Guidelines for clinical management of severe influenza infection

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Current WHO guidelines

- WHO guidance documents for the clinical management of influenza virus infection were published in 2007 and 2009.

- These documents were rapidly developed in response to emerging information about human infections with avian influenza A(H5N1) virus and the 2009 A(H1N1) pandemic.

- Since 2009, more data have become available and new threats of avian influenza A(H7N9), A(H5N6) and swine influenza A viruses have emerged.

- WHO is therefore developing new consolidated standard guidelines for the clinical management of severe influenza virus infections that will apply to all forms of influenza infection, including seasonal, pandemic and zoonotic influenza viruses, and across all resource settings.

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Guideline Development Group

- The guideline development is following GRADE methodology to ensure evidence-based recommendations emerge.
  - GRADE = Grading of Recommendations Assessment, Development and Evaluation
  - “a common, sensible and transparent approach to grading quality (or certainty) of evidence and strength of recommendations”

- The GDG includes specialists in public health, pharmacology, pulmonary medicine, intensive care medicine, internal medicine, paediatric medicine, medical education, virology, and infectious diseases.

- The co-chairs are clinicians with considerable expertise in guideline methodology.

Guideline Development Group

- The multidisciplinary composition to address the influence of viral, host and epidemiological factors on disease severity and subsequent patient outcomes.
- Consequently, members of the GDG have been selected from diverse WHO regions and a spectrum of high, middle and low-income countries.
- Two day meeting in Nov 2017, focus on the current information and evidence available but with a focus on what analyses are needed to enable the GDG to develop guidelines
- The additional work as defined by GDG is expected to be available in 2018, at which time the GDG will reconvene to generate its recommendation.
- In the interim, the 2010 guidelines continue to be the reference for decision-making.

Areas of focus

- The GDG concentrated on six main areas of interest:
  - specification of critical and important outcomes of interest
  - the definition of severe influenza infection
  - antiviral medications
  - adjunctive therapies
  - supportive therapies
  - diagnostic testing
- Meta-analyses to evaluate the evidence associated with many of these will be conducted over the next 6 months

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Antiviral medications

- A systematic review has been commissioned on antiviral medications that are widely available for the treatment of influenza, particularly oseltamivir and zanamivir, in the populations specified.
- The GDG has prioritised that an independent analysis of data from randomised controlled trials of antiviral treatment is also undertaken because published analyses have come to contradictory conclusions.
- A systematic review of observational studies is underway and will be refined based on the GDG discussions.
- The review team shall be mandated to interact with the authors of prior reviews with discordant conclusions to ensure a full review of all relevant evidence with rigorous and transparent methods.

The challenges of assessing antivirals in severely ill patients

Ethical/regulatory challenges

- Unable to conduct a placebo-controlled study or dose-ranging study with low dose control due to ethical consideration in severely ill patients
- Oseltamivir is the default standard of care despite no studies of clinical benefit in this patient population
- FDA require <u>superiority</u> over oseltamivir

Patient population

- Heterogeneous population
- Many sites throughout the world needed, but SOC differs
- Oseltamivir comparator means patients have to be able to receive oral dose

The challenges of assessing antivirals in severely ill patients

Which endpoints to use?

- There is currently no validated primary clinical endpoint
- FDA/EMA recognise that this is required but no official recommendations have been made

- Primary endpoints proposed include: duration of hospitalization, time to normalization of vital signs and oxygenation, requirements for supplemental oxygen or mechanical ventilation, and mortality.

- Virological measures?
  - Often lack of clear correlation between virologic response and clinical benefit
  - comorbidities and host factors may influence ultimate clinical outcomes, and thus evidence of influenza virus clearance may serve as a more objective marker of antiviral efficacy

IV zanamivir study

- Intravenous (IV) therapies have potential to significantly improve care in severely ill patients who cannot receive oral treatment

- Largest randomized, double-blind clinical trial of an influenza antiviral in hospitalised patients with severe influenza to ever be completed

- 600 mg IV Zan (n=209) vs 300 mg IV Zan (n=201) vs oral oseltamivir (n=205)

- Primary endpoint was “time to clinical response” – a composite of vital sign stabilization and hospital discharge

- No significant improvement in time to clinical response seen for 600 mg IV Zan vs oseltamivir or 300 mg IV Zan. All treatments had similar safety profile.

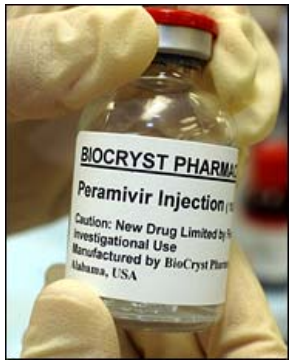
- Potentially useful compound, particularly in the context of oseltamivir-resistance, is unable to be licensed and has the potential to be unavailable in the future even for use an Emergency Investigational New Drug application

Marty FM, et al. Lancet Respir Med. 2017 Feb;5(2):135-146.

IV peramivir

- Peramivir is the only IV influenza antiviral agent currently approved by the FDA
  - But this is for out-patients with uncomplicated influenza
  - Approved in: Japan, USA, S. Korea, Taiwan, Canada and China
  - Submitted: Australia and EU (Pers. Comm. Jane Leong, Seqirus)

- Influenza infected hospitalised patients (Ison M et al. Antivir Ther. 2013;18(5):651–661.)
  - Peramivir 200 mg (n=41) or 400 mg (n=40) vs. oseltamivir (n=41) daily for 5 days
  - Median time to clinical stability not sig different: 24h (200mg) & 37h (400mg) equivalent to oseltamivir (28h)
  - Greater antiviral effect than oseltamivir in subjects with influenza B infection



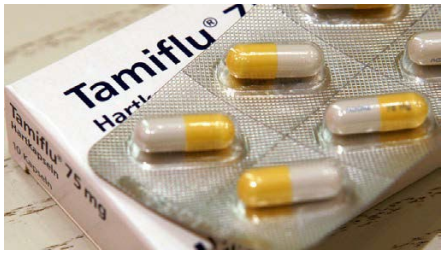
- Not currently approved for use in severely ill, hospitalised patients
- If it becomes licensed in Australia for uncomplicated influenza, it will improve access for use in severely ill patients

Summary

- WHO are in the process of developing new consolidated standard guidelines for the clinical management of severe influenza virus infections
  - Very clear focus on ‘evidence-based approach’ relying primarily on RCTs

- There a numerous challenges of assessing antivirals in severely ill patients, some which stem from the position that oseltamivir is the SOC but there have been no trials to demonstrate it’s effectiveness in this group of patients

- In 2017, WHO recommended that oseltamivir be moved from core list of ‘essential medicines’ to complementary list, and its use be restricted to severe illness in critically ill hospitalized patients



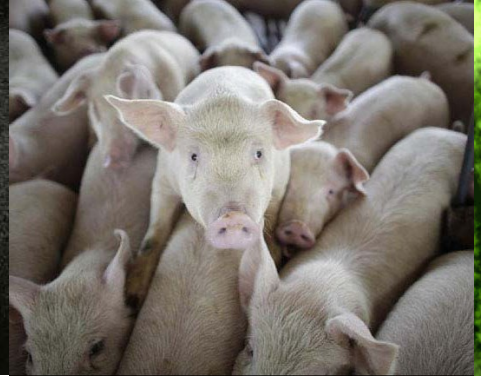
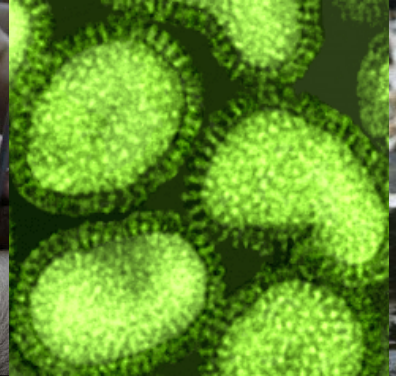
Summary

- The EML Committee noted that *"compared to when oseltamivir was first included on the Model List in 2009, there now exists additional evidence of oseltamivir in seasonal and pandemic flu which has reduced the previously estimated magnitude of effect of oseltamivir on relevant clinical outcomes".*

- In some countries this move will reduce the availability to treat severely ill patients, and may remove the availability for patients to access early oseltamivir in an out-patient setting.

- The EML noted the update in clinical guidelines but stated that "*unless new information supporting the use in seasonal and pandemic outbreaks is provided, the next Expert Committee might consider oseltamivir for deletion*".

- Hope that companies developing new antivirals work closely with regulatory agencies to try and overcome some of the challenges that currently exist


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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