

Broad-spectrum antivirals in pandemic preparedness and response

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Perspective from the World Health Organization

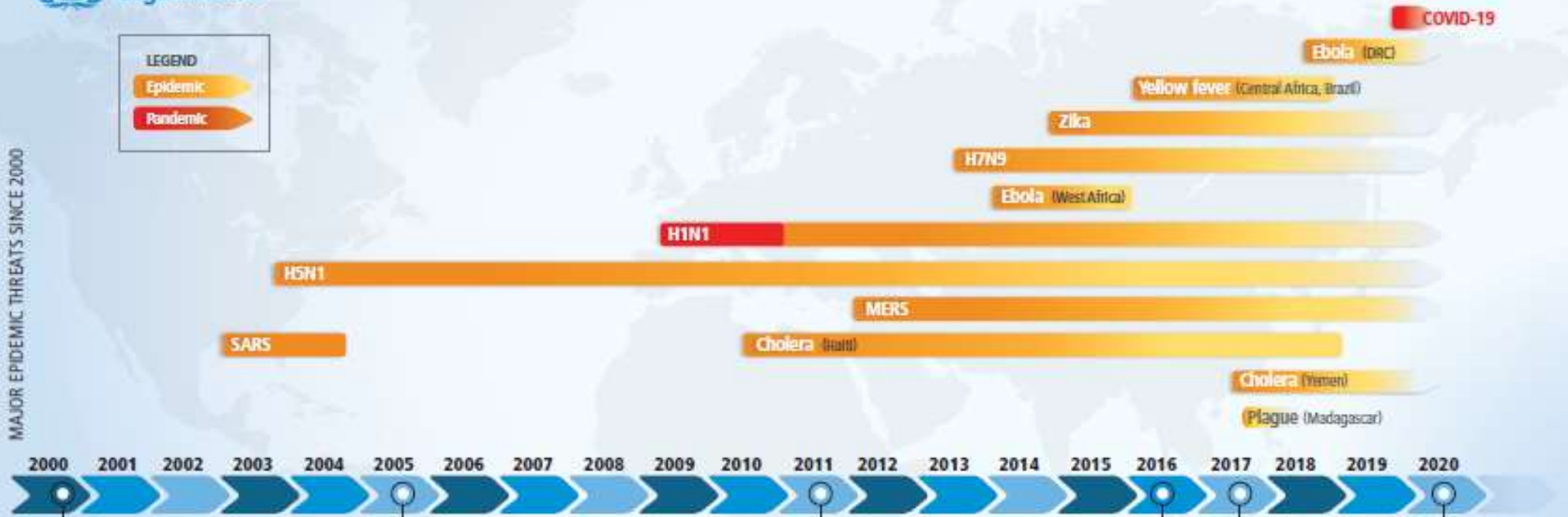


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LEGEND

Epidemic

Pandemic



GAVI Gavi, the Vaccine Alliance, is an international organisation that was created in 2000 to improve access to new and underused vaccines for children living in the world's poorest countries.

GOARN The Global Outbreak Alert and Response Network (GOARN) is a technical collaboration of existing institutions and networks who pool human and technical resources for the rapid identification, confirmation and response to outbreaks of international importance.

IHR (2005)

The International Health Regulations (2005) or IHR (2005) are an international law which helps countries work together to save lives and livelihoods caused by the international spread of diseases and other health risks. The IHR (2005) aim to prevent, protect against, control and respond to the international spread of disease while avoiding unnecessary interference with international traffic and trade.

PIP Framework

The Pandemic Influenza Preparedness (PIP) Framework brings together Member States, industry, other stakeholders and WHO to implement a global approach to pandemic influenza preparedness and response. Its key goals include:

- to improve and strengthen the sharing of influenza viruses with human pandemic potential; and
- to increase the access of developing countries to vaccines and other pandemic related supplies.

R&D Blueprint

R&D Blueprint is a global strategy and preparedness plan that allows the rapid activation of research and development activities during epidemics. Its aim is to fast-track the availability of effective tests, vaccines and medicines that can be used to save lives and avert

PIP Review

IHR Review

Access to COVID-19 Tools (ACT) Accelerator is a global collaboration to accelerate the development, production and equitable access to new COVID-19 diagnostics, therapeutics and vaccines.

ACT Accelerator

+ + = + + **Epidemics**

Pandemic and epidemic diseases : health challenges

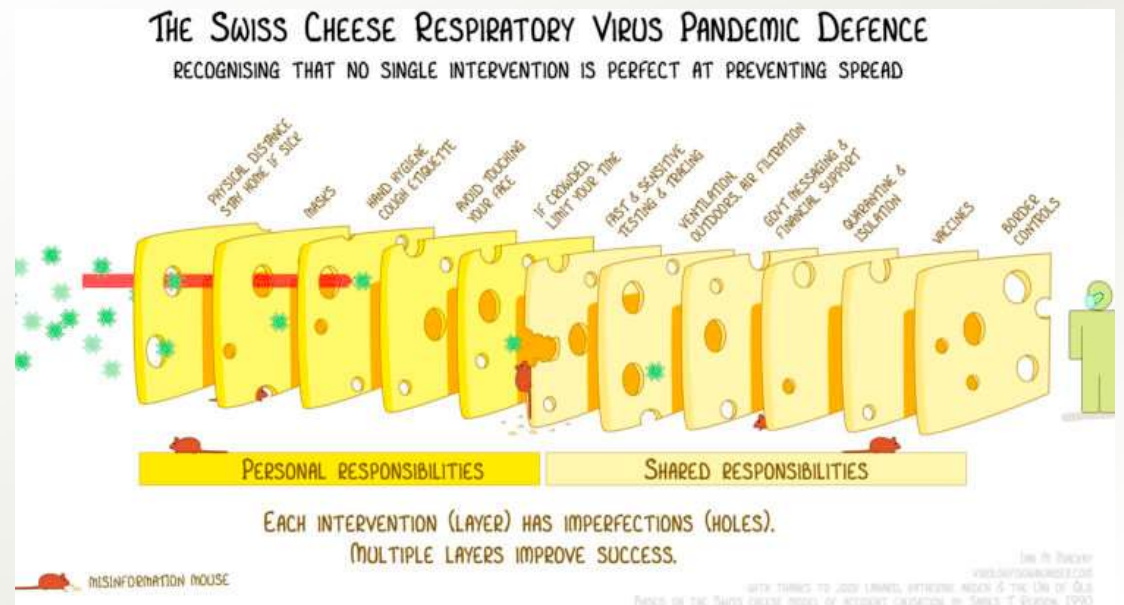
- Main characteristics

1. **Rapid spread:** → control of transmission
2. **High mortality:** → good care
3. **Impact on health systems:** → mitigation



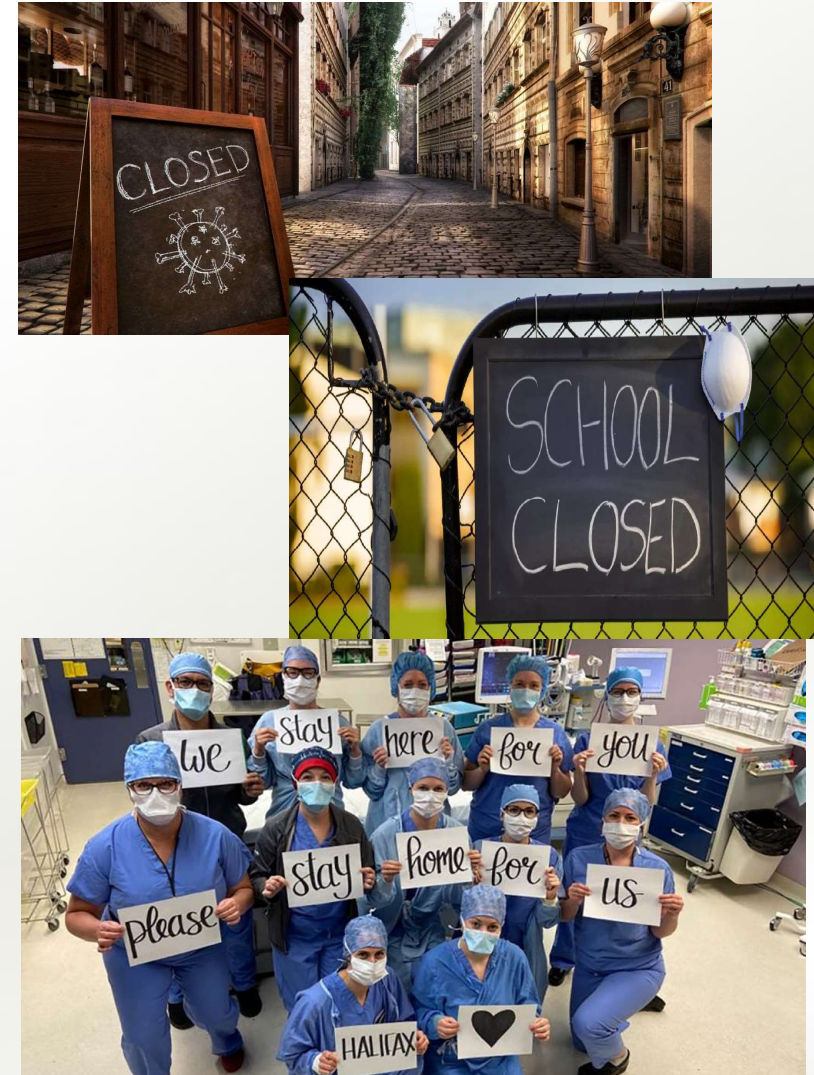
Pandemic and epidemic diseases : health challenges (1)

- **Rapid spread:** control of transmission through
 - “public health and social measures” (isolation, quarantine,...)
 - Vaccination
 - Early treatment



Pandemic and epidemic diseases : health challenges (1) COVID 19

- 'Flattening the curve' is important as in every country there are limited numbers of hospitals, nurses and doctors
- The capacity of the health system can be exceeded if too many people seek healthcare at the same time
- Many countries close schools, shops, workplaces, bars, restaurants as well as borders and ask people to stay home to limit the spread of the virus. It has been effective on transmission but has had major impact on societies and economies.
 - **Could these constraining measures have been avoided with the use of broad-spectrum antivirals?**



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Pandemic and epidemic diseases : health challenges (2)

- **High mortality:** can be reduced with good care
 - Enhanced supportive care (e.g. Ebola reduction from 75% to 43 % CFR in west Africa 2015) *E.I. Bah et al, "Clinical Presentation of Patients with Ebola Virus Disease in Conakry, Guinea" N Engl J Med 2015; 372:40-47 January 1, 2015*
 - Therapeutics: either specific or non-specific (corticosteroids)
 - Protection of the health workforce (vaccination, PPE, Post Exposure Prophylaxis)
- In case of emerging disease (e.g. disease X): there will be no vaccine for the first few months, hence the importance of having treatments available and resilient health systems able to use them.

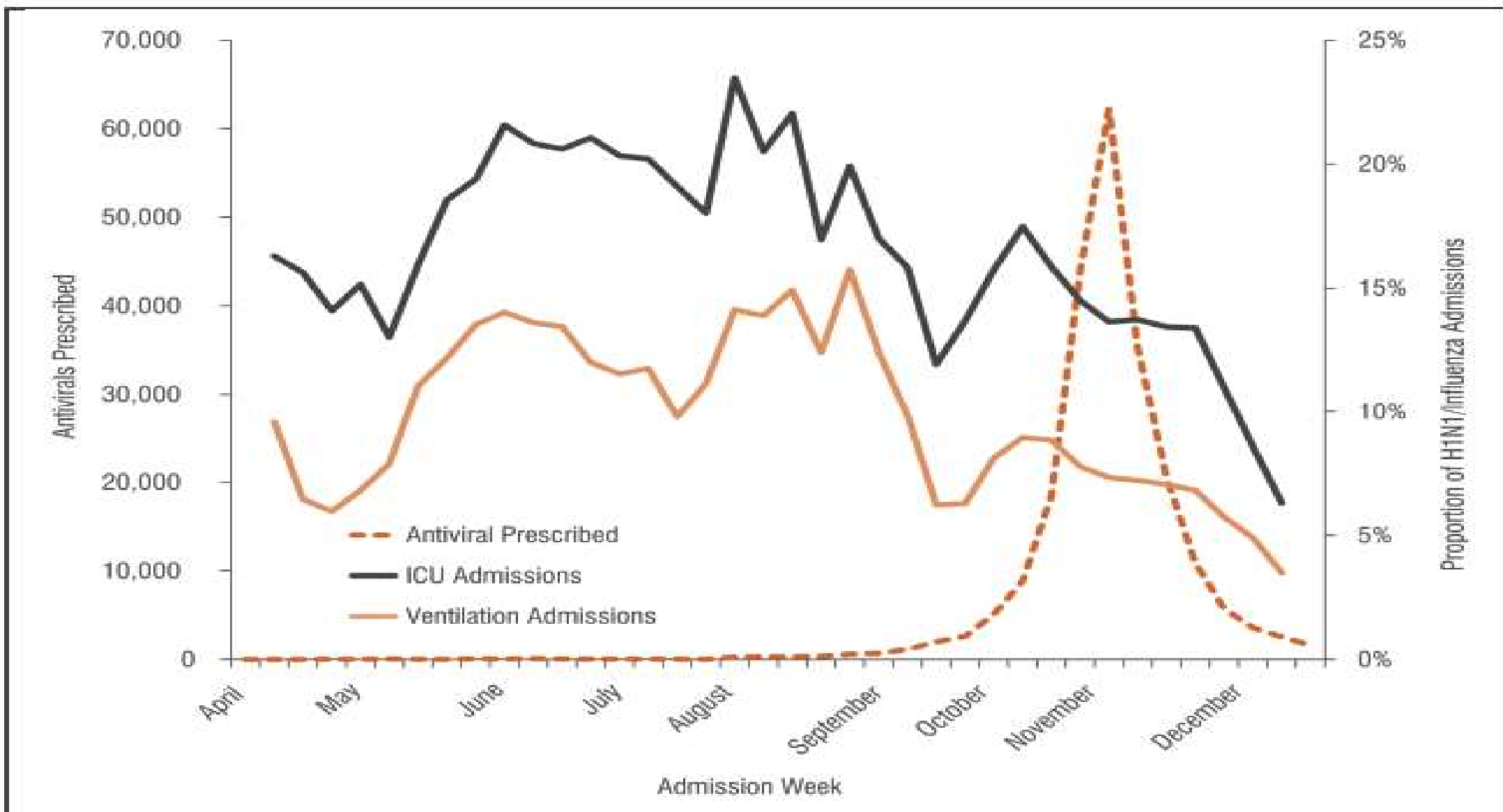


Pandemic and epidemic diseases : health challenges (3)

- Impact on health systems:
 - need surge capacity, ICU and protection of the health workforce - the response is costly
 - Mitigation with therapeutics
 - “test and treat” approach (e.g. Japan and 2009 H1N1 pandemic)
 - Reduction of ICU & hospitalization with the use of antivirals and thus the burden on health systems



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



Assessment of Severity Characteristics

Table 1 Selected severity characteristics of pandemic influenza A (H1N1) 2009 virus infections, data as of 6 November 2009^a

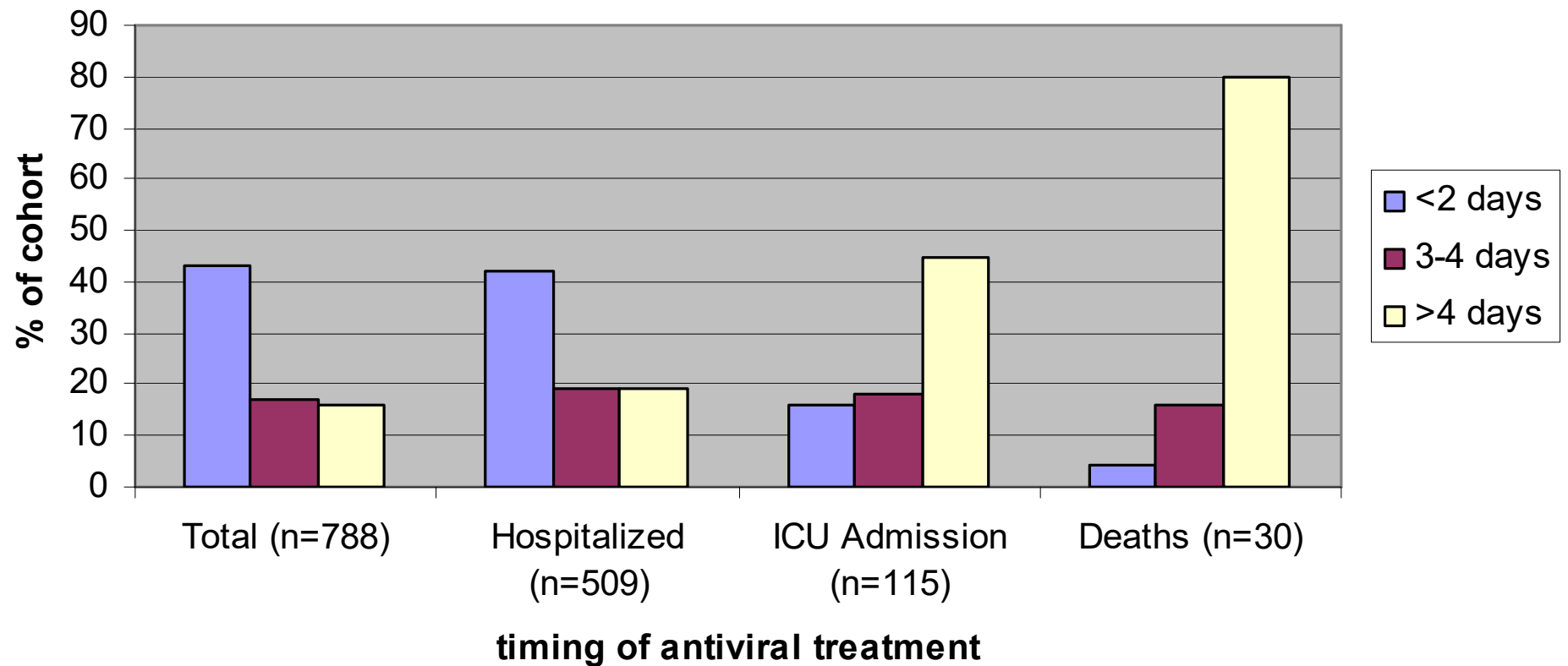
Tableau 1 Quelques caractéristiques de la gravité des infections par le virus de la grippe pandémique A (H1N1) 2009 (données au 6 novembre 2009)^a

Country – Pays	% of hospitalized cases with no co-morbidity – % de cas hospitalisés sans comorbidité	% of hospitalized cases who are pregnant – % de cas de femmes enceintes hospitalisées	Cumulative number of hospitalizations – Nombre cumulé d'hospitalisations	Incidence of hospitalization (per 100 000 population) – Incidence de l'hospitalisation (pour 100 000 habitants)	Median age of hospitalized cases (years) – Age médian des cas hospitalisés (ans)	Rate of ICU admission or hospitalization – Taux d'admission dans les services de soins intensifs ou d'hospitalisations	Number of deaths – Nombre de décès	Mortality rate (deaths per million population) – Taux de mortalité (nombre de décès par million d'habitants)
Northern hemisphere temperate zone – Zone tempérée de l'hémisphère Nord								
Canada	38	5	1 999	5.8	24	0.20	95	2.8
Japan – Japon	63	0.3	3 746	2.9	8	–	35	0.2
United Kingdom – Royaume-Uni	43	7.5	–	–	15-24	–	135	2.2
Mexico – Mexique	–	–	10 337	9.3	–	–	328	2.9
United States – Etats-Unis d'Amérique	27	7	9 079	3.0	21	0.25	1 004	3.3
Southern hemisphere temperate zone – Zone tempérée de l'hémisphère Sud								
South Africa – Afrique du Sud	–	–	–	–	–	–	91	1.8
Argentina – Argentine	47	–	9 974	24.5	20	0.13	593	14.6
Australia – Australie	51	6	4 844	22.5	31	0.13	186	8.6
Brazil – Brésil	79	8.3	17 219	8.8	26	–	1 368	7.0
Chile – Chili	47	2.4	1 852	10.8	32	0.39	140	8.1
New Zealand – Nouvelle-Zélande	–	6.5	1 001	23.3	20-29	0.12	19	4.4

Source: *Weekly Epidemiological Record*, 13 November 2009.

Pandemic 2009 Influenza Among Pregnant Women in the USA

Progression of pregnant women



Battle against Respiratory Viruses (BRaVe)

- In 2010-2011: pandemic fatigue, parliamentarians audits
- Persistence of misconceptions
 - Viral respiratory infections are mild (mild pandemic)
 - Influenza is a problem only in rich and temperate countries
 - Nothing can be done against viral respiratory infections
 - RSV is only severe in children
- The BRaVe initiative (2012) aimed at building on the progress and lessons learned during the pandemic 2009 while addressing the remaining challenges related to acute viral respiratory infections



"Ideas can spread as well"

Battle against Respiratory Viruses (BRaVe) initiative
Addressing Unmet Needs

- **Advancing the paradigm**
Since the late 19th century, vaccines, improvements of water and sanitation, and other public health interventions have saved millions of lives annually by preventing a number of infectious diseases. In the mid-20th century, the discovery of antibiotics added the promise of effective treatment for many bacterial infections to the preventive power of vaccines. Together these innovations have constituted the predominant paradigm governing the approach to infectious disease mortality reduction.



In the late 20th century, we have witnessed major breakthroughs in the fight against infectious diseases, in large part because of the development of improved diagnostics and the discovery of antiviral medicines. Progress in molecular biology, genetic engineering, and other disciplines has enabled scientists to design and produce antivirals that target key structures of the virus particles, or else block critical processes involved in viral replication. Examples now include effective antivirals for HIV, herpes, influenza, and hepatitis B and C viruses.

- **Understanding the impact of respiratory viral diseases**
Respiratory infections, exemplified by pneumonia, are the leading cause of death among infectious diseases and account for approximately 20% of mortality in children under five. All ages included, respiratory infections account for around 4 million deaths per year¹. Additionally, lower respiratory infections are the leading cause of burden of disease worldwide, accounting for 94.5 million Disability Adjusted Life Years (DALYs) i.e. 6.2% of total DALYs.











Approximately half of the respiratory infections are due to respiratory viruses. Severe pneumonia is not the only complication of viral respiratory viruses. Respiratory viruses are also responsible, directly or indirectly, of a number of other severe health conditions such as otitis media, sinusitis, acute bronchitis, exacerbation of asthma and chronic lung disorders. These chronic respiratory diseases which can be triggered by respiratory viruses are common problems in all countries, with huge medical and economic impacts. Adults with underlying conditions are particularly at risk for both deteriorations in their co-morbidities and severe infections adding to

¹ The Global Burden of Disease 2004 update, WHO:
http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf; accessed July 2012

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Shift in paradigm for preparedness

1. Revisiting the Preparedness /response cycle
 - Example of the BRaVe initiative (Battle against respiratory viruses)
 - Preparedness for pandemic embedded in endemic health priorities (e.g. burden of viral pneumonia in LIC)
2. Balance between research for vaccine and other medical products for response
3. Preparedness for groups of threats (families of viruses, based on mode of transmission)
4. Other important factors : Community engagement Resilient health care systems, diagnostics

<u>Human</u>	<u>Virus</u>	<u>Species/Sub-Sero-Genotypes</u>	
	Rhinovirus	A, B, C, >140 serotypes	RNA
	Influenza	A (H3N2,H1N1..) ,B ,C	RNA
	RSV	A and B	RNA
	<u>Parainfluenza</u>	Type 1, 2, 3 and 4	RNA
	<u>Metapneumovirus</u>	A1, A2, B1, B2	RNA
	Coronavirus	OC43, E229, HKU1, NL63	RNA
	<u>Enterovirus</u>	>100 serotypes	RNA
	Adenovirus	7 species, > 50 serotypes	DNA
	<u>Bocavirus</u>	4 species	DNA
	<u>Polyomavirus</u>	KI, WU, Merkel...	DNA

Broad-spectrum antivirals as an additional tool

- Development of antivirals are critical
 - Interventions to support the first months of the response, especially if new virus
- Need to ensure they are broad-spectrum antivirals
 - **Effective on Families of viruses** so that could be used for the response to a viral disease outbreak
 - **Not only for emergency situations** to ensure continuity of production
- Importance of **linkages with diagnostic development and access** (Test & Treat approach)
 - New molecular diagnostic technologies allow for rapid testing for multiple etiologies (viral and bacterial).
 - For viral diseases, treatments must be administered as early as possible to prevent severe forms of the disease



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Fostering the development of broad-spectrum antivirals

- Less competition – more efficiency
 - Allocate long-term grants for centers of excellence to carry out multiple studies on the same topic.
- Risk management approach: less pathogen focus, reduce severe disease vs. cure, combination of therapeutics/antivirals, mitigation vs. elimination
- More coordination between different groups
 - Standardization of research protocols between settings
 - Create platform for faster sharing of results -either positive or negative - to rapidly inform public health decision
- Promote probe studies and alternative research strategies like adaptive trial designs to speed up evidence building



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Learning the lessons from the pandemic: Ensuring equity

- **Equity** must be a guiding principle at all stages
 - Research
 - Development, production, procurement, and access
 - Allocation must be based on public health needs





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