The use of antivirals for the treatment and prophylaxis of novel influenza virus infections

Dr Aeron Hurt
WHO Collaborating Centre for Reference and Research on Influenza,
Peter Doherty Institute for Infection and Immunity
Melbourne, Australia

WHO Collaborating Centre
for Reference and
Research on Influenza
VIDRL

Currently approved influenza antivirals*

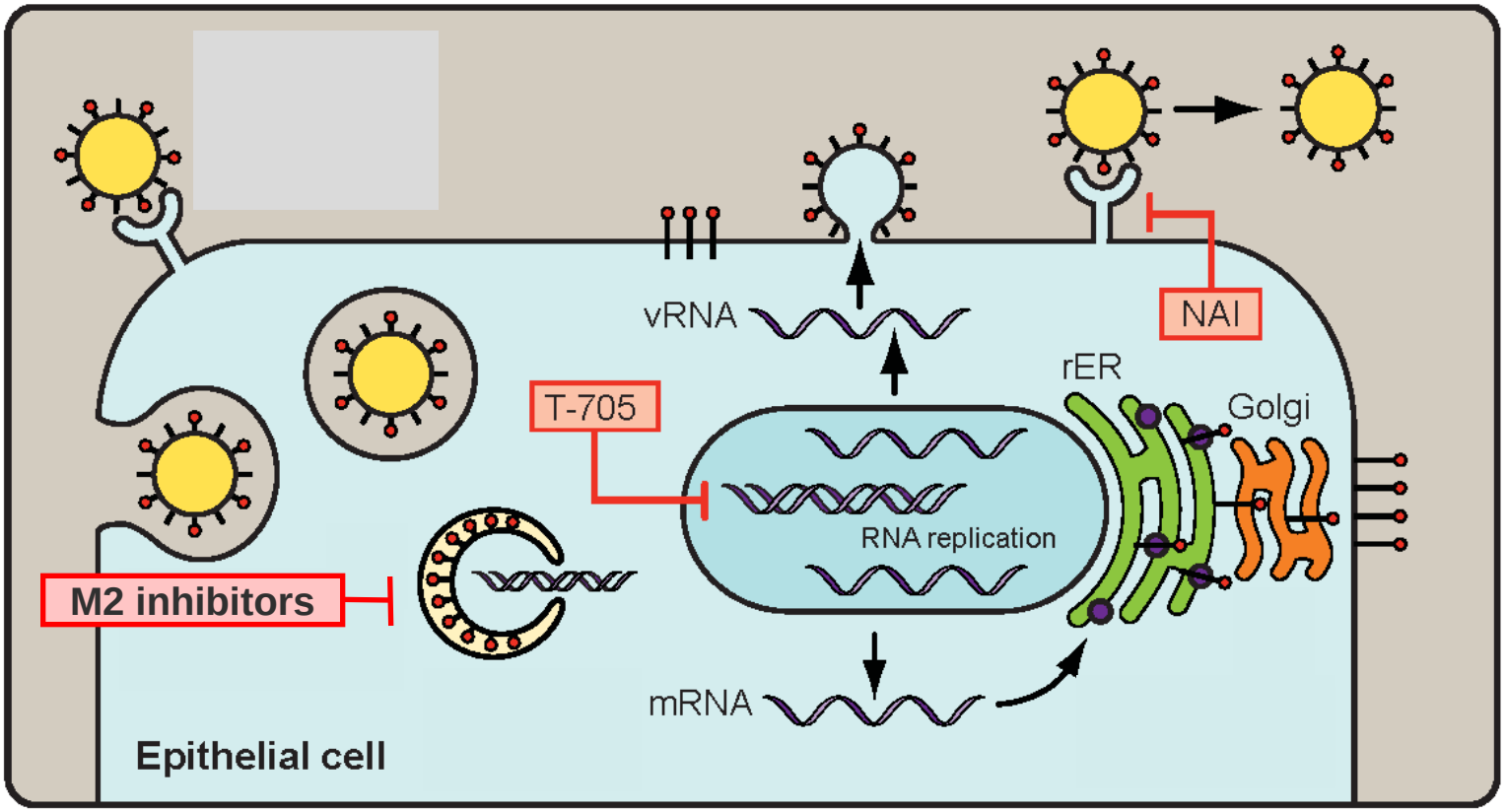
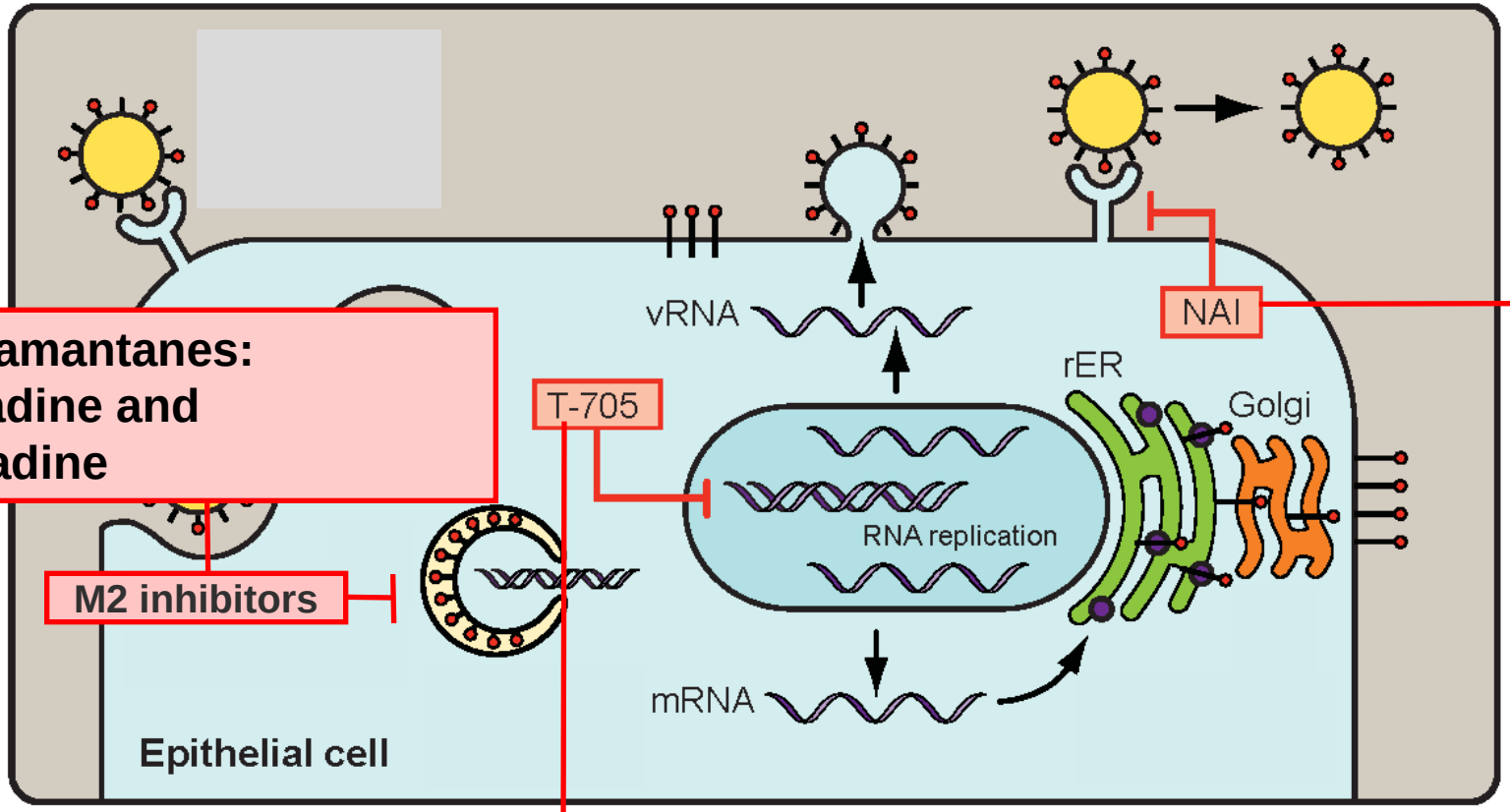


Figure taken from: Drugs in development for influenza. Boltz DA, Aldridge JR Jr, Webster RG, Govorkova EA. Drugs. 2010 Jul 30;70(11):1349-62.

Currently approved influenza antivirals*

The NA inhibitors: oseltamivir and zanamivir + some new ones: peramivir and laninamivir

The adamantanes: amantadine and rimantadine



LIMITED APPROVAL
Polymerase inhibitor – T-705
- **inhibits influenza RNA polymerase**

Figure taken from: Drugs in development for influenza. Boltz DA, Aldridge JR Jr, Webster RG, Govorkova EA. Drugs. 2010 Jul 30;70(11):1349-62.

Antivirals for treatment of novel influenza A virus associated with severe human disease

- Antivirals have an important role in treatment and prevention of human illness from novel influenza A infections
  - Particularly when no vaccine is available

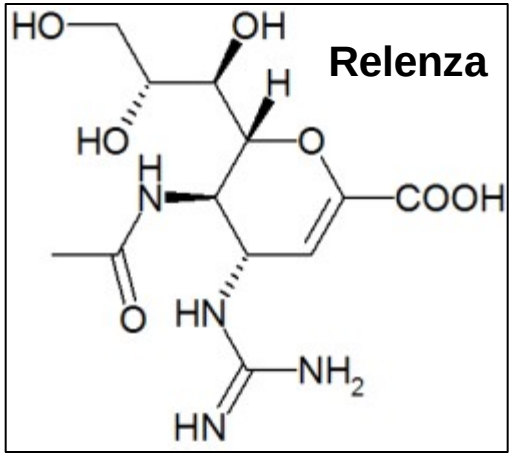
- The goal of antiviral treatment should be:
  - Early treatment of ill persons
    - reduce disease progression and development of serious complications
    - Reduce viral shedding and transmission

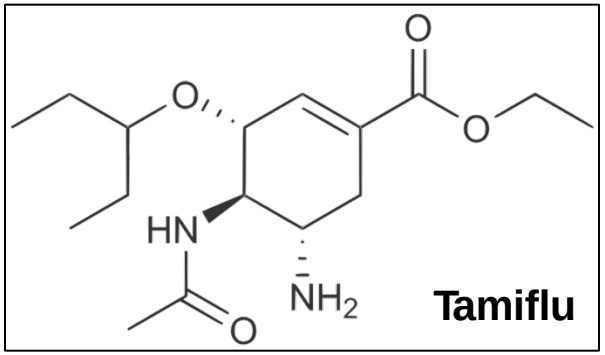
Treating novel/pandemic influenza: then and now

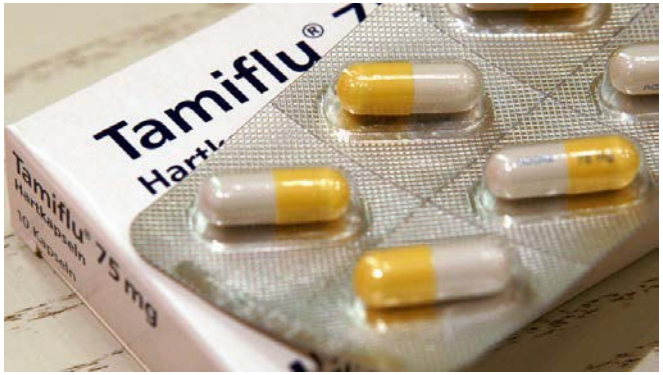
Arrowsmith, 2007

1918

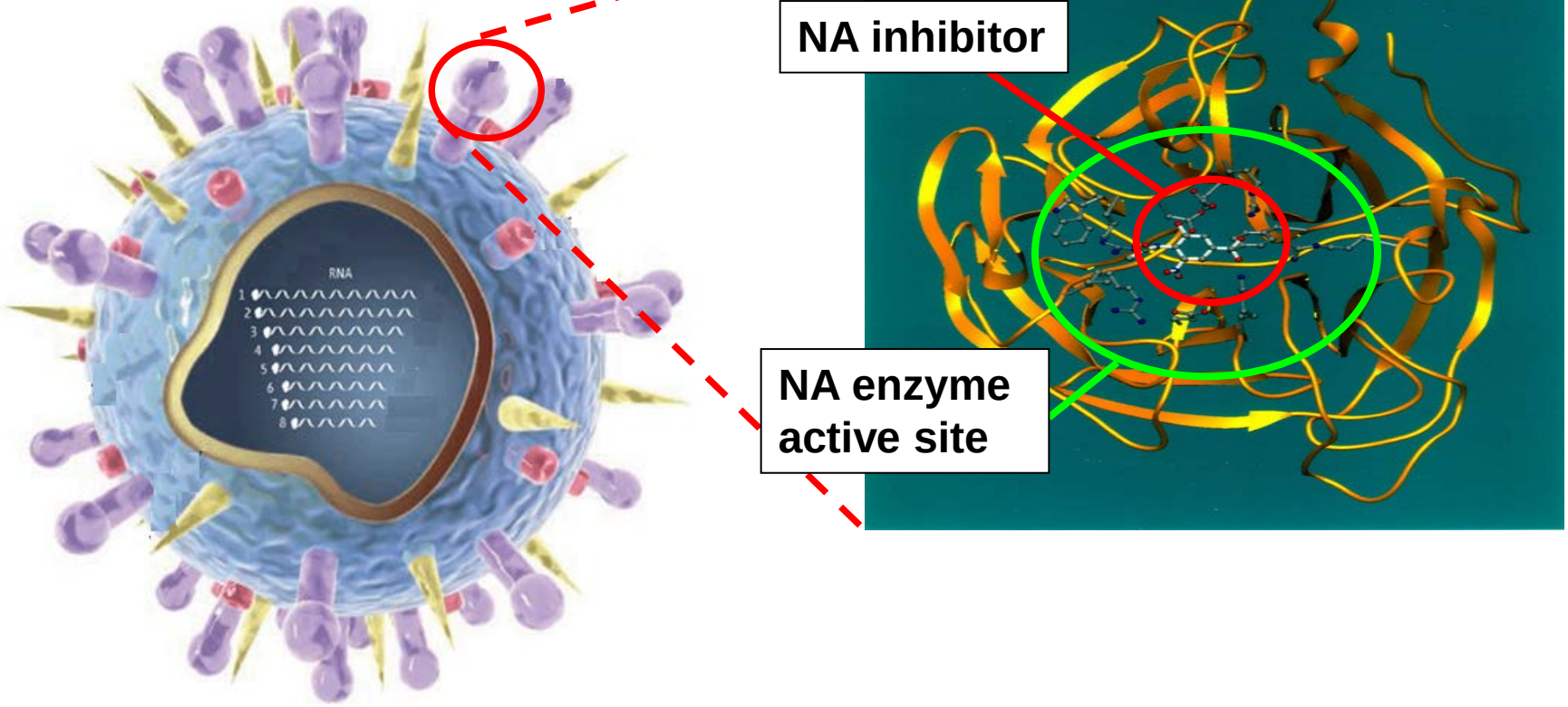
Now







NA inhibitor antiviral drugs



The NA inhibitors

Oseltamivir

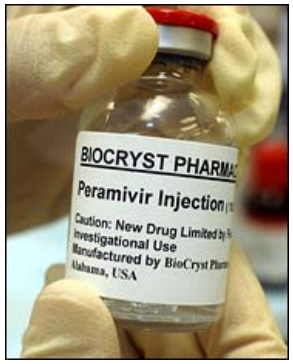
- Oral, IV(?)
- Global

Zanamivir

- Inhaled, IV(?)
- Global

Peramivir

- IV
- Japan, S.Korea, China, US



Laninamivir

- Inhaled (single)
- Japan

Infection with novel influenza viruses

Highly pathogenic avian influenza A(H5N1) viruses

- First human infections of H5N1 in 1997, re-emergence in 2003

- Guidance for antiviral treatment and chemoprophylaxis developed by WHO in 2004
  - Various modifications over the years
  - CDC, ECDC, PHE developed similar guidelines

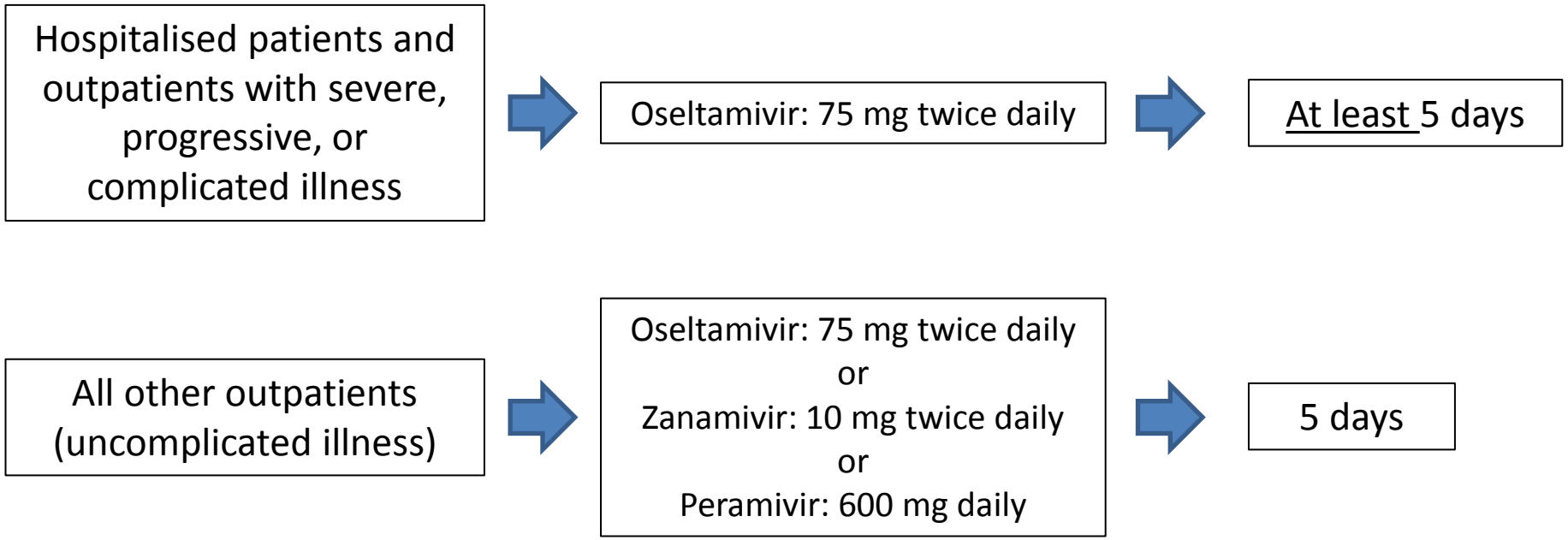
Low/highly pathogenic avian influenza A(H7N9) viruses

- Emerged in 2013
- 5th wave largest and geographically most widespread
- Clusters of cases detected have been limited, non-sustained human-to-human transmission has probably occurred

- Earlier H5N1 guidance modified by CDC to be more broadly applicable to human infections with any novel influenza A virus associated with severe disease
  - Therefore could also be applied to HPAI A(H5N6) and LPAI A(H10N8) viruses
  - Other viruses that will emerge in the future and where risk of severity and transmission is unknown

US CDC recommendations for antiviral treatment of human infections with suspected or confirmed infection novel influenza A viruses

- Treatment should not be delayed while waiting for laboratory confirmation of a novel influenza virus infection
- Treatment should be initiated even if >48 hours has elapsed since illness onset

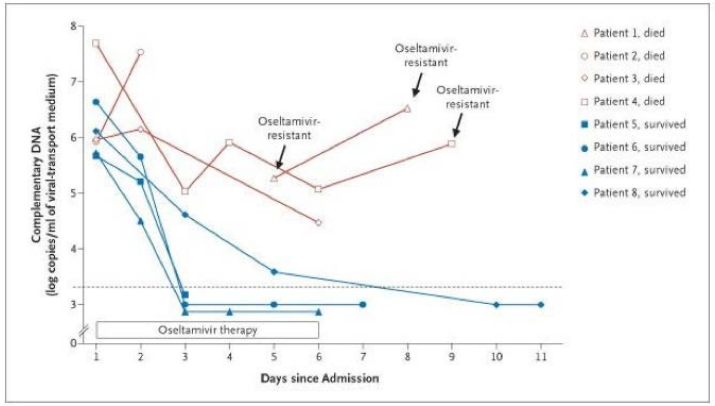


Oseltamivir: longer treatment or double dose?

- Standard dose oseltamivir is 75 mg twice daily for five days

- Longer dosing – 10 days vs 5 days
  - Yet to be rigorously evaluated

- WHO suggested considering higher does (150 mg twice daily) due to:
  - High level of H5N1 virus replication
  - Development of oseltamivir resistance during treatment with standard dose (de Jong et al., NEJM, 2005)



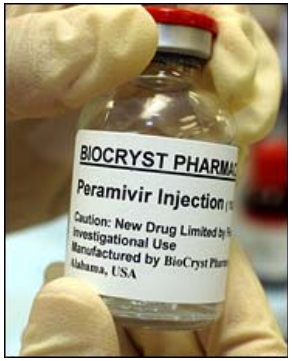
- However recent studies have not demonstrated a clinical or virological advantage with higher doses
  - Lee et al. CID, 2013
  - South East Asian Infectious Diseases Clinical Research Network, BMJ, 2013
  - Welch et al. Intensive Care Med, 2015

Zanamivir or peramivir : a role in treatment of severely ill patients?

- Lack of data on the value of inhaled zanamivir or intravenous (IV) peramivir in patients with severe influenza illness.

- Zanamivir
  - Low bioavailability outside the respiratory tract compared with oral oseltamivir, therefore maybe less effective in inhibition of virus disseminated systemically
  - Intravenous (IV) zanamivir
    - Not approved
    - Useful in patients who cannot tolerate or absorb oseltamivir (rare)
    - Benefit if treating virus that is oseltamivir (and peramivir) resistant (e.g. H275Y A(H1N1)pdm09 variant)

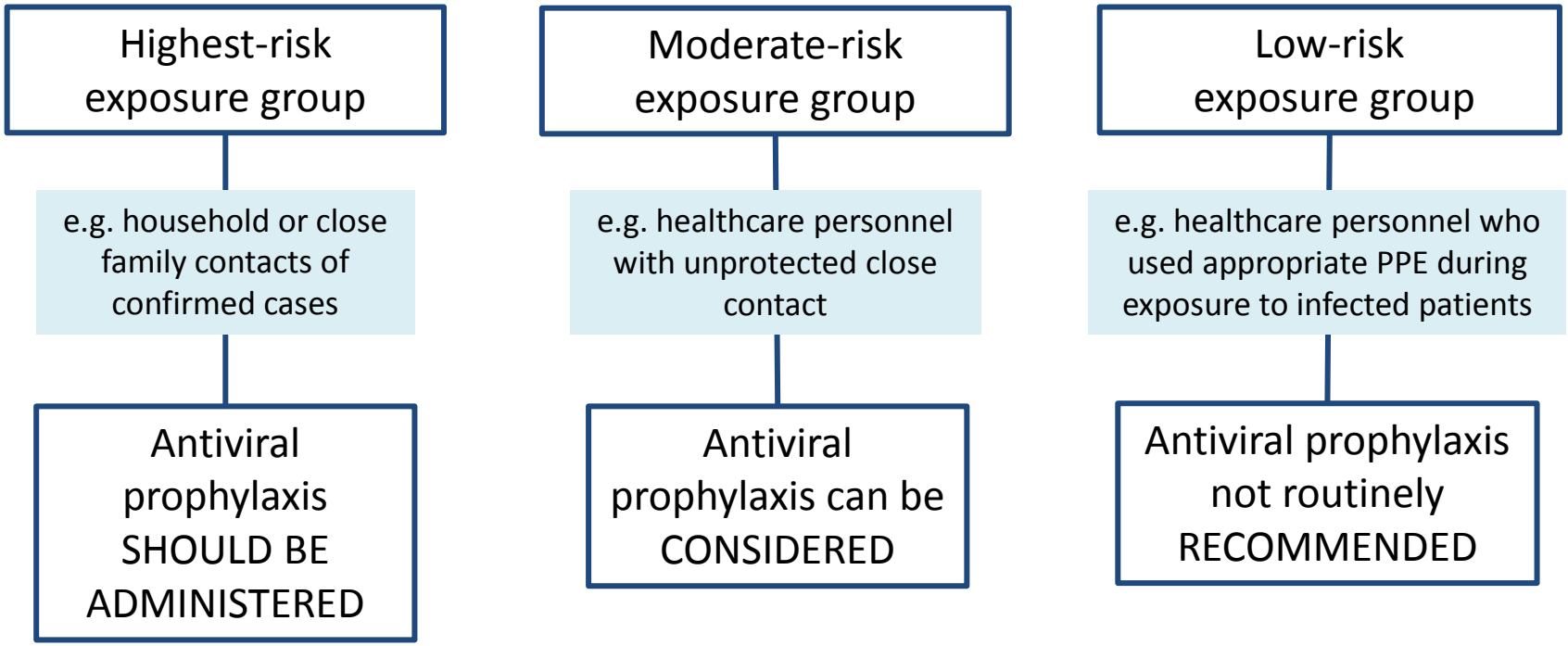
- Peramivir
  - Further studies necessary to understand clinical effectiveness in severely ill patients



Post-exposure prophylaxis

- Seasonal influenza:
  - RCTs show post-exposure prophylaxis to be 70-90% effective in preventing spread amongst household members

Who should receive post-exposure prophylaxis in a situation of a novel influenza infection?



Post-exposure prophylaxis – dose and duration

- Earlier guidance developed for HPAI A(H5N1) for post-exposure prophylaxis has been updated in WHO, CDC, PHE guidelines:

Previous guidance

1 dose once daily
(1/2 normal treatment dose)

→

Updated current guidance

1 dose twice daily
(same as normal treatment dose)

- Duration:

If exposure is likely to be ongoing

↓

10 days duration of antiviral prophylaxis

If exposure is time-limited

↓

5 days duration of antiviral prophylaxis

Post-exposure prophylaxis – twice daily

Previous guidance		*Updated current guidance*
1 dose once daily (1/2 normal treatment dose)	→	1 dose twice daily (same as normal treatment dose)

Change in recommendations based on :

- If prophylaxis is started AFTER infection, a lower prophylaxis dose would be sub-therapeutic dose which can:
  - have adverse clinical consequences
  - increase the chance of development of resistance

- Early case reports of resistance development in oseltamivir-treated A(H7N9) patients
  - lower prophylaxis dose would be even less optimal

- Ferret studies suggest show twice daily prophylaxis dosing of oseltamivir for HPAI A(H5N1) compared with once daily reduced clinical signs and lung pathology

So what about in a pandemic?

- NAIs only likely to constrain transmission if the virus has low transmissibility but high severity (i.e. highly visible to healthcare system and R0 not much >1)
  - With a highly transmissible virus post-exposure prophylaxis confers not benefits to the population and ↑ consumption of stockpile

- Focus not on containment, but on <u>mitigating complications and population impact</u>

Modelled various strategies across different pandemic scenarios in the Australian setting (Moss et al, 2016)

- Liberal distribution of antivirals for early treatment in outpatient and inpatient settings yielded the greatest benefit: ↓ hospitalisations, ICU needs and deaths
- Restriction of treatment to risk groups = effective in those groups, but failed to prevent the large proportion of cases arises from low-risk patients (bulk of popn)
- Even in most severe scenario, stockpile consumption for treatment was equivalent to 6.5% of population
- These outcomes are only likely to be achieved if NAIs can be effectively deployed within existing health care infrastructure.

Implications for Stockpiling

- Japan uses the greatest amount of NAIs in the world for seasonal influenza use
- Rapid access during the 2009 pandemic in Japan was possible because rapid access represented routine care for seasonal influenza.
- Data from Japan suggests that rapid access to stockpiled NAIs in a pandemic was necessary to achieve the benefits they observed:
    - >98% (984/1,000) Japanese children hospitalized with influenza A(H1N1)pdm09 were treated with an NAI, 89% received NAIs within 48 hours and 70% within 24 hours. Only 1% of the hospitalized children ultimately required mechanical ventilation, and 1 death was recorded (*Sugaya et al., 2011*)
    - Pregnant Japanese women were treated prophylactically after close contact with an infected person, and if infected and hospitalized, >90% were given NAIs within 48 hours of symptom onset. In comparison to the high mortality rates among pregnant women in many countries around the world (*Burioni et al., 2009*), no maternal deaths occurred in Japan during the pandemic (*Nakai et al., 2012*).

Implications for Stockpiling

- In other countries, the 2009 pandemic confirmed that centralized stockpiles did not facilitate rapid distribution (*Gutiérrez-Mendoza et al., 2012*) and that decentralized stockpiles would be more efficient.

- Stockpiles in hospitals, for example, would facilitate rapid treatment of ill patients in a pandemic but might also allow the periodic use of some material for the treatment of interpandemic seasonal influenza to avoid wastage due to an expiring stockpile (*Gutiérrez-Mendoza et al., 2012*).

- Over-the-counter administration, as has been approved in NZ, is a great example of how the drug may be able to be accessed quickly….assuming it is dispersed rapidly to pharmacies!

NAI-resistance in a pandemic scenario?

- Mutations in the NA can be selected under drug pressure = resistance

- Fitness of the resistant virus (i.e. its ability to spread) – is inherently different for each subtype/variant → it will come down to luck!!!!!

- Need to understand early in a pandemic which mutations are likely to arise in a particular virus under pressure of a particular drug
  - Known for seasonal viruses, not for a novel virus
  - Understand the level of 'cross-resistance' i.e. if a virus is resistant to oseltamivir will one of the other NAIs be effective?

- WHO GISRS will be well set-up to monitor for resistance
  - Phenotypic assays – detailed, informative, slow
  - Genotypic assays – focused on testing for key mutations, rapid

  - Important to be monitoring both patients under treatment and those in the community to assess
    - Frequency of resistance under drug pressure
    - Evidence of community spread of resistance (fit virus)

Summary

- Guidance for antiviral treatment and post-exposure prophylaxis of novel influenza strains were first developed in 2003 in response to H5N1 and has been updated/modified with the emergence of H7N9
- Treatment guidance:
  - should not be delayed while waiting for laboratory confirmation
  - should be initiated even if >48 hours has elapsed since illness onset
  - Benefit of continuing treatment longer than 5 days remains unclear
  - double dose doesn't appear to improve effectiveness
  - lack of data on effectiveness of IV peramivir or zanamivir in severely ill
- Post-exposure prophylaxis guidance:
  - household or close contacts of confirmed cases should be given antiviral prophylaxis
  - dose should be twice daily for 5 to 10 days depending on exposure
- In a pandemic:
  - liberal distribution of antivirals for early treatment in outpatient and inpatient settings are likely to yield the greatest benefit in modelling studies
  - Need effective distribution strategies to ensure early treatment and benefit
- Resistance testing will rely on understanding the mutations that are likely to arise and their impact on antiviral susceptibility and viral fitness

Thank you

The Melbourne WHO Collaborating Centre for Reference and Research on Influenza is supported by the Australian Government Department of Health.

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