2009 Legacy gaps
Virology & Diagnostics

• Operational response .......... Flexibility for containment, rapid verification of community spread
• Interventions ........ clinical networks
• Severity Assessment ... Improve targeting of Rx, prognosis & use of health resources
• Immunity vs Exposure ... Correlates Protection/ Ab repertoire
• Vaccines .......... use of adjuvanted vaccines
• Swine surveillance ........ more systematic
# Influenza Antiviral Therapy: unmet medical needs

<table>
<thead>
<tr>
<th>Population</th>
<th>Treatment Options</th>
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<tbody>
<tr>
<td>Healthy adult</td>
<td>Severe illness: IV therapy</td>
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<td></td>
<td>Combination therapy</td>
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<td>Children</td>
<td>Single dose oral</td>
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<tr>
<td></td>
<td>Reduce transmission</td>
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<tr>
<td>H5</td>
<td>IV therapy, good systemic availability</td>
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<td></td>
<td>Reduce viral load (dual target)</td>
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<td>Adjunct therapy, immune modulators</td>
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<td>Immunocompromised</td>
<td>Damp replication, adjunct therapy to reconstitute</td>
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<td>N1 viruses</td>
<td>Drug design for group 1 NAs</td>
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<td>Kinetics /antagonism</td>
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ICU Admissions with Influenza  Critical Care

- In week 13, 26 new admissions to ICU/HDU with confirmed influenza infection (15 A unknown subtype, six A(H3N2), four A(H1N1)pdm09 and one B) were reported across the UK (120/163 Trusts in England) through the USISS mandatory ICU scheme (Figures 12 and 13). A total of 820 admissions (286 B, 245 A unknown subtype, 145 A(H3N2) and 144 A(H1N1)pdm09) have been reported since week 40 2012. Seven new confirmed influenza deaths were reported in week 13 2013. Ninety-nine confirmed influenza deaths (33 A(H3N2), 31 B, 22 A(H1N1)pdm09 and 13 A unknown subtype) have been reported across the UK in ICU/HDU since week 40 (Figure 12).

Figure 12: Weekly ICU influenza admissions and deaths (USISS mandatory) by week of admission/death, UK, since week 40 2012

Figure 13: Cumulative ICU influenza admissions (USISS mandatory) by age group and flu type, UK, since week 40 2012

1113 admissions (median age 46) and 134 Deaths for 163 UK Trusts
Antiviral R&D agenda

• Improve development pipeline...Multiple viral targets
• Combination therapy
• Host immune modulation
• Emergence of resistance in different subtype
• Fitness models
• Regular analysis of outcomes
“Our major concern about the current response to H1N1 has been the dearth of any systematic, prospective, patient-oriented clinical research.”

See Comment page 2085
Response Actions for Next Threat

- Identify potential knowledge gaps and research questions
- Develop and pre-approve generic study protocols
- Use pre-funded research networks and pre-awarded, just-in-time research contracts
- Develop an on-call “ready reserve” of clinicians, scientists, and other experts

Research as a Part of Public Health Emergency Response
Nicole Lurie, M.D., M.S.P.H., Teri Manolio, M.D., Ph.D., Amy P. Patterson, M.D., Francis Collins, M.D., Ph.D., and Thomas Frieden, M.D., M.P.H.

Lurie et al., NEJM 368:1251, 2013
Different age profile of H7N9 and H5N1 infections in China

H5N1: Arima Y et al, 2013,
H7N9: PHE data
Assessment of Severity
Genetic Susceptibility to Infection

LETTER

doi:10.1038/nature10921

IFITM3 restricts the morbidity and mortality associated with influenza

Aaron R. Everitt\textsuperscript{1}, Simon Clare\textsuperscript{1}, Thomas Pertel\textsuperscript{2}, Simu F. John\textsuperscript{2}, Rachael S. Wash\textsuperscript{3}, Sarah E. Smith\textsuperscript{1}, Christopher R. Chin\textsuperscript{2}, Eric M. Feeley\textsuperscript{4}, Jennifer S. Sims\textsuperscript{4}, David J. Adams\textsuperscript{4}, Helen M. Wise\textsuperscript{5}, Leanne Kane\textsuperscript{4}, David Goulding\textsuperscript{4}, Paul Digard\textsuperscript{4}, Verner Anttila\textsuperscript{1}, J. Kenneth Baillie\textsuperscript{4,5}, Tim S. Walsh\textsuperscript{6}, David A. Hume\textsuperscript{6}, Aarno Palotie\textsuperscript{7}, Yali Xue\textsuperscript{8}, Vincenza Colonna\textsuperscript{8,9}, Chris Tyler-Smith\textsuperscript{1}, Jake Dunning\textsuperscript{1}, Stephen B. Gordon\textsuperscript{1}, The GenISIS Investigators\textsuperscript{*}, The MOSAIC Investigators\textsuperscript{*}, Rosalind L. Smyth\textsuperscript{9}, Peter J. Openshaw\textsuperscript{9}, Gordon Dougan\textsuperscript{9}, Abraham L. Brass\textsuperscript{9,10} & Paul Kellam\textsuperscript{1,10}

Preexisting CD\textsuperscript{8+} T-cell immunity to the H7N9 influenza A virus varies across ethnicities

Sergio Quiñones-Parra\textsuperscript{a}, Emma Grant\textsuperscript{a}, Liyen Loh\textsuperscript{a}, Thi H. O. Nguyen\textsuperscript{a,b}, Kristy-Anne Campbell\textsuperscript{c}, Steven Y. C. Tong\textsuperscript{d}, Adrian Miller\textsuperscript{e}, Peter C. Doherty\textsuperscript{a,f,1}, Dhanasekaran Vijaykrishna\textsuperscript{g}, Jamie Rossjohn\textsuperscript{c,h}, Stephanie Gras\textsuperscript{c}, and Katherine Kedzierska\textsuperscript{a,1}

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Severity  R&D agenda

• Clinical Outcomes analysis..Age stratified clinical studies ............BIOBANKS
• Critical Care/ECMO....value, prognosis, residual deficit
• Early infection biomarkers.....proteomics ?,
• Host genetics........GWAS, restriction factors
• Magnitude & duration virus shedding
• Tissue injury analysis...biomarkers
• Age related pathogenesis
Serological response to pandemic H1N1 adjuvanted vaccine

Emerging Immunomodulatory therapy

Convalescent blood products
Human monoclonal antibodies
Anti-inflammatory agents
Immunotherapy R & D agenda

- In vitro characterisation Human MAbs
- Proof of principle in vitro studies Human Mabs
- Cross neutralising vs Head Abs
- Phase 1 clinical studies
- Combination therapies
Diagnostics R & D agenda

• Non invasive sampling methodologies
• Early infection biomarkers
• Improve sensitivity of POC testing
• Better serology for seroepidemiology
• Analysis of Ab repertoire post infection vs post vaccine