Global disease burden and high risk populations: who should receive influenza vaccination?

Global Action Plan for Influenza Vaccines Consultation
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Centre for Population Health Sciences,
The University of Edinburgh
&
Public Health Foundation of India
Natural history of influenza infection in children

- Influenza infection
  - Influenza like illness
    - Remission
    - Secondary Bacterial Infection
      - Severe ALRI
        - Death
    - AURI
      - Acute otitis media
      - GB Syndrome/Seizures/Myositis/Myocarditis
Natural history of influenza infection in children
Methods for <5 yr child burden estimates

Incidence rates and number of new cases of influenza associated respiratory infections in young children (0-59 months & 0-11 months)

Incidence rates of influenza associated severe ALRI in infants (0-5 months vs 6-11 months)

Mortality estimates in children

Influenza burden in older children and adults

Implications for influenza immunization in young children
1625 records after duplicates removed

120 full-text articles assessed for eligibility

27 full-text articles reported incidence

12 full-text articles reported CFR

1505 records excluded as not relevant to topic

88 full-text articles excluded. Reason: 49 did not satisfy inclusion criteria; 4 reported prevalence; 35 relate to 2009(H1N1A) pandemic

4058 records identified through database searching

13 records identified through other sources

Literature Review

Nair et al., Lancet (in press)
Influenza Study Group

- Harish Nair, Harry Campbell, Igor Rudan, V Evans, Evi Theodoratou - CPHS, Edinburgh
- Thailand- Mark Simmerman, Sonja Olsen
- Bangladesh- Abdulllah Brooks
- Japan- Peter Wright, Masatoki Sato
- Philippines- Eric Simoes, Marilla Lucero
- India- Anand Krishnan, Shobha Broor
- Cambodia- Sirenda Vong, Philippe Buchy
- Kenya- Mark Katz, Maurice Ope, James Berkley, R Breiman, Walter Ochieng
- Gambia- Steve Howie, T Briese, R Tokarz
- S Africa- Shabir Madhi, Cheryl Cohen, M Venter
- Mozambique- Anna Roca, C O’Callaghan-Gordo
- Egypt- Erica Dueger
- Nicaragua- Aubree Gordon, Eva Harris
- Guatemala- Kim Lindblade
- USA- Eric Simoes, Laurie Kamimoto
- American Indians - Niranjan Bhat
- Marc-Alain Widdowson- CDC
- Brad Gessner- AMP
- Anthony Wayne Mounts- World Health Organization, Geneva
1625 records after duplicates removed

1625 records screened

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1505 records excluded as not relevant to topic

43 studies reported incidence (included in meta-analysis)

16 population based unpublished studies identified for supplementary data

Nair et al., Lancet (in press)
Location of published and unpublished studies (n=43)

Nair et al., Lancet (in press)
Methods

• Systematic review of studies published from 1995 to October 2010 – 27 studies

• Influenza Study Group – contributed unpublished data from 16 sites

• Common case definitions

• Adjustment for missing data

• Meta-analysis using random effects model

• Incidence applied to 0-4 year population in 2008 to estimate number of new episodes in 2008
Case definitions

• Influenza-associated acute lower respiratory infection (ALRI) -
  Influenza positive child with cough or difficulty breathing AND tachypnea
• **Influenza-associated severe acute lower respiratory infection (ALRI)** – Influenza positive child with a) cough or difficulty breathing AND lower chest wall indrawing OR b) hospitalization for ALRI
Influenza episodes - reflects overall burden of respiratory infections associated with influenza i.e. Influenza positive ILI + Influenza-associated ALRI + Influenza-associated severe ALRI
Influenza incidence in children 0-59 months per 1000 children / yr

<table>
<thead>
<tr>
<th></th>
<th>Influenza episodes</th>
<th>Influenza-associated ALRI</th>
<th>Influenza-associated severe ALRI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Developing countries</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of studies</td>
<td>3</td>
<td>3</td>
<td>19</td>
</tr>
<tr>
<td>Incidence (95% CI)</td>
<td>154 (84.2, 275)</td>
<td>35 (22.2, 55)</td>
<td>1.7 (1.1, 2.5)</td>
</tr>
<tr>
<td><strong>Industrialised countries</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of studies</td>
<td>6</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Incidence (95% CI)</td>
<td>54.5 (28.1, 105.7)</td>
<td>11.6 (7.5, 18)</td>
<td>1.2 (0.9, 1.7)</td>
</tr>
</tbody>
</table>

Nair et al., Lancet (in press) PLEASE DO NOT CITE OR QUOTE
### Cases of Influenza associated respiratory infections 0-59 months in 2008

<table>
<thead>
<tr>
<th>Country Type</th>
<th>Influenza episodes (95% CI) millions</th>
<th>Influenza-associated ALRI (95% CI) millions</th>
<th>Influenza-associated severe ALRI (95% CI) millions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Developing countries</strong></td>
<td>87 (48, 156)</td>
<td>20 (13, 31)</td>
<td>0.9 (0.6, 1.4)</td>
</tr>
<tr>
<td><strong>Industrialised countries</strong></td>
<td>3.1 (1.6, 5.9)</td>
<td>0.7 (0.4, 1.0)</td>
<td>.07 (.05, .09)</td>
</tr>
<tr>
<td><strong>Global</strong></td>
<td>90 (49, 162)</td>
<td>20.5 (13, 32)</td>
<td>1.0 (0.7, 1.5)</td>
</tr>
</tbody>
</table>

Nair et al., Lancet (in press) PLEASE DO NOT CITE OR QUOTE
# Influenza associated severe ALRI in children <5 y: estimates by WHO regions

<table>
<thead>
<tr>
<th>WHO Region (number of studies)</th>
<th>Incidence per 1000 children / year (95% CI)</th>
<th>Number of new episodes (95% CI) thousands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Americas (15)</td>
<td>1.2 (0.8, 1.8)</td>
<td>94 (63, 140)</td>
</tr>
<tr>
<td>Western Pacific (7)</td>
<td>2.1 (0.9, 5.1)</td>
<td>255 (105, 620)</td>
</tr>
<tr>
<td>Europe (6)</td>
<td>1.1 (0.7, 1.6)</td>
<td>55 (37, 82)</td>
</tr>
<tr>
<td>SE Asia (4)</td>
<td>1.4 (0.4, 5.6)</td>
<td>257 (65, 1020)</td>
</tr>
<tr>
<td>Africa (7)</td>
<td>1.4 (0.7, 2.5)</td>
<td>180 (97, 332)</td>
</tr>
<tr>
<td>Global estimate</td>
<td></td>
<td>1001 (665, 1503)</td>
</tr>
</tbody>
</table>

Nair et al., Lancet (in press) PLEASE DO NOT CITE OR QUOTE
### Influenza in children 0-11 months per 1000 children / yr

<table>
<thead>
<tr>
<th></th>
<th>Influenza episodes</th>
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<th>Influenza-associated severe ALRI</th>
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<tr>
<td>No. of studies</td>
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<td>3</td>
<td>19</td>
</tr>
<tr>
<td>Incidence (95% CI)</td>
<td>119.5 (76.5, 186.6)</td>
<td>22.6 (8.9, 57.2)</td>
<td>2.8 (1.9, 4.1)</td>
</tr>
<tr>
<td>Industrialised countries</td>
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</tr>
<tr>
<td>No. of studies</td>
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<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Incidence (95% CI)</td>
<td>52.4 (27.9, 98.3)</td>
<td>14.7 (13.8, 15.7)</td>
<td>2.3 (1.8, 3.0)</td>
</tr>
</tbody>
</table>

Nair et al., Lancet (in press) **PLEASE DO NOT CITE OR QUOTE**
### Cases of Influenza associated respiratory infections 0-11 months in 2008

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<tr>
<td>14.6 (9.4, 22.8)</td>
<td>2.7 (1.1, 7)</td>
<td>0.3 (0.2, 0.5)</td>
</tr>
<tr>
<td>Industrialised countries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.6 (0.3, 1.1)</td>
<td>0.2 (0.2, 0.2)</td>
<td>0.03 (.02, .03)</td>
</tr>
<tr>
<td>Global</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15.2 (9.7, 23.9)</td>
<td>2.9 (1.2, 7.2)</td>
<td>0.4 (0.3, 0.5)</td>
</tr>
</tbody>
</table>

Nair et al., Lancet (in press) PLEASE DO NOT CITE OR QUOTE
Influenza in children: mortality estimation

- 12 full text articles reported CFR data on influenza positive children hospitalised for severe ALRI
- Additionally 8 unpublished studies provided CFR data on influenza positive children with severe ALRI

- Meta-estimates of CFR (9 studies) in developing countries in children 0-59 months – 2.96% (0.79, 5.13)
- Meta-estimates of CFR (8 studies) in industrialised countries in children 0-59 months – 0.17% (0.08, 0.26)
Influenza in children: lower bound mortality estimate

Using number of new episodes of influenza severe ALRI and CFR meta-estimates, lower bounds of mortality attributable to influenza in children in year 2008-~28,000 (95% CI-7400 to 48,000) deaths in <5 year children

True mortality higher-54% to 90% of ALRI deaths in children occur outside a health facility


Please do not cite or quote
Influenza in children: upper bound mortality estimate

• Similar to methods used for RSV (Nair et al., Lancet, 2010)
• Using data from VA confirmed ALRI deaths in community by month in a site with clear seasonal influenza peak-excess ALRI mortality during influenza season attributed to influenza
• Such data available from Ballabgarh, India (2006-08)
• Based on these data upper bound of estimated global mortality due to influenza-associated ALRI in <5y children ~ 111,000 (range 21,000 to 245,000)
• Over-estimate
  ✓ attributing all excess deaths during influenza season to influenza
  ✓ shared seasonality with other respiratory pathogens (RSV)
Influenza burden in older children and adults

- Systematic review (Aug 2010, being updated)
  - children aged 5-17 years and adults (>18 years)
  - lab confirmed influenza associated respiratory infections & clear population denominator

- Only 9 studies identified (of these 8 report age group specific incidence)
  - report incidence of hospitalised influenza-associated ALRI

- All from middle and high income settings

- Based on these data global burden estimates not possible
<table>
<thead>
<tr>
<th>Study</th>
<th>0-4 y</th>
<th>5-17 y</th>
<th>18-49 y</th>
<th>50-64 y</th>
<th>65-79 y</th>
<th>80+ y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dawood (2010), USA</td>
<td>0.35</td>
<td>0.05</td>
<td></td>
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<td></td>
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<tr>
<td>Ampofo (2006), USA</td>
<td>0.87</td>
<td>0.06</td>
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<td>Coffin (2007), USA</td>
<td>2.09</td>
<td>0.19</td>
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<td>Chiu (2009), Hong Kong</td>
<td>7.24</td>
<td>0.75</td>
<td></td>
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</tr>
<tr>
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<tr>
<td>Weigl (2002), Germany</td>
<td>1.23</td>
<td>0.3</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Proff (2009), USA</td>
<td>0.8</td>
<td>0.07</td>
<td>0.05</td>
<td>0.13</td>
<td>0.4</td>
<td>1.47</td>
</tr>
<tr>
<td>Olsen (2010), Thailand</td>
<td>5.28</td>
<td>0.04</td>
<td>0.04</td>
<td>0.39</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>0.7</td>
</tr>
</tbody>
</table>
Influenza burden estimation: modelling techniques

• Alternative technique- **modelling for excess pneumonia & influenza (P&I) hospitalisations**
  - rate difference or Poisson regression model
  - High income settings
  - Estimates- 110 to 424 per 100,000 in >65 years

• **Limitations** for developing countries- require
  - clear demarcation of influenza season- difficult in tropics
  - robust virological surveillance
  - P&I hospitalization data- don’t exist and/ or not reliably coded
Influenza immunization in young children: implications

• High disease burden in young children

• 0-11 months-
  ➢ 2.9 (95% CI - 1.2, 7.2) million cases of influenza associated ALRI
  ➢ 0.4 (95% CI - 0.3, 0.5) million cases of influenza associated severe ALRI
Influenza immunization in young children: implications

• High disease burden in young children

• 0-11 months-
  - 2.9 (95% CI - 1.2, 7.2) million cases of influenza associated ALRI
  - 0.4 (95% CI - 0.3, 0.5) million cases of influenza associated severe ALRI
Influenza immunization in young children: implications

- 0-59 months-
  - 20.5 (95% CI - 13, 32) million cases of influenza associated ALRI (13% paediatric ALRI)
  - 1 (95% CI - 0.7, 1.5) million cases of influenza associated severe ALRI (7% paediatric ALRI)

- Estimated mortality attributable to influenza-associated ALRI in children <5 yrs - 28,000 to 111,000 – 2 to 7% of paediatric ALRI deaths

- These estimates do not consider bacterial co-infection – increased burden

- As pneumococcal and Hib immunization included in EPI in developing countries, proportion of viral ALRI likely to rise
Conclusions

• High influenza disease burden in <5 children

• Data are scarce to make burden estimates in older children and adults

• More studies / epidemiological data required

• Need to use influenza surveillance data to contribute to burden estimation

• Universal immunization of children < 5y with influenza vaccine likely to have a high impact on influenza disease burden
Acknowledgements

• Prof. Harry Campbell
• Influenza Study Group