Clinical concerns and pathogenesis

Wei Shen Lim
Respiratory Medicine
Nottingham University Hospitals NHS Trust
weishen.lim@nuh.nhs.uk
Importance of research

Formulate **clinical management strategies**

- who is at risk of infection/severe disease?
- which risks can be modified?

- what level of care?
- what treatment options?
- what infection control measures?
Who is at risk? Why?

2009: FLU-CIN, SWIFT, MOSAIC

Global pooled studies:
All ages (n=70,000) H1N1 \textit{van Kerkhove}, 2011
All ages (n=610,782) Pandemic + seasonal \textit{Mertz}, 2013

Host factors: obesity, pregnancy, asthma....
Host immune responses: IFITM3...

Role of bacterial infections? Exposure, colonisation
Modifiable risk factors?
Current clinical management

• Rest, fluids, oxygen
• Antipyretics
• Antibiotics
• Antivirals

• Respiratory support: CPAP, NIV, ECMO

• Infection Control measures
Clinical Trial Evidence

- Rest, fluids, oxygen: NO
- Antipyretics: NO
- Antibiotics: NO
- Antivirals: YES/NO
- CPAP, NIV, ECMO: NO/NO/NO
- Infection Control measures: EMIT
Immunomodulatory agents

<table>
<thead>
<tr>
<th>Benefit</th>
<th>Harm</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>+</td>
<td>meta-analysis</td>
</tr>
<tr>
<td>?</td>
<td>case study</td>
</tr>
<tr>
<td>?</td>
<td>case study</td>
</tr>
<tr>
<td>?</td>
<td>(RCTs in progress: sepsis)</td>
</tr>
<tr>
<td>?</td>
<td>(already in use)</td>
</tr>
<tr>
<td>?</td>
<td>animal</td>
</tr>
<tr>
<td>?</td>
<td>animal</td>
</tr>
</tbody>
</table>

- Corticosteroids
- Convalescent plasma
- IVIG
- N-acetylcysteine
- Statins
- Macrolides
- PPAR agonists
- Metformin
NIHR pandemic portfolio (8 studies)

Cohort studies:
- Health survey: Population susceptibility, severity, spread (PIPS)
- Primary care: Evaluation of community assessment tools (FLU-CATs)
- Hospital: Triage in the Emergency Department (PAINTED)
- Hospital: Maternal and perinatal outcomes of flu in pregnancy

Clinical trial:
- Hospital: Adjuvant steroids in adults with pandemic flu (ASAP)
Other UK (international) studies

Mechanistic studies:

Hospital ISARIC-WHO SARI Biological Sampling Protocol
Hospital MRC FLU003

→ mechanistic understanding of disease processes
Pandemic clinical research

Pre-pandemic set-up ✓
Approvals process ✓

Delivery of research during a pandemic:
Integration with clinical pandemic plans □
Prioritisation of resources □
Co-enrolment □
Patient consent □
Gaps to consider

Who is at risk? Modifiable risks?
• Host susceptibility & risk factors
• Host-viral interactions; viral-bacterial interactions

What level of care? When to step down?
• Hospital based study, including ICU (FLU-CIN, SWIFT)

What treatment options?
• Clinical trials of interventions
• Immunomodulatory agents
• Antibacterial strategies; biomarkers

Providing the evidence base
• Delivery of pandemic research

BRaVe Initiative - Future Virol 2013;8: 953 - 968