Maternal influenza immunisation

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Global causes of death in children <5 in 2010

Global Trends in Burden of Childhood Deaths in 2000–2010

Major causes of death in children under age five

1. Diarrhea 11%
2. Neonatal causes 40%
3. Pneumonia 14%
4. Other 18%
5. Malaria 7%
6. Injury 5%
7. Meningitis 2%
8. AIDS 2%
9. Measles 1%

Number of deaths (millions)

Year

Public health importance of influenza

• Annually globally seasonal influenza
  – 1 billion infections
  – 3-5 million cases of severe disease
  – 300,000-500,000 deaths
  – Absenteeism etc.

• In South Africa, annually
  – 17,000-22,000 respiratory hospitalisations
  – 2500-5700 respiratory deaths

• Potential for global pandemics

• Pandemic vaccine supply linked to seasonal usage

Tempia et al CID 2014, Kyelagire BMC ID 2015
WHO SAGE Influenza Vaccine Working Group

- In April 2012, WHO’s SAGE approved new recommendations for use of influenza vaccines in member countries
- Update to 2005 WHO recommendations
  - Focused on elderly and persons with underlying high risk conditions e.g. heart and lung disease
  - Acknowledged other possible risk groups
  - Highlighted lack of data on need and vaccine performance in many parts of the world

In countries using or considering introducing seasonal influenza vaccination

- Pregnant women
- Health care workers
- Young children
- Elderly persons
- Persons with high risk conditions
Impact of seasonal influenza on pregnant women

• Pregnant women have a higher risk of influenza-associated hospitalization that non-pregnant women
  – Risk of hospitalization increases by trimester
  • Women in 3rd trimester w/o other risk factors had 10.5 influenza-attributable hospitalizations per 10,000 women-months; compared with 1.91 and 1.16 per 10,000 women-months in nonpregnant and postpartum, respectively. (Neuzil, K. et al. Am J Epidemiol 1998;148:1094-102)
  – Risk comparable with adults with HR conditions
  – Pregnant women with other risk factors had even higher risk of admission (Neuzil 1998; Hartert, et al., American J Obstet Gynecol 2003;189:1705-12)

• Excess mortality attributed to influenza observed among pregnant women from 1998-2005 in the US, particularly in the 3rd trimester. (Callaghan, Obstetric Gynecol 2010; 115: 919-23.)
**Interim report on pandemic H1N1 influenza virus infections in South Africa, April to October 2009: Epidemiology and factors associated with fatal cases**

B N Archer (bretta@nicd.ac.za)\(^1,2\), C Cohen\(^1,3\), D Naidoo\(^4\), J Thomas\(^1,3\), C Makunga\(^1\), L Blumberg\(^1,4\), M Venter\(^1,5\), G A Timothy\(^3\), A Puren\(^1,4\), J M McAnerney\(^1\), A Cengimbo\(^1\), B D Schoub\(^1,4\)

**Selected clinical characteristics of pandemic H1N1 influenza-associated deaths, South Africa, 28 April - 12 October 2009 (n=91*)**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Frequency of factor / Number of cases with data available</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection</td>
<td>17 / 32</td>
<td>53</td>
</tr>
<tr>
<td>Pregnancy or puerperium</td>
<td>25 / 88</td>
<td>28</td>
</tr>
<tr>
<td>Obesity</td>
<td>16 / 73</td>
<td>22</td>
</tr>
<tr>
<td>No co-morbidities identified</td>
<td>16 / 76</td>
<td>21</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11 / 72</td>
<td>15</td>
</tr>
<tr>
<td>Cardiac disease†</td>
<td>9 / 71</td>
<td>13</td>
</tr>
<tr>
<td>Active tuberculosis (TB)</td>
<td>7 / 72</td>
<td>10</td>
</tr>
</tbody>
</table>

† Cardiac disease includes: previous stents, mitral stenosis, cardiomyopathy, congestive cardiac failure, previous valvular replacement, recent myocardial infarction, and previous cardiac bypass surgery; excludes hypertension.

* Patients may have had multiple factors.

HIV: human immunodeficiency virus.
### Case-Control Study of Risk Factors for Hospitalization Caused by Pandemic (H1N1) 2009

Ward KA. EID Vo. 17, No.8 Aug. 2011

Table 3. Risk factors for mechanical ventilation because of pandemic (H1N1) 2009 infection, Sydney, Australia, 2009*

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>No. (%) case-patients, n = 37</th>
<th>No. (%) controls, n = 603</th>
<th>OR (95% CI)</th>
<th>p value</th>
<th>Adjusted OR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health condition‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma</td>
<td>13 (65)</td>
<td>93 (15)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No regular medication</td>
<td>5 (14)</td>
<td>48 (8)</td>
<td>2.2 (0.8–6.1)</td>
<td>0.0061</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular medication</td>
<td>8 (22)</td>
<td>45 (7)</td>
<td>3.8 (1.6–8.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart disease§</td>
<td>3 (9)</td>
<td>41 (7)</td>
<td>1.3 (0.4–4.3)</td>
<td>0.7136</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney disease¶</td>
<td>1 (3)</td>
<td>8 (1)</td>
<td>2.1 (0.3–16.9)</td>
<td>0.5013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental health problem</td>
<td>6 (16)</td>
<td>49 (8)</td>
<td>2.2 (0.9–5.5)</td>
<td>0.0958</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic problem</td>
<td>3 (8)</td>
<td>42 (7)</td>
<td>1.2 (0.3–4.0)</td>
<td>0.792</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>1 (3)</td>
<td>22 (4)</td>
<td>0.7 (0.1–5.6)</td>
<td>0.7655</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>2 (5)</td>
<td>23 (4)</td>
<td>1.4 (0.3–6.4)</td>
<td>0.6296</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung disease</td>
<td>6 (16)</td>
<td>31 (5)</td>
<td>3.6 (1.4–9.2)</td>
<td>0.0084</td>
<td>8.6 (2.6–28.5)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Diabetes</td>
<td>5 (14)</td>
<td>38 (6)</td>
<td>2.3 (0.9–6.3)</td>
<td>0.0977</td>
<td>4.4 (1.2–15.6)</td>
<td>0.0383</td>
</tr>
<tr>
<td>Liver disease</td>
<td>2 (5)</td>
<td>20 (3)</td>
<td>1.7 (0.4–7.4)</td>
<td>0.503</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>8 (22)</td>
<td>7 (1)</td>
<td>23.4 (8.0–69.2)</td>
<td>&lt;0.001</td>
<td>40.5 (9.7–168.1)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
Influenza Vaccines in pregnant women

- Used since ~ 1960 in pregnant women
- Excellent safety profile
- Consistently equally immunogenic as in non-pregnant women in small clinical studies
- No clinical effectiveness studies done in women using laboratory-confirmed influenza outcomes
  - Vaccine effectiveness among adults proxy to benefit among pregnant women
Effectiveness of Maternal Influenza Immunization in Mothers and Infants

K. Zaman, M.B., B.S., Ph.D., Eliza Roy, M.B., B.S., D.C.H.,
Shams E. Arifeen, M.B., B.S., Dr.P.H., Mahbubur Rahman, M.B., B.S., Ph.D.,
Rubhana Raqib, Ph.D., Emily Wilson, M.H.S., Saad B. Omer, M.B., B.S., Ph.D.,
Nigar S. Shahid, M.B., B.S., M.P.H., Robert F. Breiman, M.D.,
and Mark C. Steinhoff, M.D.

- Clinical trial
- Maternal pneumo vs influenza vaccine
- VE in infants:
  - 63% lab-confirmed flu
  - 29% resp illness with fever
- VE in mothers:
  - 36% resp illness with fever

Figure 2. Cumulative Cases of Laboratory-Proven Influenza in Infants Whose Mothers Received Influenza Vaccine, as Compared with Control Subjects.
Testing for influenza antigen was performed from December 2004 to November 2005.
Studies suggesting that influenza vaccine reduces adverse birth outcomes
For countries considering the initiation or expansion of programmes for seasonal influenza vaccination, WHO recommends that pregnant women should have the highest priority. Additional risk groups to be considered for vaccination, in no particular order of priority, are children aged 6–59 months, the elderly, individuals with specific chronic medical conditions, and health-care workers. Countries with existing influenza vaccination programmes targeting any of these additional groups should continue to do so and should incorporate immunization of pregnant women into such programmes.
Challenges

• No global recommendation that countries should vaccinate and in what circumstances
• Limited evidence base especially from LMIC
• Many groups not classically targeted for vaccination through EPI
• Strongly influenced by pandemic
• Subsequent critical review
RESEARCH

Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis

Dominik Mertz assistant professor1 2, Tae Hyong Kim researcher3, Jennie Johnstone researcher2, Po-Po Lam researcher4, Michelle Science staff physician1, Stefan P Kuster staff physician4, Shaza A Fadel researcher1, Dat Tran assistant professor2, Eduardo Fernandez researcher2, Neera Bhatnagar librarian1, Mark Loeb professor4

of bias. GRADE framework to evaluate the quality of evidence.

Results 63537 articles were identified of which 234 with a total of 610 782 participants met the inclusion criteria. The evidence supporting risk factors for severe outcomes of influenza ranged from being limited to absent. This was particularly relevant for the relative lack of data for non-2009 H1N1 pandemics and for seasonal influenza studies. Limitations in the published literature included lack of power and lack of adjustment for confounders was widespread: adjusted risk estimates were provided for only 5% of risk factor-outcome comparisons in 39 of 260 (15%) studies. The level of evidence was low for “any risk factor” (odds ratio for mortality 2.77, 95% confidence interval 1.90 to 4.05 for pandemic influenza and 2.04, 1.74 to 2.39 for seasonal influenza), obesity (2.74, 1.56 to 4.80 and 30.1, 1.74 to 2.39), cardiovascular diseases (2.92, 1.76 to 4.86 and 1.97, 1.06 to 3.67), and neuromuscular disease (2.68, 1.91 to 3.75 and 3.21, 1.84 to 5.58). The level of evidence was very low for all other risk factors. Some well accepted risk factors such as pregnancy and belonging to an ethnic minority group could not be identified as risk factors. In contrast, women who were less than four weeks post partum had a significantly increased risk of death from pandemic influenza (4.43, 1.24 to 15.81).

Conclusion The level of evidence to support risk factors for influenza related complications is low and some well accepted risk factors, including pregnancy and ethnicity, could not be confirmed as risks. Rigorous and adequately powered studies are needed.

Introduction

Influenza is a major global cause of illness and death, resulting in an estimated three to five million cases of severe influenza illness and 250 000 to 500 000 deaths annually.1 2 The risk of complications from influenza, including lower respiratory tract infection, admission to hospital, and death vary depending on factors such as age and the type of comorbidity that may be present.1 2 Currently, the World Health Organization and most countries prioritise specific high risk groups for vaccination.2 6 Although some recommendations are consistent, such as vaccination of healthcare workers, pregnant women, and those with certain high risk conditions, there are also discrepancies, such as the age groups that need to be prioritised (table 1)). Despite the widely accepted public health policy of recommending vaccination to groups believed to be at high risk for complications of influenza, a comprehensive and systematic review of the evidence defining these groups is lacking.
Conclusions

- Evidence for increased hospitalisation in pregnant women for H1N1 but not seasonal
- In LMIC higher risk of mortality
- Quality of evidence low
- Few data from LMIC
- Lack of data limits assessment
- BUT does not mean no association

Two studies with Women of Reproductive Age as comparator: OR 3.3 (0.52 to 20)
Three studies limited to LMIC: OR 2.1 (0.49 to 9.0)
Influenza vaccine policy in South Africa
Data need to guide vaccine policy

• Burden of disease (outpatient, hospitalisations and mortality)
• Risk groups for severe outcomes
• Relative prevalence of risk groups
• Intervention effectiveness (in risk groups)
• Cost and cost-effectiveness
• Above from low and middle-income countries
• Impact data where intervention implemented
Incidence of influenza-associated pneumonia hospitalisation by age group, Soweto, South Africa, 2009-2011

Peak incidence in young children

Second peak in young adults
Incidences of influenza and HIV

Daniel R Feikin, Maurice O Ope, Barrack Aura, James A Fuller, Stella Girunju, John Vulule, Zipporah Ng'ang'a, M Kariuki Njenga, Robert F Breiman & Mark Katz

Fig. 2. Age- and gender-specific annual influenza-associated hospital admissions (per 100 000 people), Bondo district, Kenya, June 2007–May 2009

Incidence (per 100 000) of influenza-associated ALRI by HIV infection status, SARI surveillance, South Africa, 2009

HIV-infected individuals have 6 times greater odds of death once hospitalised

Feikin et al. Bull WHO 2012
Options for the control of influenza 2010. Cohen et al.
Mortality Associated with Seasonal and Pandemic Influenza among Pregnant and Non-Pregnant Women of Childbearing Age in a High HIV Prevalence Setting – South Africa, 1999-2009

- Pregnant women **seasonal** influenza-associated mortality compared to non-pregnant women **RR 2.8 95% CI 2.1-3.7**
  - HIV infected **RR 2.9 95% CI 2.1-3.7**
  - HIV-uninfected **RR 2.4 95% CI 2.1-2.7**
- In 2009 **pandemic RR 3.2 95% CI 2.3-4.1**

Tempia et al. submitted
Pregnancy as a risk factor for hospitalisation in South Africa

• Compared outpatients with influenza-like illness to hospitalised pneumonia patients
• Among women of childbearing age 15-49 years
  – 12.5% (2/16) SARI pregnant vs
  – and 1.7% (3/172) ILI pregnant OR 8.0 95% CI: 1.2-52.2
• Multivariable analysis pregnancy significantly associated with increased risk of influenza-associated SARI hospitalization OR 21.5 95% CI 2.5-185.9*

Tempia et al. Manuscript in preparation

*adjusting for duration of symptoms, age, underlying medical conditions, smoking of cigarettes, HIV infection, and co-infection with other respiratory viruses
Influenza Vaccination of Pregnant Women and Protection of Their Infants

Shabir A. Madhi, M.D., Ph.D., Clare L. Cutland, M.D., Locadiah Kuwanda, M.Sc., Adriana Weinberg, M.D., Andrea Hugo, M.D., Stephanie Jones, M.D., Peter V. Adrian, Ph.D., Nadia van Niekerk, B.Tech., Florette Treurnicht, Ph.D., Justin R. Ortiz, M.D., Marietjie Venter, Ph.D., Avy Violari, M.D., Kathleen M. Neuzil, M.D., Eric A.F. Simões, M.D., Keith P. Klugman, M.D., Ph.D., and Marta C. Nunes, Ph.D., for the Maternal Flu Trial (Matflu) Team*

- Vaccine efficacy
- HIV uninfected moms
  - Mothers 50% (95%CI 15-71)
  - Infants 49% (12-70)
- No effect on birth outcomes but not powered

- HIV infected moms
  - Mothers 58% (0.2-82)
  - Infants 27% (-132-77)

September 4, 2014
### Numbers of individuals in groups targeted for influenza vaccination in South Africa, 2011

<table>
<thead>
<tr>
<th>Target group</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children ≤5 years</td>
<td>5 189 528</td>
</tr>
<tr>
<td>Adults ≥65 years</td>
<td>2 538 955</td>
</tr>
<tr>
<td>All pregnant women</td>
<td>852 831</td>
</tr>
<tr>
<td>Pregnant women (HIV-uninfected)</td>
<td>595 276</td>
</tr>
<tr>
<td>Pregnant women (HIV-infected)</td>
<td>257 555</td>
</tr>
<tr>
<td>HIV-infected (5-64 years, not pregnant)</td>
<td>5 023 017</td>
</tr>
<tr>
<td>Tuberculosis and without HIV infection (5-64 years)</td>
<td>138 953</td>
</tr>
<tr>
<td>Specific high-risk underlying conditions (5-64 years)</td>
<td>6 643 032</td>
</tr>
<tr>
<td>Health care workers</td>
<td>72 000</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>20 458 316</strong></td>
</tr>
</tbody>
</table>

Currently < 1 million doses annually in public sector
Risk-group based vaccination challenging
Conclusions

• There are data to support vaccination of pregnant women but limitations
• Data from low and middle income countries are needed to guide policy
  – Disease burden
  – Vaccine effectiveness
  – Cost effectiveness
• Surveillance data can provide useful information to guide local, global and regional recommendations
Thank you
BACKUP SLIDES
Influenza vaccination strategies

**Risk-group based**
- Many countries including South Africa
- Focus on individuals at increased risk of severe outcomes
- Reduce costs
- Minimal indirect effect benefit

**Universal**
- United States since 2010
- All aged >6 months
- Protect those severe cases not in risk groups
- Benefit from indirect effect
Figure 4. Excess Deaths Attributed to Pneumonia and Influenza over a 50-Year Period in Japan and the United States. The five-year moving average is also shown. The history of the rates of use of vaccine in each country is superimposed (shaded bars). Tick marks represent the beginning of the years indicated.
Influenza-associated excess respiratory deaths among individuals ≥5 years of age by age group in South Africa, 1998-2009

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Number Mean (95% CI)</th>
<th>Rate/100,000 person years</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-19 year</td>
<td>96 (60-137)</td>
<td>0.6 (0.4-0.9)</td>
</tr>
<tr>
<td>20-44 years</td>
<td>778 (416-1144)</td>
<td>4.2 (2.3-6.2)</td>
</tr>
<tr>
<td>45-64 years</td>
<td>1106 (696-1562)</td>
<td>16.8 (10.6-23.8)</td>
</tr>
<tr>
<td>65-74 years</td>
<td>626 (416-852)</td>
<td>43.4 (28.9-59.1)</td>
</tr>
<tr>
<td>≥75 years</td>
<td>1005 (704-1323)</td>
<td>132.3 (92.9-174.2)</td>
</tr>
<tr>
<td>≥5 years</td>
<td>3613 (2292-5018)</td>
<td>8.5 (5.8-11.2)</td>
</tr>
</tbody>
</table>

Tempia..., Cohen et al. submitted
# Working Group’s Assessment of Influenza Risk and Influenza Vaccine Characteristics in Various Risk Groups

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Feasibility of Delivery</th>
<th>Disease Severity</th>
<th>Vaccine Effectiveness</th>
<th>Indirect Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant women</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Healthcare workers</td>
<td>++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Children, 2-5 years</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Children, &lt; 2 years</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Elderly</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Underlying Health Conditions</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
Target risk groups for influenza vaccination, SAGE WG on Influenza Vaccines

In countries using or considering introducing seasonal influenza vaccination

- Pregnant women
- Health care workers
- Young children
- Elderly persons
- Persons with high risk conditions

Based on reviews of:
- Epidemiology
- Burden
- Vaccine safety
- Vaccine effectiveness
- Cost-effectiveness
- Feasibility and operational issues
Is maternal influenza infection associated with adverse birth outcomes?

Preterm birth (n=15 Studies)

Summary

- **Few studies**
  - Particularly non-pH1N1
  - None from resource poor settings
- **Notable deficits in methodologies**
- **High heterogeneity in exposure measurement and outcome definitions**
- **Some evidence for increased risk of preterm birth and fetal death associated with pH1N1, particularly severe illness; magnitude unclear**
- **Uncertainty**
  - Existence of effect
  - Magnitude of effect
  - Contribution of contextual factors: influenza serotype, illness severity, underlying illness, trimester of infection
  - Contribution of nuances in outcome definition: fetal death, gestational age
Mortality Associated With Seasonal and Pandemic Influenza and Respiratory Syncytial Virus Among Children <5 Years of Age in a High HIV Prevalence Setting—South Africa, 1998–2009

Stefano Tempia,1,2,3 Sibongile Walaza,2 Cecile Viboud,4 Adam L. Cohen,1,2 Shabir A. Madhi,3,5,6 Marietjie Venter,3,7 Johanna M. McAnerny,3 and Cheryl Cohen18

Highest rate of influenza-associated mortality in <1 year HIV-infected ~ 12 times more likely to die of influenza

Table 4. Estimated Seasonal Influenza and Respiratory Syncytial Virus Mean Annual Associated Deaths and Relative Risk for Mortality Due to HIV Infection in Children <5 Years of Age in South Africa, 1998–2009*

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Total</th>
<th>HIV-Positive</th>
<th>HIV-Negative</th>
<th>Relative Risk (HIV-Positive vs HIV-Negative) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No., Mean (95% CI)</td>
<td>Rateb, Mean (95% CI)</td>
<td>Percentage Mortality Over Model Baseline, Mean (95% CI)</td>
<td>No., Mean (95% CI)</td>
</tr>
<tr>
<td>Seasonal influenza virus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All respiratory</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 y</td>
<td>240 (117–368)</td>
<td>22 (11–34)</td>
<td>4 (2–7)</td>
<td>72 (33–110)</td>
</tr>
<tr>
<td>1–4 y</td>
<td>212 (110–313)</td>
<td>5 (2–7)</td>
<td>9 (7–11)</td>
<td>71 (36–104)</td>
</tr>
<tr>
<td>&lt;5 y</td>
<td>452 (227–681)</td>
<td>8 (4–13)</td>
<td>5 (4–8)</td>
<td>143 (69–214)</td>
</tr>
</tbody>
</table>
Overall summary

• Influenza disease burden data in pregnant women lacking
• Few data from low income settings
• Lack of data prevents assessment of the impact of a maternal influenza vaccine programme on severe maternal, fetal and newborn outcomes
• Absence of data is not evidence of absence
• Additional clinical trials add data