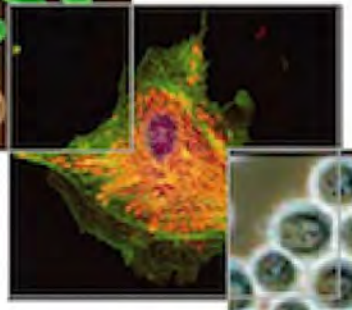
Goal: Development of technology that will address unmet needs



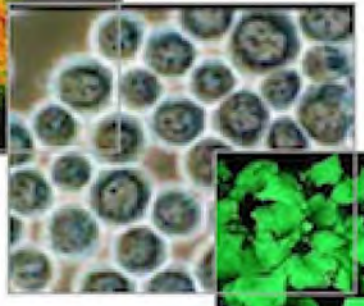
Safety

Capacity

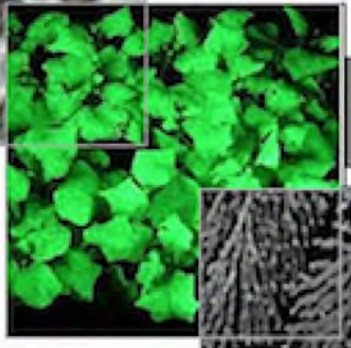
Low Cost

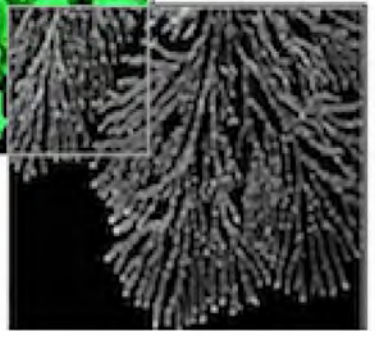


Rapid Response

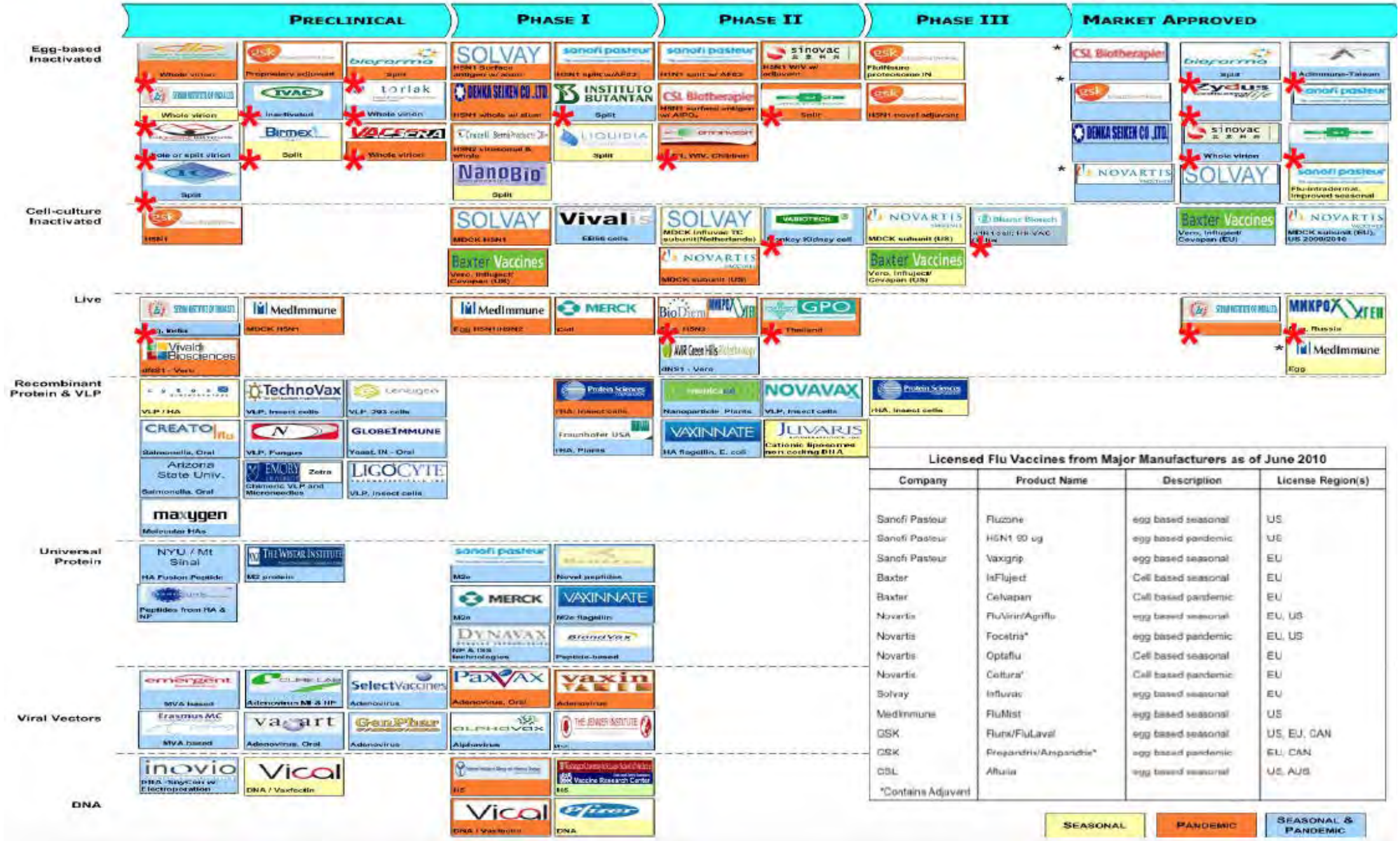


Simple Manufacture





Influenza Vaccine Technology Landscape (05/2015)



Licensed Flu Vaccines from Major Manufacturers as of June 2010

Company	Product Name	Description	License Region(s)
Sanofi Pasteur	Fluzone	egg based seasonal	US
Sanofi Pasteur	H5N1 90 ug	egg based pandemic	US
Sanofi Pasteur	Vaxigrip	egg based seasonal	EU
Baxter	InFluject	Cell based seasonal	EU
Baxter	Celvapan	Cell based pandemic	EU
Novartis	FluVirin/Agriflu	egg based seasonal	EU, US
Novartis	Focetria*	egg based pandemic	EU, US
Novartis	Optaflu	Cell based seasonal	EU
Novartis	Celtura*	Cell based pandemic	EU
Solvay	Influvac	egg based seasonal	EU
MedImmune	FluMist	egg based seasonal	US
GSK	Flurix/FluLaval	egg based seasonal	US, EU, CAN
GSK	Prepandrix/Arnpandrix*	egg based pandemic	EU, CAN
CSL	Afluria	egg based seasonal	US, AUS

*Contains Adjuvant

The Nagoya Protocol

WHO Switch 3 Meeting

June 7-9th 2017

https://www.cbd.int/abs/

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What is it?

- International agreement which aimed at sharing the benefits arising from the utilization of genetic resources in a fair and equitable way
  - Flows from the Convention for Biological Diversity (1992) (150 signatories)
- Key elements are
  - **Access**: rules and procedures covering provision of access to resources by owner
  - **Benefit Sharing**: rules and procedures covering utilization of resources by user
  - **Compliance**: obligation to monitor and enforce
    - Due diligence requirements for users to ensure materials have been properly sourced
    - Key checkpoints identified for scrutiny (e.g. sale of a product)
- Came into force in Oct 2014
  - 99 countries (parties) have now ratified the Nagoya protocol
  - Notable exceptions: US, China

To whom does it apply?

- All organisations, individuals, commercial, not for profit, academic operating in countries who have signed the Nagoya Protocol

Why is it a problem for GISRS?

- Pathogens have been considered as ‘in scope’ of Nagoya
  - EU interpretation is very clear
  - Other countries likely to adopt same interpretation
- Implications
  - Access to materials could be restricted by provider countries
- System depends on constant extremely rapid transfer of materials around the world
  - 143 NICS, 6 CCs, 4 ERLs, many vaccine manufacturers
- So little knowledge/understanding of Nagoya that finding a national focal point a challenge

Potential Consequences

- Range of materials available for analysis and utilisation for vaccine production may be restricted

Likely that supply of materials from NICs will carry on, but..

- Labs in Nagoya countries will be technically breaking national laws
- Manufacturers in Nagoya Countries won't want to use materials for which Nagoya obligations have not been met
  - Key checkpoint when products sold

What can be done?

For pandemic materials

- Formally recognise PIP as an international instrument (EU lead)

For seasonal materials

- Favourable interpretation of Nagoya
  - Pathogens excluded from national legislation
  - Use sequence information only for building vaccine candidates

Acknowledgements

- **Switch Meetings:**
  - John Wood, Otfried Kistner, Nancy Cox, Bram Palache, Derek Ellis, Stephen Ingliss (consultants)
  - Bruce Gellin and Jacki Katz (Switch Meeting Chairs)
- **Biocontainment meeting (TRS941)**
  - Jerry weir, Othmar Engelhardt, Tiequn Zhou
- **GAP**
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  - IVB/IVR, Health Systems and Innovation, EMP, GIP
- **Rick Bright and BARDA colleagues**