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# HOW EFFECTIVE ARE ANTIVIRAL DRUGS AGAINST INFLUENZA?

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# Antivirals Currently Used in Influenza

- Previously, M2-inhibitors (amantadine and rimantadine)
- From 1999, Neuraminidase inhibitors (NIs) including zanamivir (Relenza®), oseltamivir (Tamiflu®)
- Recently, peramivir (Rapiacta®, Peramiflu®, Rapivab®) approved for treatment in Japan, South Korea and US.
- Laninamivir (Inamivir®) approved in Japan for prophylaxis and treatment.

# SUMMARY OF KEY EVIDENCE ON ANTIVIRAL EFFECTIVENESS

# JEFFERSON ET AL. (2014): UPDATED COCHRANE REVIEW

- Meta-analysis of data from 20 Roche sponsored clinical trials (n=8551) conducted for regulatory purposes (pre-pandemic)
- Oseltamivir treatment (compared to placebo)
- Participants: previously healthy adults and children
- Key findings: faster symptom relief (~ 1 day)
- For every 100 adults treated, influenza-related pneumonia (self-reported) was prevented in 1 person
- Limitation: Only pooled study-level risk estimates rather than individual level data; non-standardised data across trials

# Dobson et al. (2015): Independent re-analysis of Roche trials data

- Commissioned by the Multiparty Group for Advice on Science (MUGAS) foundation to address limitations of the Cochrane meta-analysis
- Included all published and unpublished Roche-sponsored randomised placebo-controlled, double blind trials of 75mg twice a day oseltamivir in adults
- Conducted an individual patient data meta-analysis (standardised and pooled individual level data)
- Included data from 9 trials (n= 4328)

# Dobson et al. (2015): Key findings

- Broadly consistent with Cochrane review findings (though more favourable to treatment)
- ~1 day (25.2 hours) faster symptom relief with oseltamivir
- Fewer lower respiratory tract (LRT) complications requiring antibiotics; need to treat 26 people to prevent 1 LRT complication (NNT= 26)
- Increased risk of nausea (1 in 27) and vomiting (1 in 21)
- Fewer hospital admissions (NNT= 90)

# Muthuri et al. (2014): Observational data on hospitalised pandemic influenza patients

- Individual patient data from 78 centres (n= 29,234) standardised and pooled for meta-analysis
- Both oseltamivir and zanamivir studied
- Primary outcome studied: influenza-related mortality
- Sub-group analysis: adult, children, pregnant women, critically ill (ICU patients)

# Muthuri et al. (2014): Key findings in laboratory confirmed A(H1N1)pdm09 patients

Overall findings for the outcome influenza-related mortality (all age groups):

- NI treatment within 2 days of illness onset: ↓52%
- NI treatment at any point following illness onset: ↓18%
- Late treatment (>2 days from illness onset) with NI could benefit critically ill patients: ↓35%

Findings suggest some patient groups experience greater benefit:

- Adults (≥16 years), pregnant women and critically ill adult patients
- No significant reduction in mortality observed in children

# What does the combined evidence tell us about NI Antiviral effectiveness?

- Reduction in time to symptom alleviation, fewer influenza-related complications requiring antibiotics and hospital admissions in healthy patients with mild/moderate influenza
- Reduction in mortality in more severe influenza illness cases
- Optimal benefit with early treatment (≤2 days of illness onset)
- Some indication that treatment administered >2 days following symptom onset may confer mortality reduction benefits in critically ill patients.
- Good safety profile

# POLICY IMPLICATIONS- CLINICAL GUIDELINES 1

Pragmatic approach based on presented evidence and resource considerations:

Mild influenza cases can be managed in primary care without viral diagnostics with early NI treatment of influenza-like illness emphasised for high-risk patients and other patients who are markedly unwell or obviously deteriorating.

Use rapid influenza diagnostic tests (RIDTs) if available.

# POLICY IMPLICATIONS- CLINICAL GUIDELINES 2

In hospitalised patients with more severe influenza, who may already be several days into the illness, NI treatment should be presumptive, based on clinical suspicion of influenza (or RIDT results); and immediate, with the emphasis on early treatment.

Treat alongside antibiotic treatment if bacterial aetiology cannot be firmly excluded as bacterial pneumonia is a frequent complication in patients hospitalised with influenza.

If virology tests subsequently fail to confirm influenza, stop NIs.

# POLICY IMPLICATIONS- CLINICAL GUIDELINES 3

- Should we stop prescribing NI antivirals in children?

Wider debate needed; watch for evidence updates and use clinical judgement for now.

- Which NI should be preferred?

Evidence presented primarily relates to oseltamivir- use clinical judgement and consider ease of administration & resistance

# POLICY IMPLICATIONS- ANTIVIRAL STOCKPILES-1

- Was the previous decision to stockpile the right one?

Muthuri et al. (2014) study suggests 'yes' based on estimated mortality reduction alone

- Should we stockpile NAI antivirals in the future?

Stockpiling decisions are multifaceted; effectiveness evidence alone not sufficient- use as part of decision matrix

# POLICY IMPLICATIONS- ANTIVIRAL STOCKPILES-2

- Which antivirals should be stockpiled?

Evidence presented more generalisable to oseltamivir but mixed stockpile sensible; for future decisions consider all available options, resistance, ease of administration, safety profile, storage, economics

# KEY POLICY ACTORS

- Organisations with a public health policy remit at all levels (international, regional, national): WHO, CDC, ECDC, PHE etc.
- Politicians and civil servants with remit for health
- Clinicians (general practitioners in the community, chest physicians in hospitals, paediatric infectious disease specialists etc.)
- Virologists, public health specialists
- Pharmaceutical industry
- Media
- Public

# CHALLENGES FOR POLICY IMPLEMENTATION

- Controversy surrounding NIs driven by biased reporting in media
- RCT vs. real-world data debate
- Addressing public and clinician misconceptions
- Bridging evidence gaps: NIs in children, interactions with other medication, non-standard dose considerations, prophylaxis
- Dealing with resistance to NI antivirals
- Promoting early administration of NIs
- Resource considerations

# TRANSPARENCY DECLARATION

- PM has co-authored the Muthuri et al. (2014) study which was supported by an unrestricted educational grant from F. Hoffman La Roche.
- PM was a MUGAS Review Board member that reviewed the oseltamivir data (both from randomised controlled trials and observational studies including data from the 2009/10 pandemic) and agreed on evidence gaps and a statistical analysis plan that would address these gaps.

# Bibliography

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