

Situation Update Pandemic (H1N1) 2009

1st September 2009



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Read before using the presentation

- The presentation will be updated weekly: Every Thursday by 17:00
- It will be accessible on the sharedrive: [K:\cldata\A \(H1N1\) swine flu US_Mexico April 2009\Generic Slide Set](#)
- Contact person for comments and suggestions
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 - Ms Marie H el ene Vannson vannsonm@who.int
- The presentation can be used entirely or partially. Speakers notes accompany the slides and are updated by relevant experts.
- See the target audience, the purpose and the objectives on the next slides



Users and target audience

This slide set is to be used by the WHO technical staff to inform:

- ↪ WHO staff in HQ, Regional or Country Offices,
- ↪ Partners and other international agencies,
- ↪ Participants to meetings (Scientifics, donors, etc...)

Purpose

About the pandemic (H1N1) 2009:

- To provide an update and an overview of the situation
- To describe the epidemiology
- To describe the characteristics of the infection and the evolution of the virus
- To explain the clinical management strategies
- To explain the strategy of production and supply of the vaccines and antivirals



Outline

- Introduction and timeline
- Epidemiology
- Evolution of the new virus
- Clinical management
- Vaccines and antivirals





Introduction

- April 2009: WHO received reports of sustained person to person transmission with a new influenza A (H1N1) virus in Mexico and USA
- Virus currently spread in all regions
- Current alert level: Phase 6
- Group of experts developed advice based on available information on influenza A (H1N1), seasonal and avian H5N1 influenza virus





Timeline (1)

- **April 12:** an outbreak of influenza-like illness in Veracruz, Mexico reported to WHO
- **April 15–17:** notification of clusters of rapidly progressive severe pneumonia in Distrito Federal and San Luis Potosi
- A case of atypical pneumonia in Oaxaca State promoted enhanced surveillance
- **April 15-17:** two cases of the new A (H1N1) virus infection identified in two southern California counties in U.S.A.
- **April 23:** new influenza A (H1N1) virus infection confirmed in several patients in Mexico.



Timeline (2)

- **April 26:** 38 cases reported from Mexico and the US
- **April 27:** Canada and Spain reported confirmed cases
- **April 28:** UK, Israel, New Zealand
- **April 27:** WHO declared phase 4
- **April 29:** WHO declared phase 5
- **June 11:** WHO declared phase 6 - pandemic

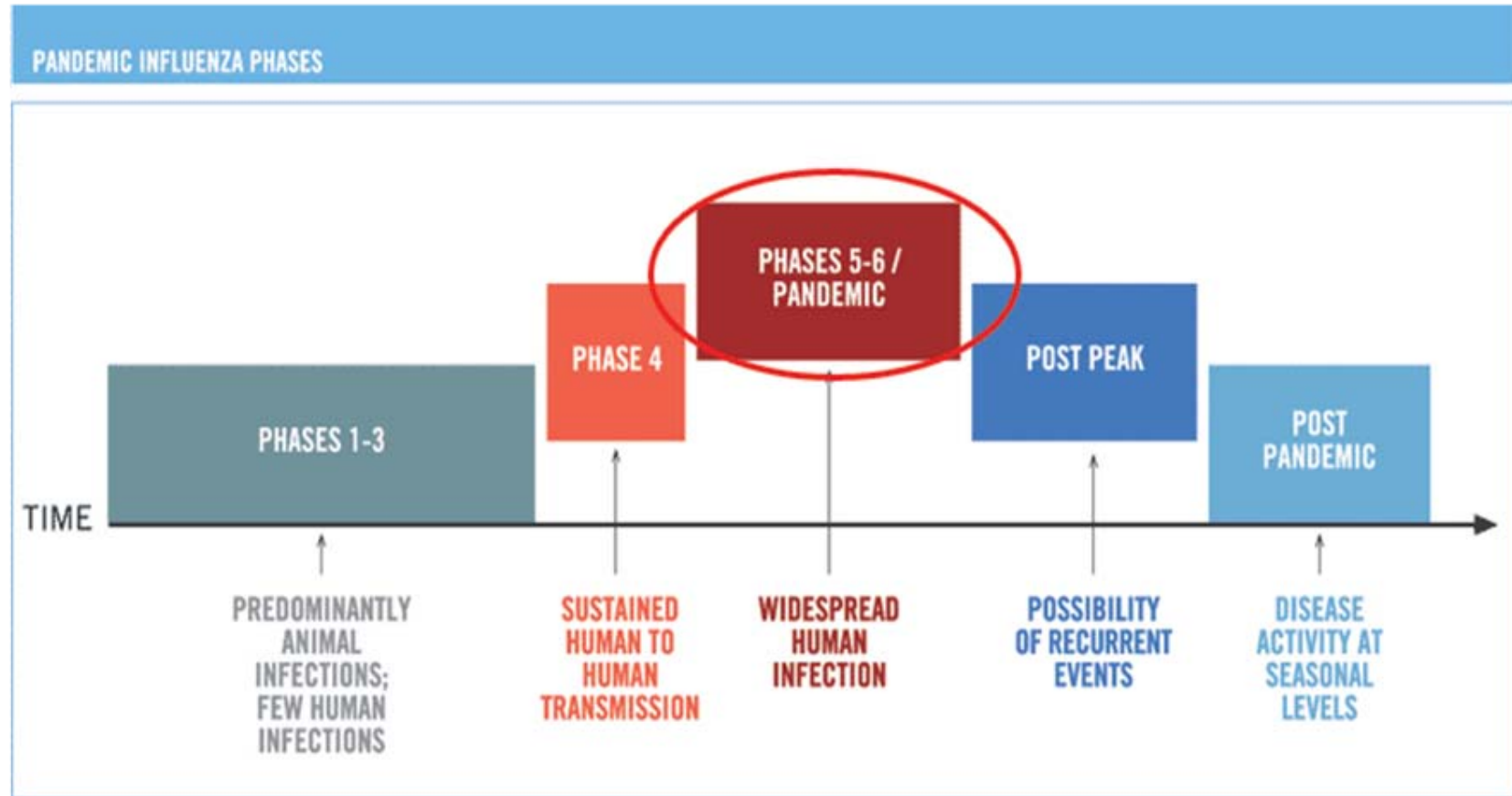


Epidemiology of Pandemic (H1N1) 2009



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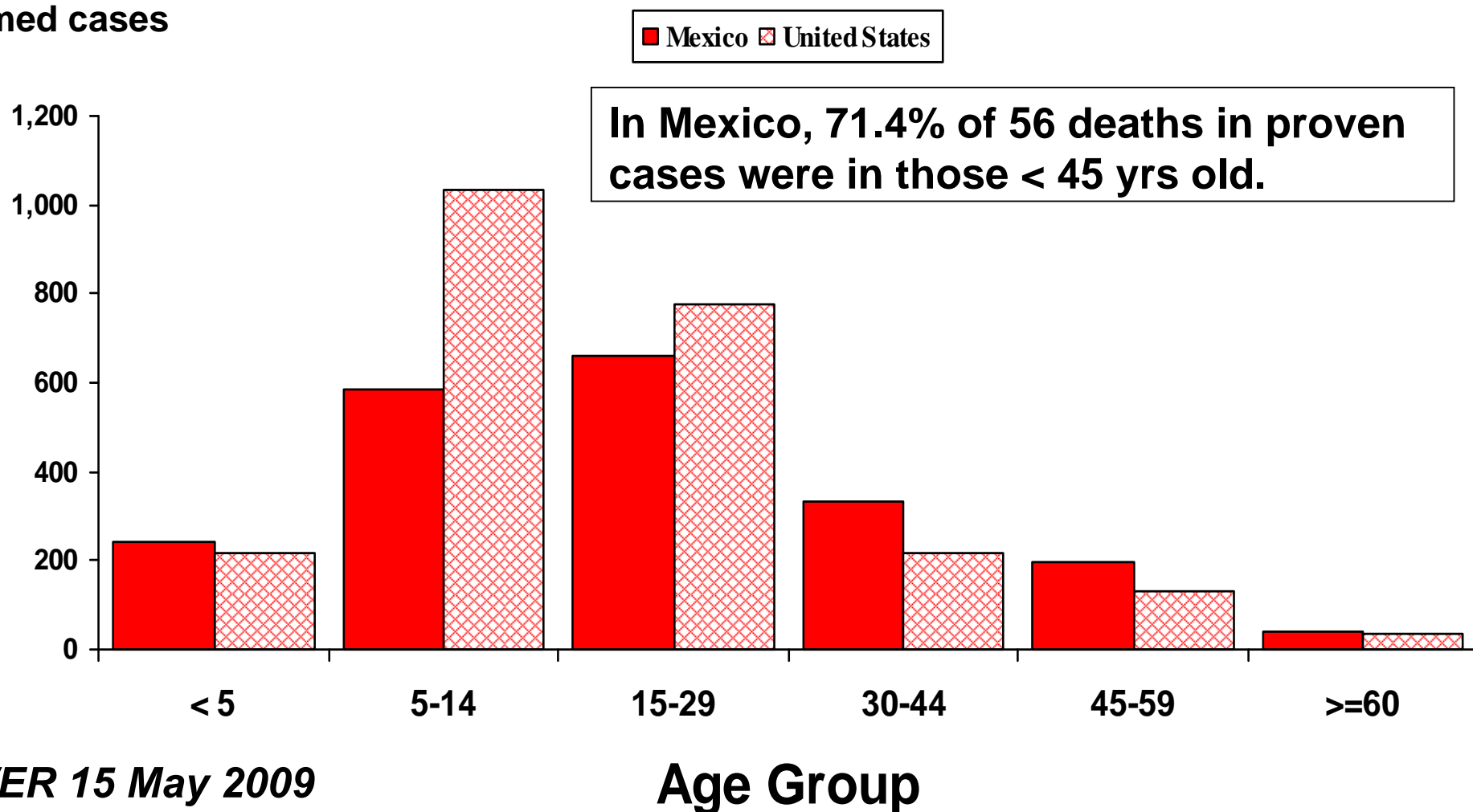
WHO Pandemic Phases



- Phases 5 & 6 are based on geographic spread, not severity

Age distribution of confirmed pandemic influenza A (H1N1) 2009 cases in Mexico and United States

Confirmed cases



WHO. WER 15 May 2009

Age Group



Epidemiology of Pandemic (H1N1) 2009 Virus Infection (1)

- 5-45 yrs of age most commonly affected
- Hospitalization and case/fatality in young adults higher than seasonal influenza
- Epidemiologic and serologic evidence for low susceptibility in older adults
- At risk groups: Pregnant women, people with chronic diseases and underlying health conditions, young children, people with immunosuppression





Epidemiology of Pandemic (H1N1) 2009 Virus Infection (2)

- Efficient, rapid person-person transmission
- International travel has facilitated geographical spread
- Cases have been reported in all regions.
- More cases in urban centers before wider geographical spread within the countries.
- Most countries reporting an increasing trend.
- Continued circulation outside of usual influenza season



Reporting- New recommendations

- Increasing nb of cases in many countries with sustained community transmission is making impossible, for countries to confirm them. => counting of individual cases is now no longer essential in such countries
- Still need in all countries to closely monitor unusual events
 - clusters of cases of severe or fatal pandemic (H1N1) 2009 virus infection,
 - clusters of respiratory illness requiring hospitalization,
 - or unexplained or unusual clinical patterns associated with serious or fatal cases.

(WHO briefing note 16 July 2009)



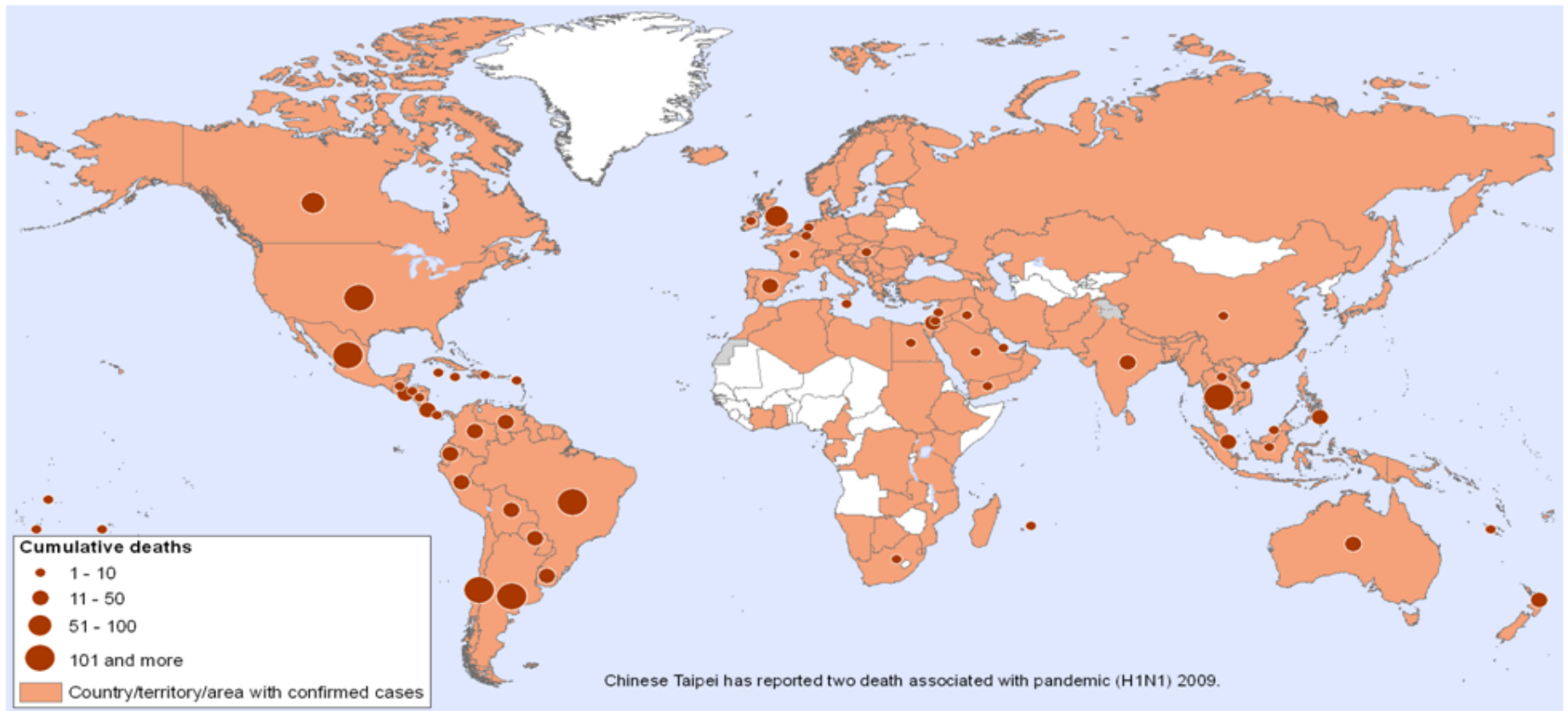
Pandemic (H1N1) 2009

Number of laboratory confirmed cases as reported to WHO (23 August 2009)

Pandemic (H1N1) 2009

Status as of 23 August 2009

Countries, territories and areas with lab confirmed cases and number of deaths as reported to WHO



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Map produced: 27 August 2009 09:50 GMT

Data Source: World Health Organization
Map Production: Public Health Information
and Geographic Information Systems (GIS)
World Health Organization



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Emergence of the Pandemic (H1N1) 2009 virus



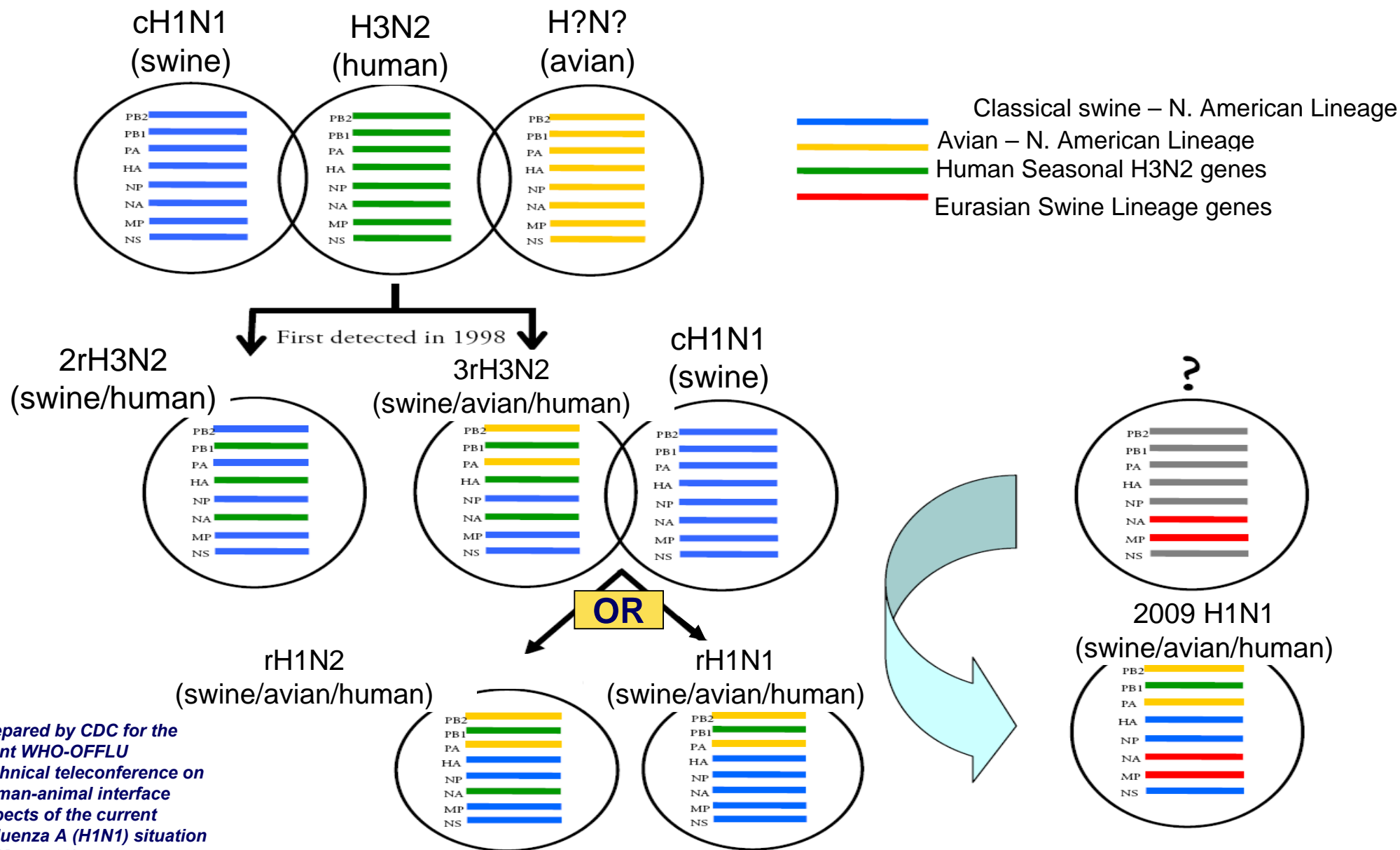
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Swine Influenza Viruses: *Background*

- **1930's:** Classical H1N1 swine influenza viruses (SIVs) first detected in North America
 - Probably circulating since 1918
- **Since 1998:** Triple reassortant SIVs circulating in swine globally, primarily reported from North America and Asia
- **Sporadic** (2-3 per year) human infections with triple reassortant swine influenza viruses and other SIVs (e.g. H1N1, H1N2, H3N2) reported from USA, Europe, and Asia
- **No previous reports** of sustained community-level human to human transmission of SIVs.
 - Fort Dix, NJ, USA, 1976: outbreak of H1N1 SIV infection in humans, >200 infected, 4 pneumonias, 1 death



Proposed Evolution of Swine Influenza Viruses in North America



Sources, references and acknowledgements

- http://www.who.int/csr/resources/publications/swineflu/WHO_OFFLU_2009_05_15.pdf
- Acknowledgements:
 - Centre for Diseases Control and prevention (CDC), Atlanta, USA
 - Dr Ian Brown, Veterinary Laboratories Agency, UK



Clinical management of human infection with Pandemic (H1N1) 2009 virus



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H1N1 infection – findings (1)

- Most cases in children and young adults
- Spectrum of disease range from non-febrile, mild upper respiratory tract illness to severe or fatal pneumonia. Occasional gastrointestinal symptoms (diarrhoea, vomiting)
- Most frequent symptoms: cough, fever, sore throat, malaise and headache

WHO – WER – 24 July 2009 confirmed in 27 August 2009



H1N1 infection – findings (2)

- Vast majority of cases have clinically mild disease and a small proportion have experienced complications requiring hospitalization
- Lower respiratory tract disease due to primary viral pneumonia in hospitalized patients
- Other complications: secondary bacterial infections, rhabdomyolysis with renal failure, myocarditis and worsening of underlying conditions

WHO – WER – 24 July 2009 confirmed in 27 August 2009



Infection control (1)

- Appropriate Infection Control measures should be adhered at all times for all patients

Standard Precaution

- general measures designed to reduce infection spread and minimize direct contact between non-intact skin and blood, body fluids or secretions.

- For patients with influenza like illness (ILI)

Add Droplet Precaution to Standard Precaution





Infection control (2)

Droplet Precautions: key elements

- Used for protection against respiratory pathogens transmitted by large droplets.

For patients with ILI, Droplet Precautions should always be added to Standard Precautions, and include:

- use of a **medical mask when within 1 metre/3 feet** of the patient (includes entering patient's room);
- placement of patient in single room, cohorted or separated from others by at **least 1 metre**;
- **limitation of patient movement** and use of a medical mask by patient when outside their room.





Infection control (3)

- **For aerosol generating procedures associated with increase in risk of disease transmission*:**

Particulate Respirators (N95 or FFP2 equivalent), eye protection, gown, and gloves







- **Carry out procedures in an airborne precaution room; naturally or mechanically ventilated**
- **Allow only essential people in the room**



Infection control (4)

HOW TO CHOOSE PERSONAL PROTECTIVE EQUIPMENT (PPE)

INFECTION CONTROL PRECAUTIONS IN SPECIFIC SITUATIONS WHEN CARING FOR PATIENTS WITH INFECTIOUS ACUTE RESPIRATORY DISEASES (ARDs)^{1, 2}

Scenario	Hand hygiene 	Gloves 	Medical mask 	Eye protection 	Gown 	Particulate respirator 
FOR ROUTINE CARE: when working in direct contact with patients, Standard and Droplet Precautions should always be applied						
Before and after patient contact	✓		✓			
If direct contact with blood and body fluids, secretions, excretions, mucous membranes	✓	✓				
If there is risk of splashes into the body	✓	✓	✓		✓	
If there is risk of splashes into the body and face	✓	✓	✓	✓	✓	
FOR AEROSOL GENERATING PROCEDURES: wear a particulate respirator and eye protection. Perform the procedure in a adequately ventilated room. Avoid unnecessary individuals in the room						
Resuscitation, intubation, aspiration of respiratory tract and bronchoscopy	✓	✓		✓	✓	✓
FOR LABORATORY SPECIMENS COLLECTION						
Blood sample, (if performed during the acute infectious phase)	✓	✓	✓			
Nasal swabs and nasal wash	✓	✓	✓	✓	✓	
Nasopharyngeal aspirate, nasopharyngeal swab, throat swab, or bronchial aspirate	✓	✓		✓	✓	✓



Diagnosis

- Laboratory confirmation of influenza A (H1N1) has important implications for:
 - Case management
 - Antiviral treatment
 - Avoid inappropriate use of antibiotics
- RT-PCR: provides the most timely and sensitive evidence of infection
- Clinical diagnosis (based on fever and cough) can be increasingly predictive as the prevalence increase
- Commercially available "Point-of-care" rapid tests for seasonal influenza: uncertain sensitivity and lack specificity. Interpret with caution
- Samples for lab testing: nasal swab, naso-pharyngeal swab, throat or bronchial aspirate.
- Specimen collection should be done with appropriate infection precautions





General treatment considerations

- Hospitalization or antiviral therapy is not likely to be required for most patients
- Supportive care: antipyretics and rehydration – No aspirin for children and adolescents (<18years): risk of Reye's syndrome
- Specific risk factors that predict increased risk of progressive disease are incompletely understood (young, previously healthy)
- Clinicians/care-givers should take into account:
 - Signs of clinical deterioration
 - Refer such patients to hospital
 - Underlying conditions(pregnancy, chronic cardiovascular, pulmonary, diabetes, immuno-deficiency)
- Pregnant women are at risk from seasonal, H5N1 and previous pandemic influenza infection. Warrant close observation and early antiviral treatment.





Oxygen therapy

- Monitor oxygen saturation by pulse oximetry at presentation or triage and routinely during subsequent care
- Provide supplemental oxygen to correct hypoxaemia
- Maintain oxygen saturation > 90%
- Patients with severe hypoxaemia need high-flow oxygen delivered by mask
- Difficulties in compliance may require involvement of nursing staff and family members





Antibiotic therapy

- Antibiotic chemoprophylaxis should not be used
- Pneumonia: follow recommendations from guidelines for community-acquired pneumonia
- Seasonal and past pandemics have been associated with and increase in *Staphylococcus aureus* infections
- Ventilator-associated pneumonia or hospital acquired pneumonia caused by typical nosocomial pathogens have been reported



Antiviral therapy (1)



- The new H1N1 virus is currently
 - susceptible to NAIs (oseltamivir and zanamivir)
 - Resistant to M2-inhibitors (amantadine and rimantadine)
- Clinical efficacy data not yet available
- NAIs might reduce severity and duration and might contribute to prevent progression of severe disease and death (based on seasonal influenza, H5N1 influenza studies and *in vitro observation*)



Antiviral therapy (2)

- **May be beneficial especially in:**
 - Pregnant women
 - Patients with progressing disease or pneumonia
 - Patients with underlying conditions
- **Can be used:** ideally early, and at any stage of active disease when ongoing viral replication is observed
- **Important pharmacological differences of oseltamivir and zanamivir**
 - Oseltamivir: administered orally, higher systemic level. Recommended treatment for lower respiratory tract complications
 - Zanamivir: oral inhalation , low systemic absorption



Antiviral therapy (3)

- WHO recommendations
 - Treatment of severe or complicated illness
 - Oseltamivir preferred, zanamivir is alternative
 - Treatment start as soon as possible but at any time
 - All patients (includes pregnancy, neonates)
 - Treatment of patients in at risk groups with mild or uncomplicated illness
 - Oseltamivir or zanamivir
 - Treatment not necessary for otherwise healthy, mild or uncomplicated illness
 - Chemoprophylaxis not recommended



Corticosteroids

- Should **NOT** be used routinely to treat patients with influenza A(H1N1) virus infection
- Low doses may be considered for patients with septic shock who require vasopressors and have suspected adrenal insufficiency.
- Prolonged use can result in serious adverse events including opportunistic infections and possible prolonged viral replication





Advance respiratory support

- Treatment of ARDS should be based upon evidence-based guidance
- Lung protective mechanical ventilation strategies should be used



Summary of clinical management of the Pandemic (H1N1) 2009 virus infection

Modalities	Strategies
Antibiotics	In case of pneumonia, empiric treatment for community acquired pneumonia (CAP)
Antiviral therapy	oseltamivir or zanamivir
Corticosteroids	Moderate to high dose steroids are <u>NOT</u> recommended.
Infection control	Standard plus Droplet Precautions. For aerosol generating procedure, use particulate respirator, eye protection, gown, gloves, and an airborne precaution room.
NSAIDS, antipyretics	Paracetamol or acetaminophen given orally or by suppository. Avoid aspirin.
Oxygen therapy	Monitor oxygen saturation and maintain SaO ₂ over 90%

WHO requests for more data to better understand the disease

- Additional clinical and treatment data is needed
- Clinical data and serial samples from virological monitoring should be collected prospectively in the context of clinical protocol
- Reports on clinical findings to WHO will facilitate the better understanding of the new disease and development of further management guidance

Data form available at

<http://www.who.int/csr/resources/publications/swineflu/caseformadapted20090508.pdf>

Sources and references

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http://www.who.int/csr/resources/publications/infection_control/en/index.html
- Laboratory testing
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- Oxygen therapy
 - http://whqlibdoc.who.int/hq/1993/WHO_ARI_93.28.pdf
 - <http://whqlibdoc.who.int/publications/2003/9241546220.pdf>
- Antiviral therapy
 - http://whqlibdoc.who.int/publications/2006/924159084X_eng.pdf (treatment for pregnant women and newborns)
 - <http://www.cdc.gov/mmwr/PDF/wk/mm5817.pdf>
 - [2] <http://www.fda.gov/medwatch/safety/2008/safety08.htm#Tamiflu>



Surveillance and monitoring

WHO new recommendations – 16 July 2009



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Surveillance Guidance (1)

(WHO new recommendations – 16 July 2009)

Early Detection

- For countries not yet affected:
 - The first confirmed pandemic (H1N1) 2009 virus infection detected in a country should be immediately reported by the IHR National Focal Point
- And afterwards:
 - Any changes in the epidemiological, virological or clinical presentation
 - Any unusual or unexpected public health events, e.g. clusters of severe unexplained acute respiratory illness or unexplained deaths



Surveillance Guidance (2)

Description and Assessment

- Describe the epidemiological and virological features of cases to guide control and prevention activities
- Assess disease severity
- Laboratory testing priorities
 - confirming infection in new areas
 - Testing severe cases
 - Monitoring the co-circulation of pandemic (H1N1) 2009 virus and seasonal viruses



Surveillance Guidance (3)

Continuous Monitoring

Report data to allow tracking of:

- global geographical spread
- disease trend
- prevalence
- impact of the pandemic on health-care services
- changes in viral antigenicity and antiviral sensitivity
- deaths from acute respiratory disease.



Output Expected

- A composite picture of severity and transmission characteristics primarily based on local interpretation of data and investigations.
- A description of clinical presentation, course, complications, and risk factors
- Virologic data for strain selection and antiviral sensitivity assessment
- Numbers of cases, hospitalizations, and deaths
 - Reflects laboratory capacity as much as it does disease activity
 - In high demand by the media



Key Related Decisions

- Target groups for intervention with vaccine or antivirals
 - Risk groups in need protection.
 - Target groups that might have greatest impact on transmission.
- Strain to use for vaccine.
- Which antivirals to use.
- Role of nonpharmaceutical interventions.
- Appropriate management practices



Vaccines and antivirals



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Shipments of diagnostic kits

138 countries, 675 kits (map produced: 31 July 2009)



Shipments of diagnostic kits



- **Diagnostic kits for real-time RT-PCR are sent from the WHO-CC in CDC US, ATCC is distributing kits on behalf of CDC.**
- **WHO-GIP with WHO-CC in CDC – are monitoring the kits distributions to GISN.**
- **CDC will continue supporting requests from NICs and national influenza reference laboratories for the rt-PCR primers, probes and positive control for the currently circulating "pandemic H1N1 2009" virus, free of charge.**

Pandemic(H1N1) 2009 vaccine virus development

- **WHO GISN/WHO CC/WHO ERL's –**
 - Closely monitoring the evolution of viruses.
- **WHO recommendation of candidate vaccine virus- 26 May 09-**
 - **A/California/7/2009 (H1N1)v - like virus**
- **WHO GISN/WHO CC/WHO ERL's –**
 - Development and distribution of Candidate vaccine viruses (CVV) for vaccine development- 409 shipments of CVV till date
- **Guidelines-**
 - Bio containment requirements for vaccine production- WHO Web
 - Transport of reassortant candidate vaccine viruses - WHO Web
- **Vaccine Potency Testing Reagents –**
 - Developed by ERL's and being distributed to vaccine manufacturers and NRL's



Candidate vaccine viruses

- **Wild type Vaccine Viruses**

- *A/California/4/2009*

- *A/California/7/2009*

- *A/Texas/5 /2009*

- *A/England/195/2009*

- **9 Reassortants (2 Classical and 7 Reverse Genetics)**

- NYMC-X179A

- IVR-153

- IDCDC-RG15

- CBER-RG2

- IDCDC-RG-18

- NIBRG-121

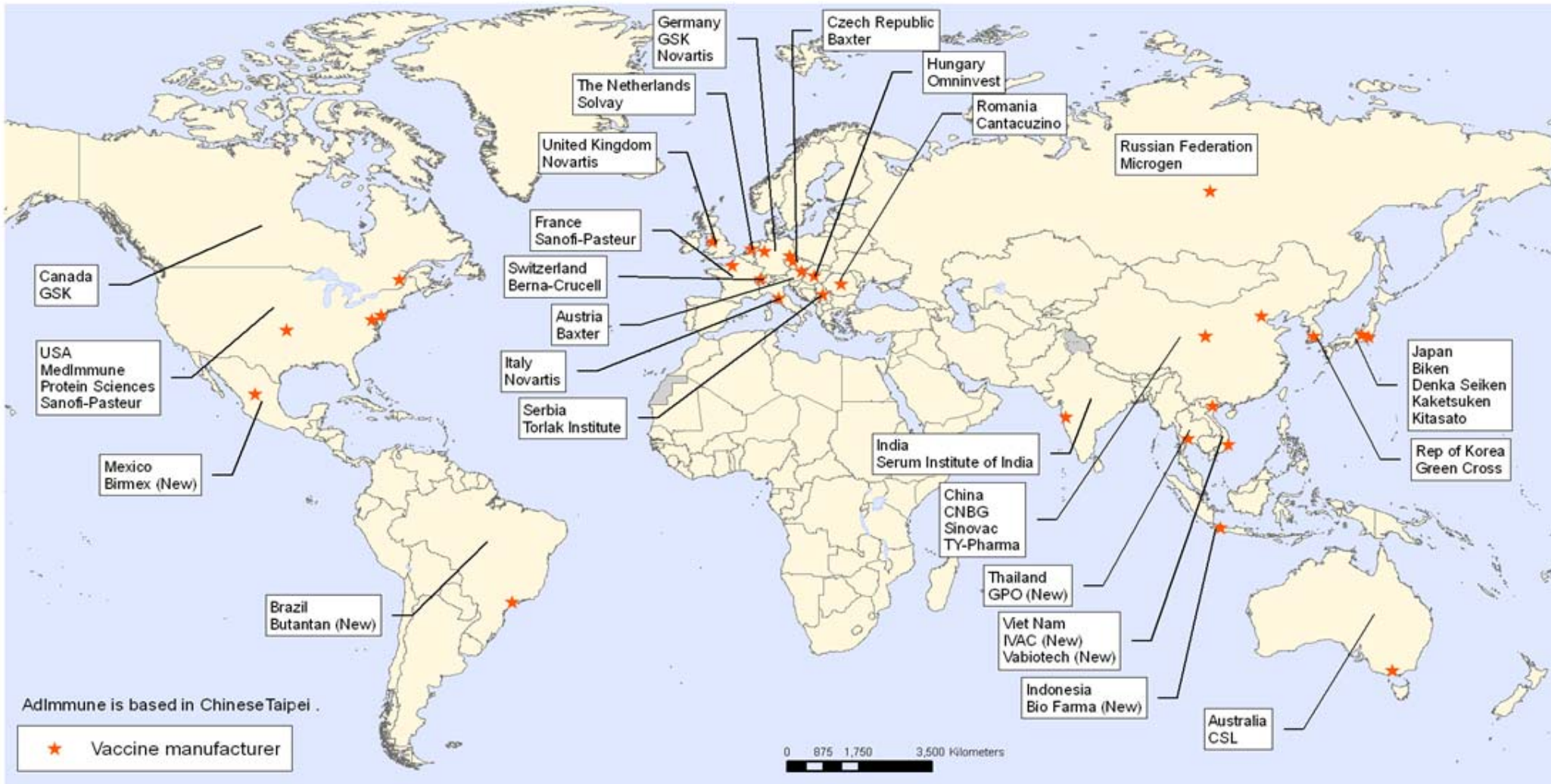
- IDCDC-RG-20

- NIBRG-122

- IDCDC-RG-22



New influenza A H1N1: Vaccine Manufacturers



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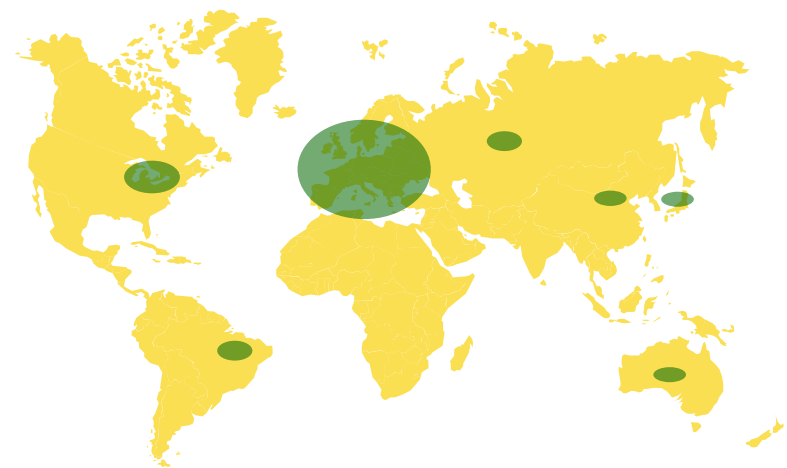
Pandemic Vaccine Development

- Vaccine manufacturers- working with seed virus
 - Egg based vaccine
 - Cell culture based vaccine
- Weekly TC's with WHO CC / WHO ERL's on vaccine virus and potency test reagents development, validation & distribution
- Weekly TC's with vaccine manufacturers on vaccine development / yield status
- Weekly TC's with vaccine regulators for licensing procedure and other regulatory issues
- Weekly TC's with vaccine task force on progress and need



Challenges for pandemic Influenza vaccines

- Lag time between declaration of the pandemic and availability of vaccines (4-6 months)
- Gap between vaccine potential demand and anticipated supply
- Regional disparity between vaccine production regions and the global need for vaccines
- Lower than optimal immunogenicity of non-adjuvanted inactivated split vaccines (for H5N1)



65-70% of global vaccine production located in Europe

Source: EVM Press Release 30 April 2004



Global seasonal trivalent vaccine production capacity

	Total annual capacity (10 ⁶ doses)	2008 Northern hemisphere production (10 ⁶ doses)	2009 Southern hemisphere production (10 ⁶ doses)	2009 planned Northern hemisphere production (10 ⁶ doses)
Companies A	560.1	299.6	103.0	322.8
Companies B	316.4	170.4	9.5	170.0
All companies	876.4	470.0	112.5	492.8

Companies A (n=7): capacity to produce at least 2.10⁶ doses of new H1N1 vaccine / week
Companies B (n=18): other smaller companies

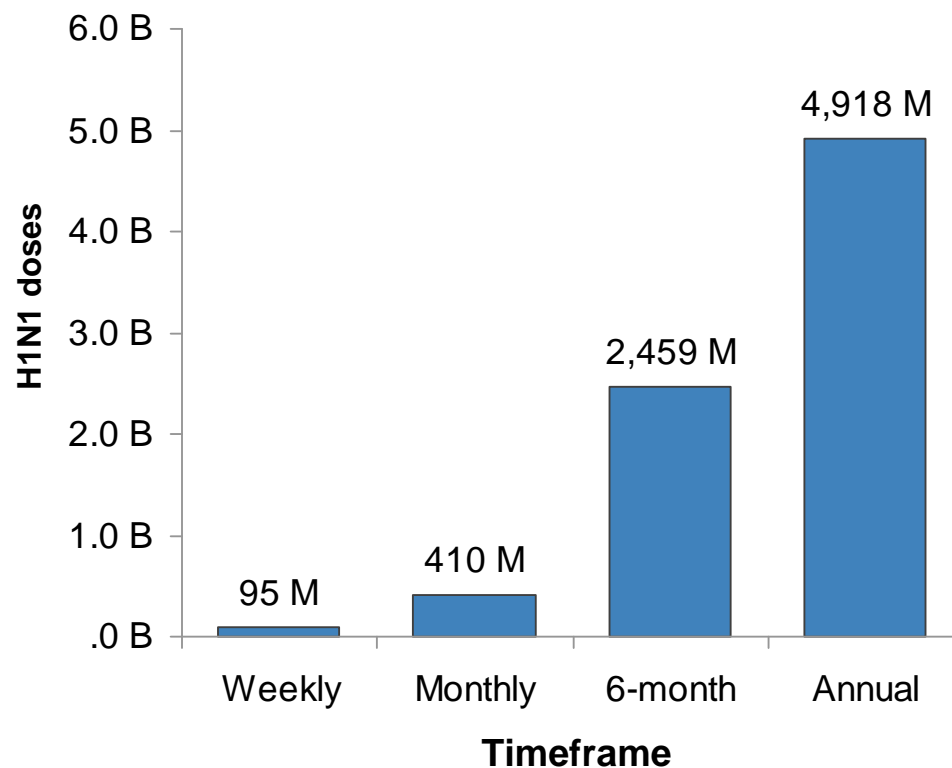
Pandemic vaccine baseline capacity was estimated at 94.5M doses per week

Assumptions / Methodology

- Survey sent to 36 potential influenza vaccine manufacturers
 - 100% response rate
 - All 21 current influenza vaccine producers responded
 - 26 manufacturers that intend to produce pandemic vaccines
 - Includes LAIV and one recombinant vaccine capacity
- Survey assumes
 - 1:1 H1N1 to seasonal yields
 - Most dose sparing formulation for **each** manufacturer
 - Use of full production capacity

Estimated H1N1 Vaccine Capacity

At 1:1 yields, most dose-sparing formulation, full capacity



Source: WHO survey

Countries are drawing against this capacity in different ways

Segments	Access Strategy	Population	% of H1N1 Capacity ¹
High-income (e.g., U.S., Canada, Europe, Japan, Australia)	<ul style="list-style-type: none"> ▪ Mostly open system: Countries negotiate contracts for vaccine with major, industrialized country manufacturers <ul style="list-style-type: none"> – Facilities serve home countries and export to other markets 	893 M	90%
Low / Middle Income with local supply (e.g., China, Russia)	<ul style="list-style-type: none"> ▪ Mostly closed system: Will procure vaccine mainly from within country <ul style="list-style-type: none"> – Limited or no plans by manufacturers to export 	3,114 M	10%
Low / Middle Income without local supply	<ul style="list-style-type: none"> ▪ No current access to H1N1 vaccine 	2,662 M	N/A

¹ Refers to portion of capacity located within these countries.
 Source: UNPD population dataset , WHO survey

A (H1N1) vaccine supply projection

	All companies	Companies A	Companies B
Weekly output (Best case)	94.5 Million (M)	81.3 M	13.2 M
Yearly output (Best case)	4.91 Billion (B)	4.23 B	0.68 B
Manufacturers with advanced purchase agreements	16 / 25	7 / 7	9 / 18
<i>Number of doses already reserved *</i>	$\geq 1.5 B$		
Manufacturers willing to reserve at least 10% of doses for developing countries	11 / 25	2 / 7	9 / 18
<i>Doses committed to DC / year</i>	56.0 M		
Manufacturers still undecided about the above question	14 / 25	5 / 7	9 / 18
<i>Potential additional doses / year</i>	435.5 M		

Best case scenario = at full capacity, yields similar to seasonal vaccine, most dose-sparing formulations

** = WHO Secretariat lower boundary estimate*

Scenarios for A (H1N1) influenza vaccine availability in low and middle income countries*

Scenarios →	1) Best case scenario	2) No use of oil-in-water adjuvants	3) With normal 2010 Southern Hemisphere vaccine production	4) No use of oil-in-water adjuvants and with normal 2010 Southern Hemisphere vaccine production
Weekly output	94.5 M	58.6 M	87.8 M	52.0 M
Yearly output	4.91 B	3.05 B	4.57 B	2.70 B
Time to complete global vaccination (6B people; 1 dose per person) with equal share of vaccines between Member States	1.2 years	2 years	1.3 years	2.2 years
Time to complete LMIC (5B people) vaccination (1 dose per person) with 1.5B doses committed to high income countries (1B people)	1.5 years	3.3 years	1.7 years	4.2 years

* Does not take into consideration Northern Hemisphere 2010-2011 vaccine production

Delivery of H1N1 vaccines: Ongoing WHO activities

- Deployment guidelines
 - Generic guidance document developed and being translated into all UN languages
 - Regional and sub-regional workshops are ongoing to assist countries in developing or updating national vaccine deployment plans
- Forecasting tool and user guide developed to assist programme managers in calculating:
 - volume of vaccine dose per cm³, other ancillary supplies and their value
 - the space to be occupied
 - indication of the equipment required to store and transport them.
 - In addition the tool provides for scenario analysis given the introduction of new vaccine.
- Assessment of AD syringe and safety box supplies for delivery of vaccine (survey of manufacturers) ongoing



Pandemic (H1N1) 2009 vaccine availability

- Earliest expected vaccine availability- August/Sept. 09
- On discussion
 - Sanofi Pasteur- Donation to WHO- 100 million doses.
 - GSK donation to WHO- 50 million doses
 - Both the donations are targeted to provide access to low and middle income countries without access to vaccine.

