Safety and Pandemic Preparedness

Medicines and associated regulatory issues in the pandemic context

Dr Philip Bryan
Pharmacovigilance Assessor, VRMM
ICDRA, 16 September 2008
BACKGROUND

• Previous influenza pandemics have had a major impact on society

• Three in last century
  - 1918/19 (Spanish Flu – H1N1)
    - ~40m deaths
  - 1957 (Asian flu – H2N2)
  - 1968 (Hong Kong flu – H3N2)

• Current seasonal flu strains – H3N2 and H1N1 (previous pandemic strains) – up to ½ million deaths per year

• Impossible to predict strain, timing, or impact of next pandemic - can only model range of scenarios
MODELLING THE IMPACT

- Mathematical modelling informs strategic and operational planning for a future pandemic
  - Based on assumptions and data from previous epidemics/pandemics
- Range of scenarios on permutations of case fatality and clinical attack rates
  - e.g. UK modelling

<table>
<thead>
<tr>
<th>Overall case fatality rate (%)</th>
<th>Clinical attack rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>25</td>
</tr>
<tr>
<td>0.4</td>
<td>55,500</td>
</tr>
<tr>
<td>1.0</td>
<td>150,000</td>
</tr>
<tr>
<td>1.5</td>
<td>225,000</td>
</tr>
<tr>
<td>2.5</td>
<td>375,000</td>
</tr>
</tbody>
</table>

c.f. the usual seasonal range of clinical attack at 5% to 15% and ~12,000 deaths
MODELLING THE IMPACT

- Total cases could occur over one or more waves, weeks or months apart

- Local/regional time course could be shorter with greater peak

Figure 1: Single wave national profile showing proportion of new clinical cases by week.
WORST CASE SCENARIO?

• Need to plan for reasonable worst case to maximise flexibility in response
  
  • Up to 50% of population with clinical symptoms (over one or more waves)
  
  • Up to 25% with flu complications
  
  • Up to 4% hospitalised (for 6 to 10 days)
  
  • Up to 2.5% of those who become symptomatic may die
  
  • Up to 22% of cases expected during ‘peak weeks’ of a pandemic wave
KEY COUNTERMEASURES

• Effective countermeasures essential to mitigate impact

• Infection control

• Social and travel

• Clinical
  - Pre-pandemic influenza immunisation (e.g. H5N1)?
  - Pandemic-specific influenza vaccine – timing?
  - Antibiotics
  - Antivirals

→ Regulators have critical role in delivery of the clinical response to the national outbreak
REGULATORY ROLE

• Key role – to ensure there are no regulatory barriers to supply of medicines/vaccines, whilst ensuring they are used safely

  · Must also maintain other critical business

- Requires effective pre-pandemic planning and robust pandemic business continuity plan

- Support licensure of key pharmaceuticals
  · e.g. EMEA’s ‘mock-up’ and pre-pandemic vaccines

- Rapid licence variation, storage, distribution, imports and unlicensed supply

- Pharmacovigilance planning for key pharmaceuticals

- Monitoring counterfeits in supply chain
SPECIFIC CHALLENGES

• Normal healthcare systems overwhelmed
• Delivery of healthcare under extreme and unusual conditions
• Supply and administration of medicines/vaccines via novel mechanisms
• Medicines/vaccines (some novel) supplied to mass populations, and new risk groups
• Need for unlicensed medicines - e.g. oseltamivir to those aged less than 1 year

→ Safety in use is paramount
SAFETY OF MEDICINES

• Key issues in pandemic
  - May be used off-label (e.g. dosage, duration, warnings)
  - Longer-term prescriptions needed
  - Doctors will have little time to monitor patients
  - Non-physicians will need to supply + or - prescription
    · Telephone ‘prescription’ (triage) may be required
  - Others may need to take responsibility to monitor and report adverse reactions
SUPPLY OF MEDICINES

• Normal restrictions on supply of medicines may not be feasible during pandemic
  · may hinder delivery of healthcare

- For critical POMs, insufficient prescribers available

- Usual outlets may be closed (e.g. pharmacies)
  · Need for other collection/distribution points

- Relaxed requirements for imports/unlicensed manufacture?

• May require review of national legislation before pandemic
UK PLAN FOR AV SUPPLY

• National antiviral stockpile – plan for 30m courses
oseltamivir

  - Treatment only
  - Requires treatment within 48 hours (aim for 12-24 hrs)
  - National telephone line

    • Cases confirmed via clinical algorithm – no prescription
    • Unique reference number assigned
    • ‘FluFriend’ will pick-up antivirals
    • Designated local collection point

• Those with complications may need to see physician
  - ?Need for supply of other key medicines via similar
    mechanism to minimise complications
PAEDIATRIC ANTIVIRALS

• Oseltamivir unlicensed under 1 year of age

• This group will need to see physician
  • Individual assessment

• Capsules may not be palatable in other young children
  • Licensed oseltamivir solution (shorter shelf life)
  • API suspension
  • Dissolution of capsule contents - by parents?

• Dosage – expert advice required to support use in under 1s

• Need to ensure no barriers to extemporaneous preparations
  (not just antivirals)
OSELTAMIVIR SAFETY

• Majority of worldwide use mainly limited to Japan

• New safety concerns emerging
  · Neuropsychiatric, hepatic

• Mass stockpiling - unprecedented level of use during pandemic

• New patient populations and risk groups exposed
  · New risks will emerge during pandemic

• Pharmacovigilance planning must meet the challenges of a pandemic, especially due to mechanisms of AV delivery
NEUROPSYCHIATRIC ADRS

- In 2005, 2 fatal incidents in Japanese teenagers following use of oseltamivir
- Review of data – labelling updates (precautionary)
- Now, >1000 cases, mostly Japan, mainly in adolescents
  - wide range of symptoms (delirium, panic, confusion, disorientation, hallucination, suicide)
- In 2007, Japanese Health Ministry restricted use in adolescents
- Causality not established - could be manifestation of flu-related illness
- Risk (if real) may not be limited to adolescents
  - Artefact of disproportionate exposure/flu rates?
- Also cases with zanamavir – stimulated reporting?
NEUROPSYCHIATRIC ADRS

• Pandemic issues

  - Background rates of illness much higher

  - Regardless of causality
    • mass exposure and higher rates of flu will lead to increased reporting of such events
    • societal impact of pandemic may increase psychiatric event reporting

  - Even more difficult to assess causality

  - Robust assessment necessary to confirm risk or give reassurance to support delivery of the antiviral strategy
    • Ideally before the pandemic
SAFETY MONITORING

• Real-time surveillance essential

• Passive ADR reporting may be only source of safety data during pandemic

• Active surveillance/studies – resource intensive
  - But, scope for active follow-up in early pandemic?

• Disruption to postal services
  - Backlogs, loss of data
  - Need to discourage postal reporting?

• Establish on-line ADR reporting
  - More rapid signal generation
SAFETY MONITORING - AVs

- Patients could be main ADR reporters
  - Need mechanism for follow-up and clinical confirmation

- Antiviral ADRs may overwhelm reporting systems – need to preserve surveillance of all other products
  - Separate reporting system for antivirals?

- Discourage reporting of recognised and non-serious ADRs?

- Tie-in with national antiviral distribution scheme
  - Communications at collection/distribution points

- MAH’s should also develop specific and robust plans to overcome challenges
BUSINESS CONTINUITY

• Surveillance must be maintained in face of staff shortages

• Up to 50% of workforce absent for 6 to 10 days each during whole pandemic (one or more waves)

• Absences rates (due to illness) could reach 15-20% in peak weeks
  • Additional staff absences likely for other reasons

• Small organisational units/teams within larger organisational units likely to suffer higher percentages of staff absences – up to 30–35% over a 2-3 week period at the local peak.
CONCLUSIONS

• Pandemic will present unique and unprecedented challenges for medicines safety evaluation

• Pandemic will be (relatively) short-lived – surveillance must be real-time

• Tailored pharmacovigilance plans to take account of:
  - national plans for delivery of healthcare
  - likely constraints on infrastructure (e.g. post, IT)
  - severe staff shortages and reduced and/or different ADR reporter base
  - new and vulnerable patient populations

• Where possible, should evaluate new, uncertain risks in pre-pandemic period