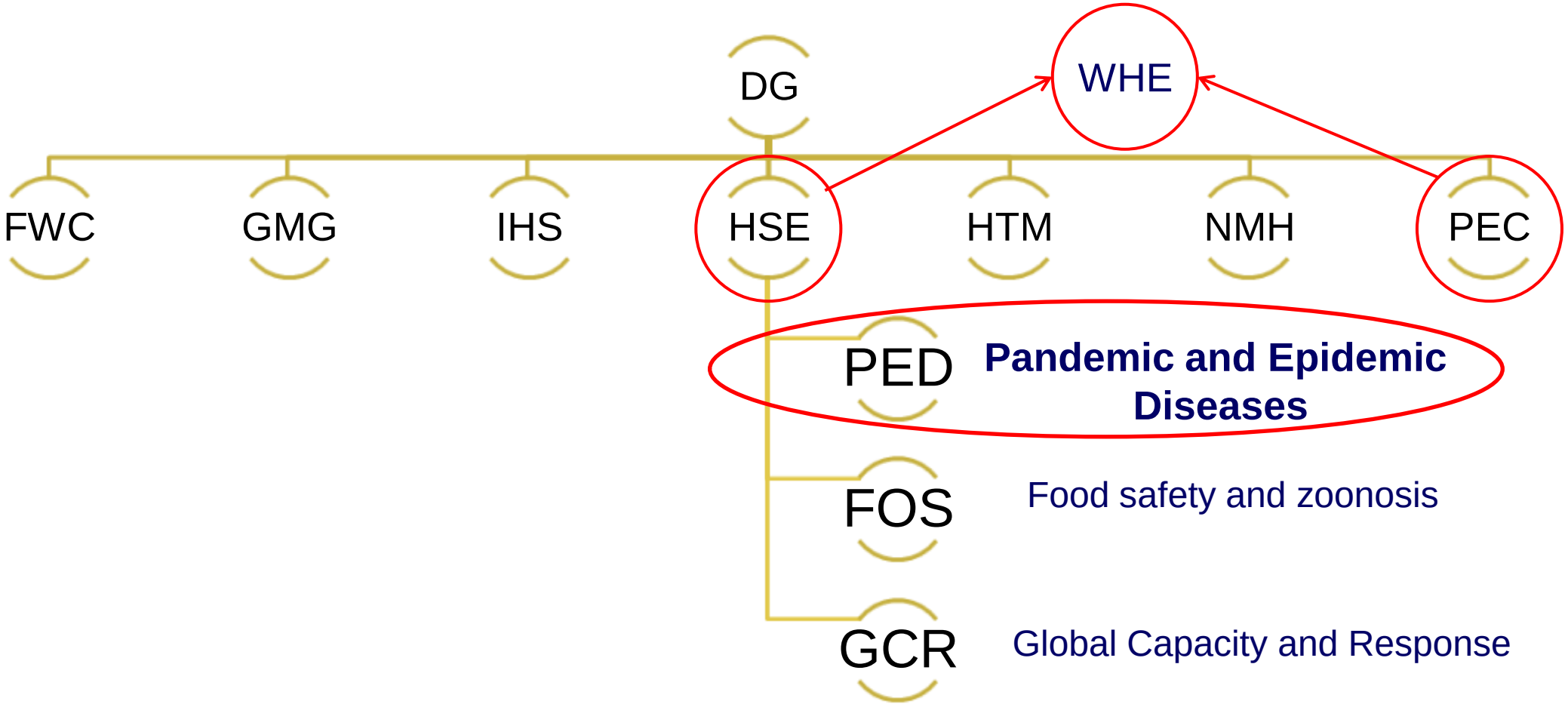
Public Health Plenary Session: Addressing the public health threat of influenza: Recognition, prevention and Treatment, Options IX for the Control of Influenza
Chicago, August 24-28, 2016

# Outbreak and Pandemic Response: Role of Antivirals

N. Shindo MD, PhD.
Coordinator
BRaVe Secretariat
Epidemic Clinical Management
Pandemic and Epidemic Diseases Department

World Health Organization

# WHO Emergency Reform



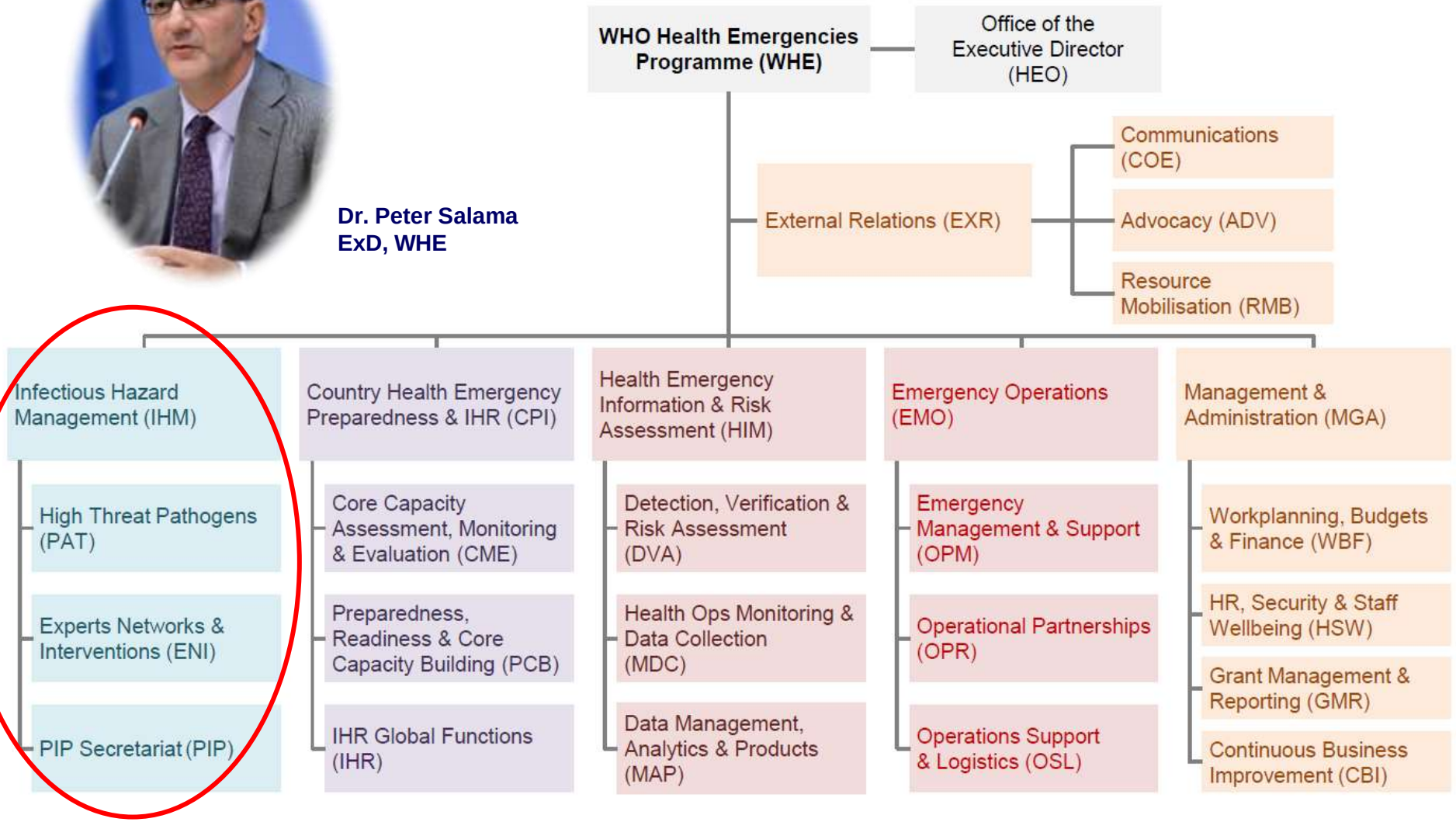

WHE = WHO's Health Emergency (WHE) Programme



World Health Organization

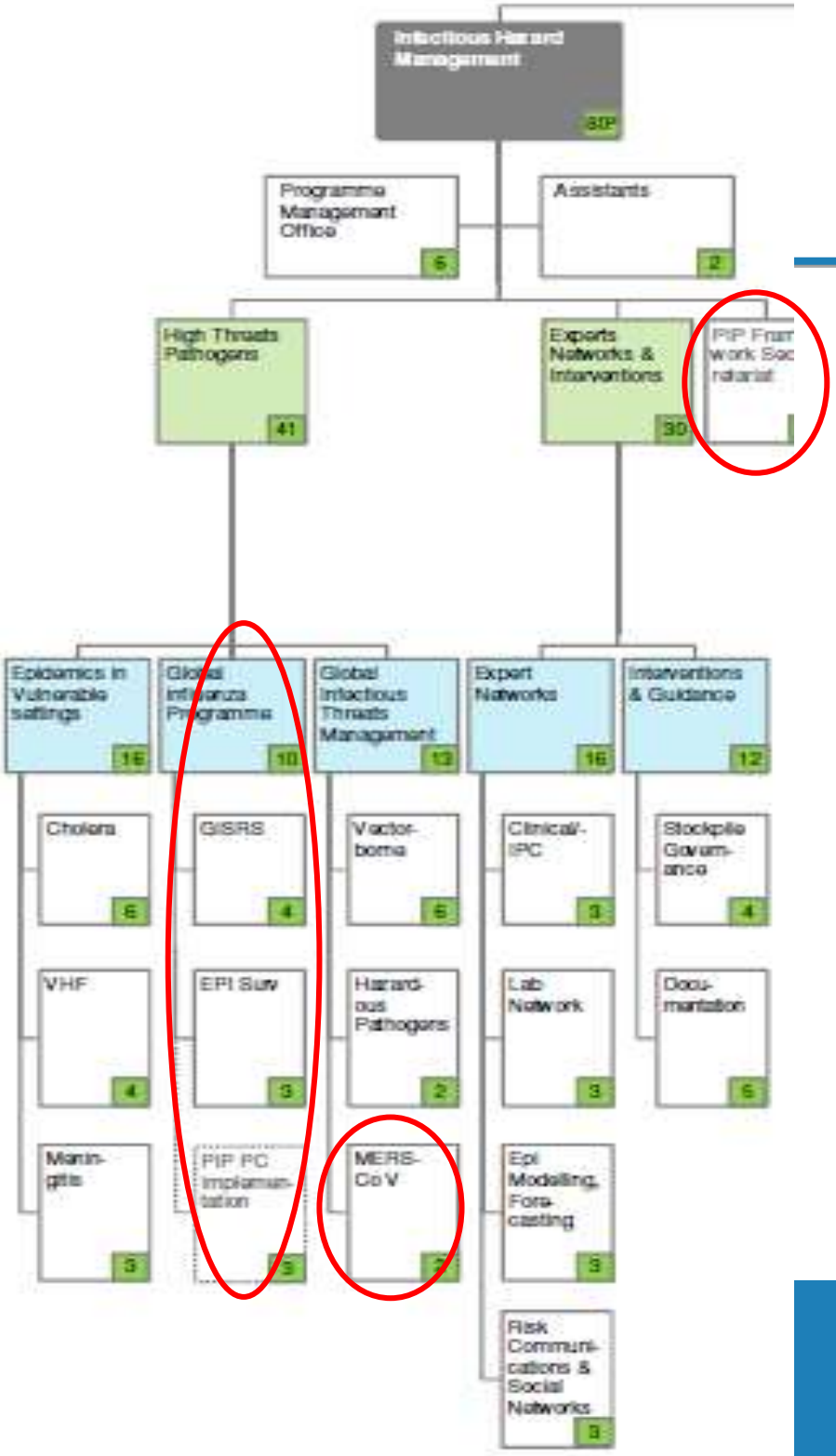
# WHO Health Emergencies Programme

**Dr. Peter Salama**
**ExD, WHE**






World Health Organization




## Infectious Hazard Management (Department)

**Pandemic Influenza Preparedness (PIP) Framework**

**Global Influenza Programme**

**MERS CoV**

**Job vacancies:**
**http://www.who.int/employment/vacancies/en/**

World Health Organization

# Infectious Hazard management activities

**Diseases**

- Cholera
- Emerging diseases
- Hendra virus infection
- Influenza (avian, seasonal, pandemic)
- Leptospirosis
- Meningitis
- Nipah virus infection
- Plague
- Rift Valley fever
- SARS and MERS coronavirus infections
- Smallpox and human monkeypox
- Tularemia
- Viral Haemorrhagic fevers (Ebola, Marburg, Lassa, CCHF)
- Yellow fever, ZIKA

**Cross-cutting initiatives and networks**

- Battle against Respiratory Viruses (BRaVe) initiative
- Communicable Disease Control in Humanitarian Emergencies (DCE)
- Emerging and Dangerous Pathogens Laboratory Network (EDPLN)
- Emerging Disease Clinical Assessment and Response Network (EDCARN)
- International Coordinating Group (ICG) for yellow fever, meningitis and cholera
- Global Infection Prevention and Control Network (GIPCN)
- Global Influenza Surveillance and Response System (GISRS)
- Global Leptospirosis Environmental Action Network (GLEAN) and Meningitis Environmental Risk Information Technologies (MERIT) project
- Pandemic Influenza Preparedness framework (PIP)

# Addressing the public health burden of respiratory viruses: the Battle against Respiratory Viruses (BRaVe) Initiative

**Anaïs Legand*[1], Sylvie Briand[1], Nikki Shindo[1], W Abdullah Brooks[2,3], Menno D de Jong[4], Jeremy Farrar[5], Ximena Aguilera[6] & Frederick G Hayden[7]**

[1]WHO, Pandemic & Epidemic Diseases, Geneva, Switzerland
[2]Johns Hopkins University, Bloomberg School of Public Health, USA
[3]International Center for Diarrhoeal Disease Research, Bangladesh
[4]Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands
[5]Oxford University Clinical Research Unit, Wellcome Trust MOP, Hospital for Tropical Diseases Vietnam, SEAICRN & ISARIC, Vietnam
[6]Centre of Epidemiology & Public Health Policy, Faculty of Medicine Clínica Alemana, Universidad del Desarrollo, Chile
[7]University of Virginia School of Medicine, Charlottesville, VA, USA
*Author for correspondence: leganda@who.int

Review
Future Virology

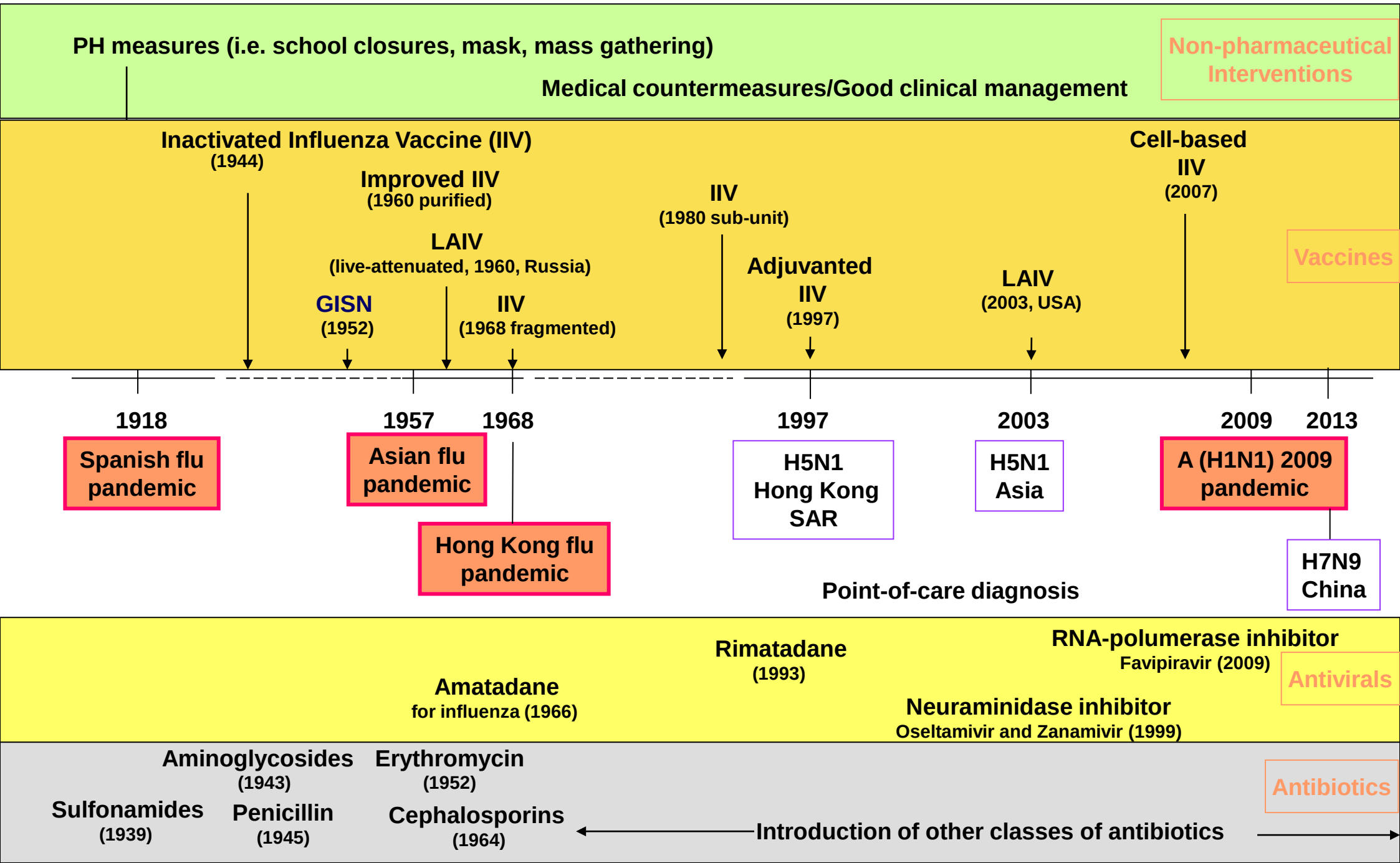
*Future Virol.* (2013) 8(10), 953–968



World Health Organization

Ensuring WHO's capacity to prepare for and respond to future large-scale and sustained outbreaks and emergencies

# Pandemic Response Tools



We have imperfect vaccines, and imperfect antivirals.

Role of antivirals?

# Development of WHO Standard Guideline on Clinical Management of Influenza Virus Infection

World Health Organization

# Scope

## Clinical management of severe influenza disease

- Treatment of severe influenza e.g. viral pneumonia, ARDS, multiple organ failure, septic shock;

- Pharmacological interventions for treatment, including influenza antiviral drugs, anti-inflammatory drugs and adjunctive therapies;

- Non-pharmacological clinical interventions, such as mechanical ventilation, oxygen and fluid management.

- Preventing development of severe influenza; including treatment of patients at higher risk of progression to severe disease and prevention of infection in highest risk patients

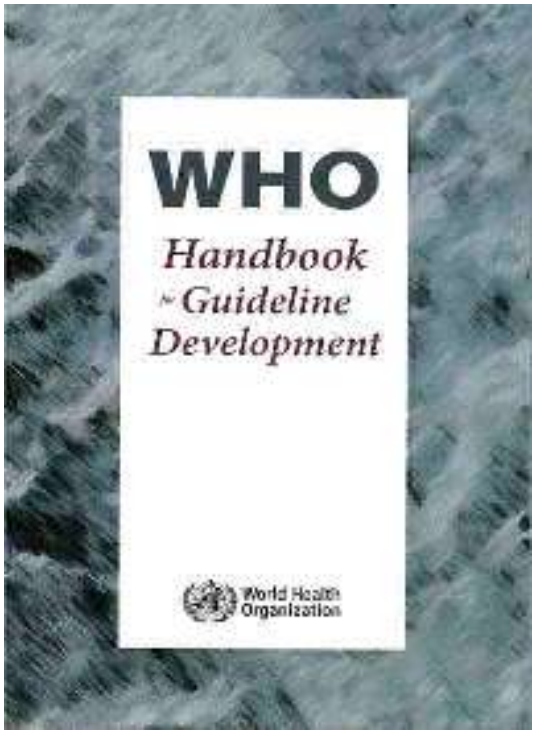
# Formulating questions and choosing outcomes based on the PICOT framework

| | |
|---|---|
| **Population** | All patients presenting with severe or deteriorating influenza illness<br>All patients in groups defined as at higher risk of severe or complicated disease |
| **Intervention** | Influenza antivirals (including investigational products)<br>Adjunctive therapies, such as immunomodulators, serum or plasma products<br>Other pharmacological and non-pharmacological clinical interventions |
| **Comparator** | There are currently few established standards; comparator is generally no intervention or placebo |
| **Outcome** | Prevention of infection (in higher risk individuals)<br>Prevention of disease progression<br>Time to resolution of severe illness<br>Reduction in hospital or ICU admission or length of hospital stay<br>Reduction in mortality |
| **Time** | Short term (to resolution of illness) |

# Process

In accord with WHO standard for guideline development; requires substantial evidence review and assessment.

- Commissioning of systematic reviews and GRADE assessments
- Followed by panel review with good regional representation




**http://www.who.int/kms/guidelines_review_committee/en/index.html**

**http://www.gradeworkinggroup.org/index.htm**



World Health Organization

# GRADE

- Grading of Recommendations, Assessment, Development and Evaluations

- Systematic method of linking evidence quality evaluations to clinical recommendations

# Introduction

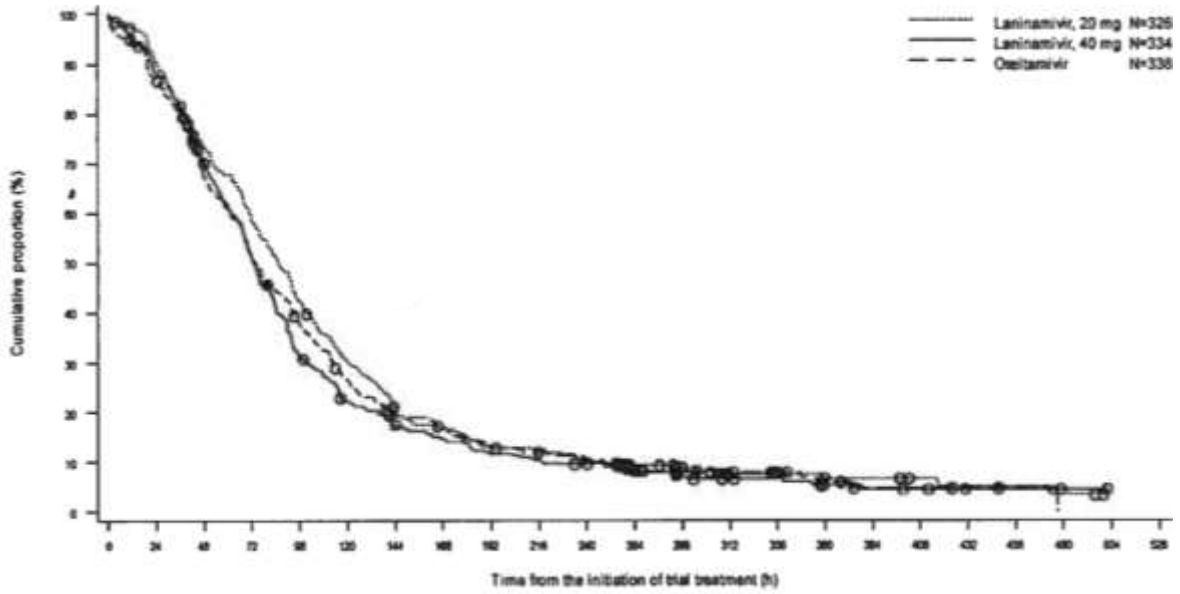
- Licensed influenza antivirals
  - M2-inhibitor (M2I): amantadine, rimantadine,
  - Neuraminidase inhibitors (NAI): zanamivir, oseltamivir, laninamivir, peramivir
  - Other mechanisms: not licensed or extremely limited availability
- All currently circulating human influenza viruses are resistant to M2Is. NAI resistance is rare.
- Oseltamivir is licensed in >80 countries for prophylaxis and treatment for influenza virus infection; only antiviral suitable for use in children<5, US FDA approval lowered to 2 weeks of age in December 2012.

# Future prospects

- Inhaled Laninamivir
- IV Peramivir
- Oral Favipiravir
- IV  Zanamivir
- Novel PB2 and PA inhibitors
- Antibodies

Long-Acting Neuraminidase Inhibitor Laninamivir Octanoate versus Oseltamivir for Treatment of Influenza: A Double-Blind, Randomized, Noninferiority Clinical Trial

Akira Watanabe,[1] Shan-Chwen Chang,[3] Min Ja Kim,[4] Daniel Wai-sing Chu,[5] and Yasuo Ohashi[2]; for the MARVEL Study Group*






World Health Organization

# Regional and other antivirals

- Arbidol
- Ingavirin
- Ribavirin
- Others.....



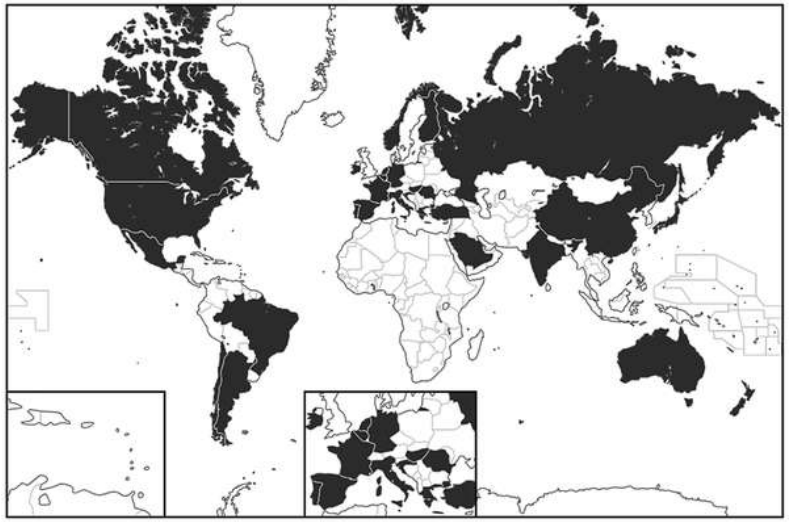

World Health Organization

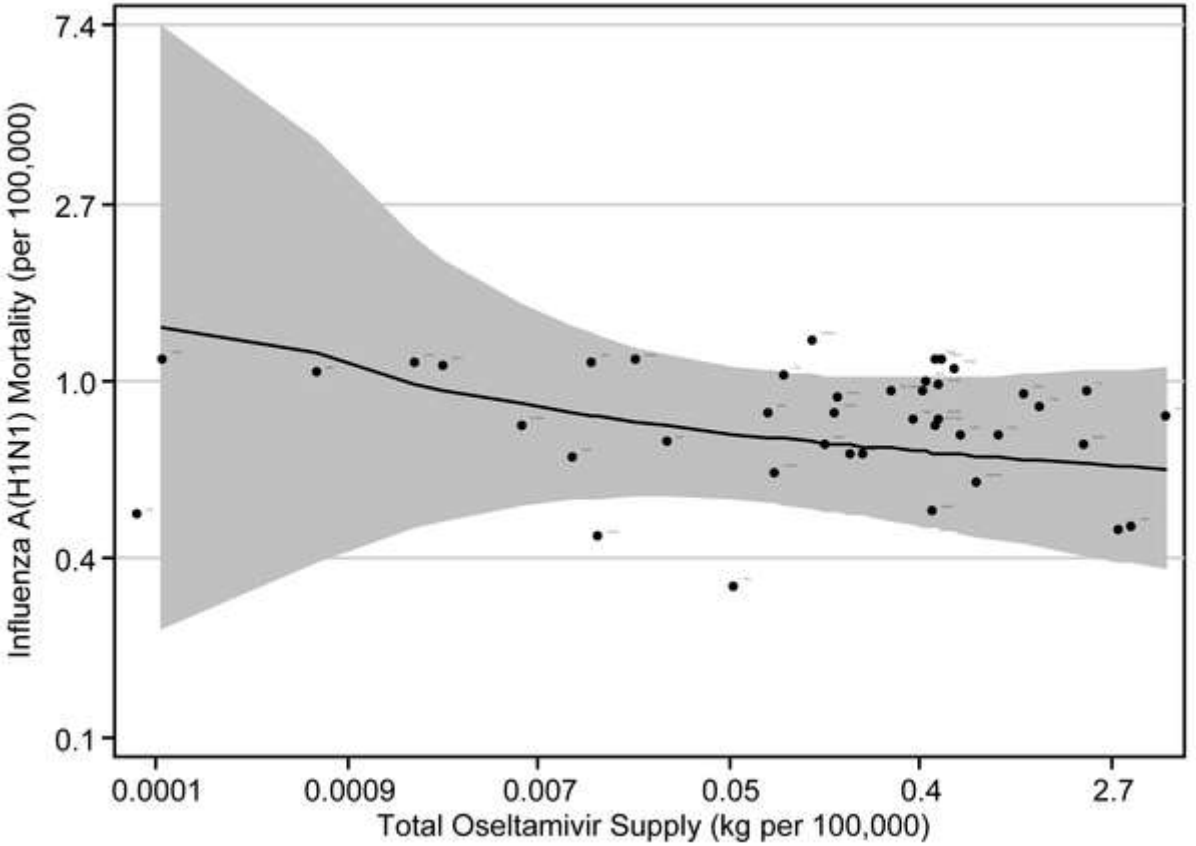
# Evidence

- Clinical trial data
- Observational data
  - Hsu et al. 2012
  - Muthuri et al. 2013
  - MUGAS 2015
  - PRIDE 2015
- Public Health observations
  - Canada, Japan, Argentina
  - Miller et al. 2012

# Supply of Neuraminidase Inhibitors Related to Reduced Influenza A (H1N1) Mortality during the 2009–2010 H1N1 Pandemic: An Ecological Study

Paula Miller, Aksharananda Rambachan, Roderick Hubbard, Jiabai Li, Alison Meyer, Peter Stephens, Anthony W. Mounts, Melissa Rolfes, Charles Penn



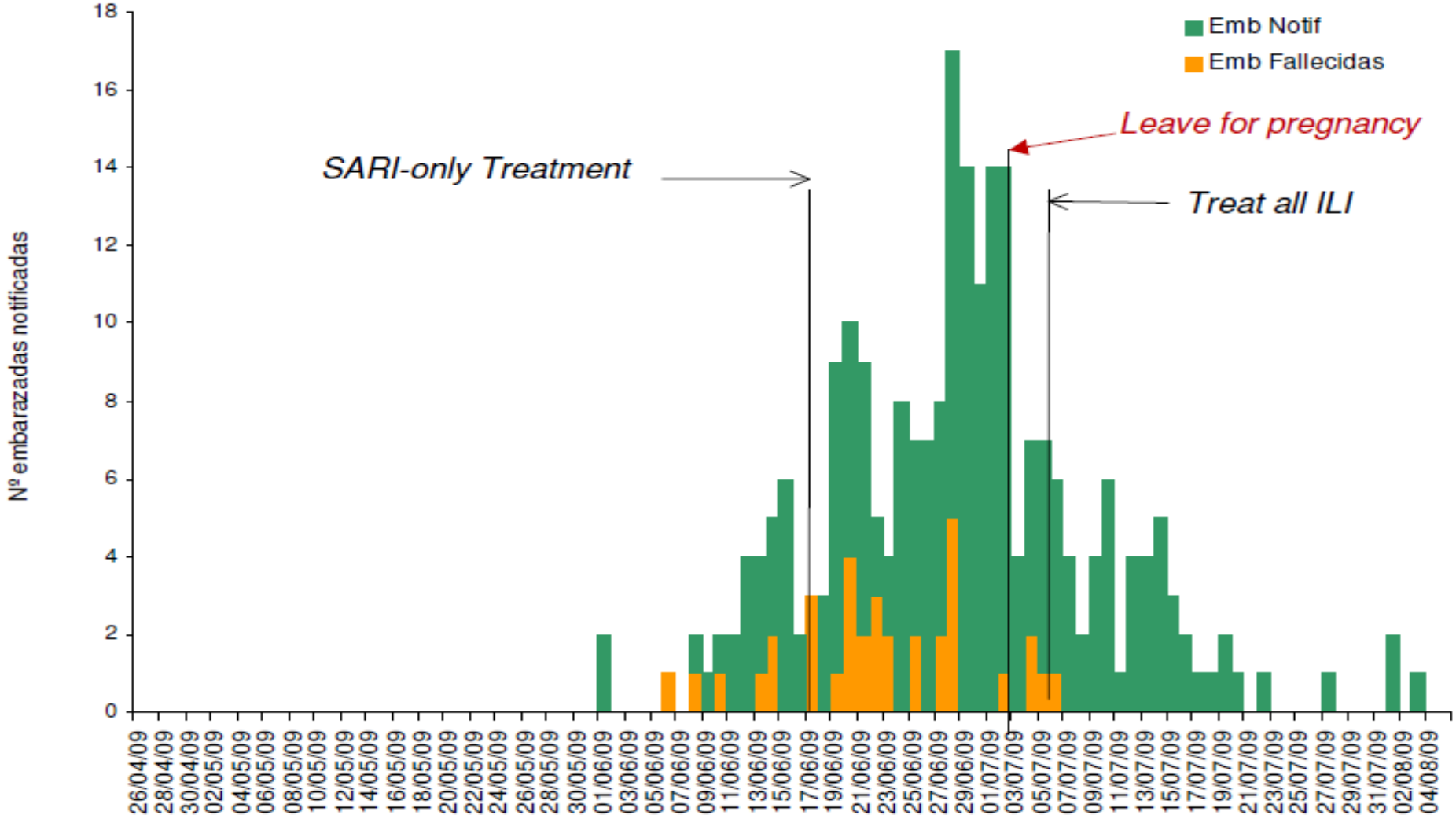





World Health Organization

# Policy case study: Argentina 2009

*N °of H1N1 cases among pregnant women, 2009 by day according to date of symptom onset. Argentina Year 2009 (n = 243 *)*

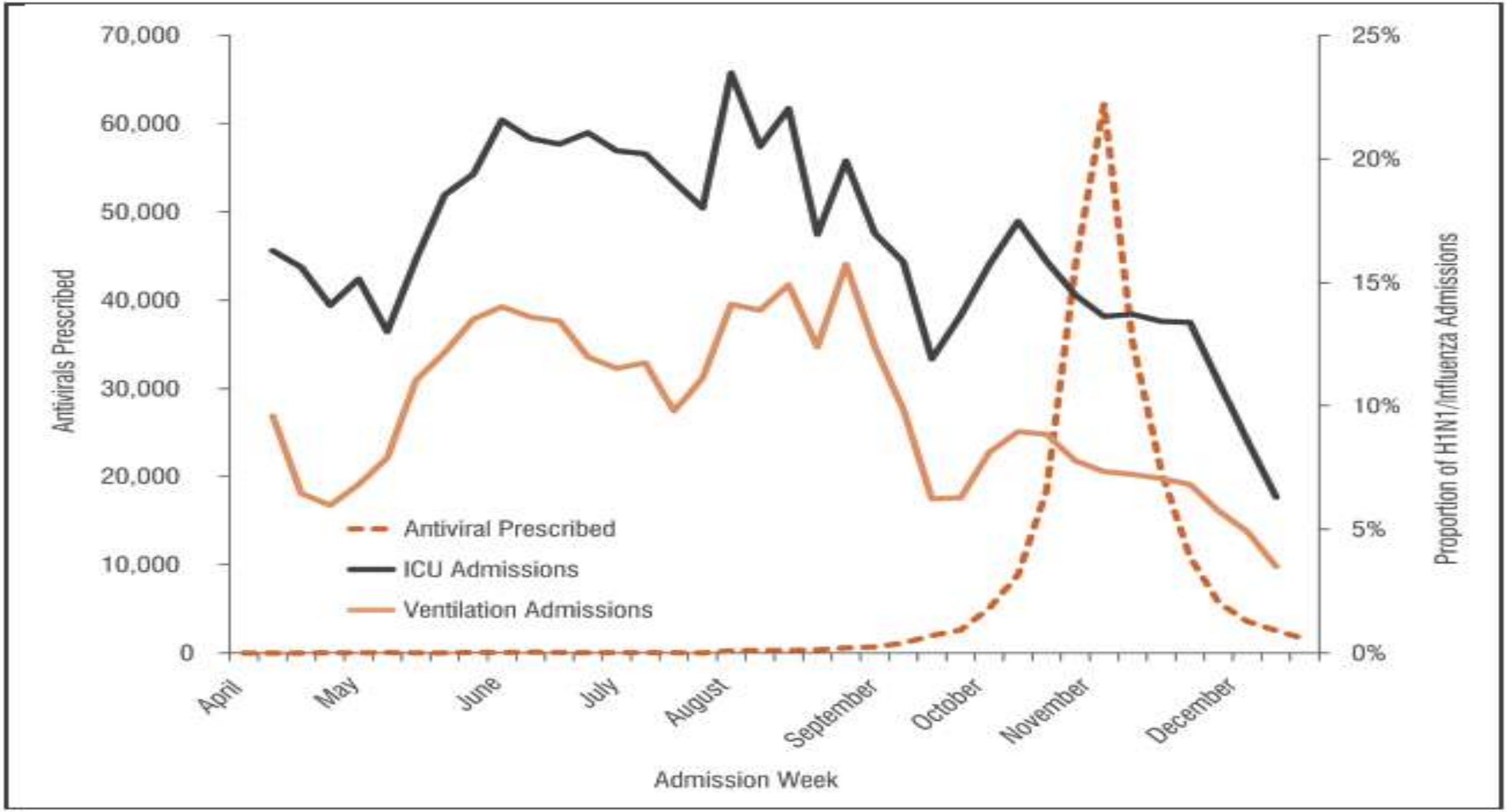



Presidencia de la Nación

*Fecha Actualización: 17-08-09*

Fuente: SIVILA Ministerio de Salud de la Nación

## Figure 9: Antivirals Prescribed Compared to ICU and Ventilation Admissions (by Admit Date), April to December 2009






World Health Organization

# Public health aim

- To mitigate severe or complicated illness
- Reduce hospitalization (incidence, duration)
- Prevent death

- NOT to shorten self limiting, uncomplicated illness

# Existing WHO Guidelines

- 2006 Rapid Advice Guidelines in Pharmacological Management of Humans Infected with Avian Influenza A (H5N1) Virus
- Rapid advice guidelines for the treatment of pandemic H1N1 influenza (H1N1pdm09)
  - First published in August 2009, and revised in February 2010.
  - 2010-12, WHO reviewed its guidelines for clinical management of severe influenza and developed a set of Standard Guidelines that include use of influenza antivirals. These standard guidelines are in the final stage of completion, following a full review of evidence and expert consultation.
- 2014 Emergency guidance for avian influenza A(H7N9) virus
  - Post-exposure antiviral chemoprophylaxis of close contacts of a patient with confirmed H7N9 virus infection and/or high risk poultry / environmental exposures.

# Recommendations

- Use of  oseltamivir for treatment of severe or complicated influenza, and for treatment of influenza in patients at higher risk of developing severe disease.
- Prophylactic use of oseltamivir for persons with a high risk of exposure to avian influenza H5N1 to prevent illness that has a high case fatality rate.
- WHO does not recommend prophylactic use for seasonal influenza nor for the recent pandemic virus (H1N1pdm09).
- Antiviral chemoprophylaxis following exposure to H7N9 virus is generally not recommended. Symptomatic individuals with exposure to H7N9 virus should receive prompt antiviral treatment with a neuraminidase inhibitor.

# Increasing accessibility

- Qualified inclusion on model list of Essential Medicines (in the context of influenza pandemic)
- Rapid deployment (donations) from a global stockpile
- Prequalified products
- Guidelines for use
  - Does not displace vaccination

# Relevant WHO work

- Oseltamivir is on EML since 2010
- WHO has prequalified oseltamivir formulations from several companies to facilitate equitable access to the medicine.
- WHO Prequalified products for influenza http://apps.who.int/prequal/query/ProductRegistry.aspx
- Antivirals as one of 'benefits' along with vaccines and surveillance/diagnostics capacity of the PIP Framework

# WHO global strategic antiviral stockpiles

**Tamiflu™**

*** treatment courses**

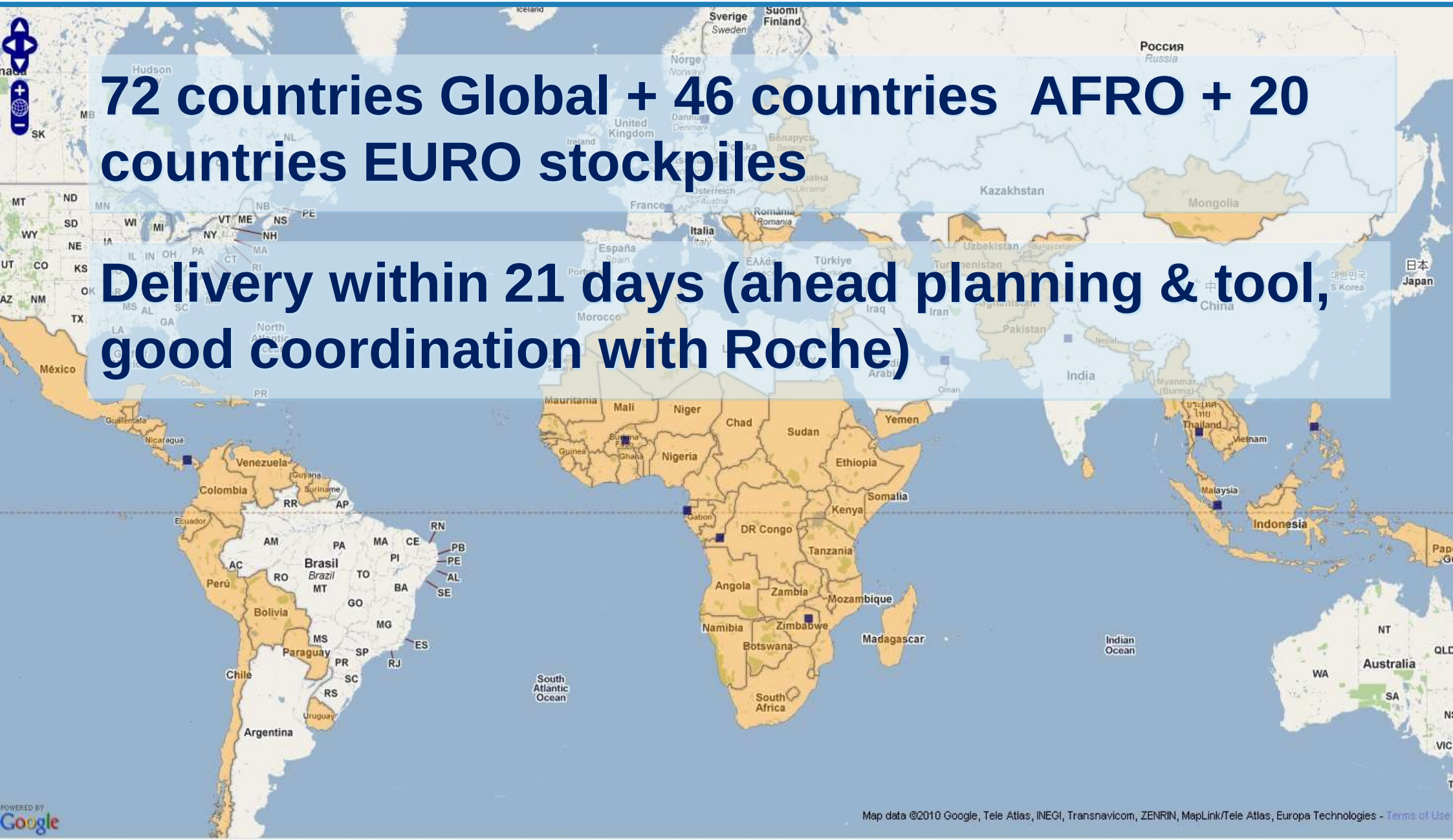
- Rapid response stockpile (3.65M*, 3M adult, .65M* paediatric)
  - Draft SOP ready for expert review (scenario-based)
  - MS to request deployment
  - Deploy, not deploy or continue preparatory actions to be decided based on technical, operational and legal/policy information

- Regional stockpile – for LMIC (2M*)

  ROs to work with MS on risk / needs assessment
  - To control outbreaks caused by human and non-human influenza,
  - To control severe influenza epidemics,
  - For potential pandemic or pandemic response

**Relenza™** (2M* donation+8M* affordable prices), SMTA2. SOP, deployment details to be determined.

# 2009 (H1N1) pandemic Antiviral deployment



# WHO antiviral deployment

- **Continued support after 2009-10 Influenza pandemic : up & running**
- **Tamiflu™ adult and paediatric formulations**
- **Total 13 deployment in response to human and poultry outbreak responses**
- ****Providing clinical support/training as a package. (WHO Training → See Poster presentation)**

**Courses*: treatment courses – 10 capsules of 75/45/30 mg oseltamivir phosphate**

| Year | Country | formulation |
|---|---|---|
| 2011 | Bhutan | paediatric |
| 2013 | Iraq | paediatric |
| | Mozambique | paediatric + adult |
| | Tunisia | adult |
| | Yemen | adult |
| | Zambia | adult |
| 2014 | Pakistan | adult |
| | Syrian, Arab Republic | adult |
| 2015 | Nigeria | adult |
| | Jordan | adult |
| 2016 | Armenia | adult |
| | Ghana | adult |
| | Palestinian Territory** | paediatric |
| | Kenya** | paediatric + adult |
| | Fiji** | Adult |

# Antiviral WHO Stockpile deployment

- Under PIP Framework (2011)
- Standard Operating Procedure (SOP) currently under development
  - Scenario-based deployment plans: 12 scenarios, including containment operation
  - Identification of variables to characterise and plan for deployment (R0, clinical attack rate, generation interval, etc)

  SOP and scenario ready for expert review (contact: shindon@who.int )
- Deployment drills to be conducted

# Need for research


World Health Organization

# Research agenda progress review


- Literature reviews conducted for high priority research topics.
- Over 4,000 articles reviewed in more than 200 journals.
- Work related to H1N1pdm09 dominated the body of work.
- Increased knowledge in some topics.
- WHO-lead approach needs evaluation.

http://www.who.int/influenza/resources/research/en/

# Thank you


World Health Organization