Protection through life – the key role of indirect immunity

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Content

• Development of the concept of herd immunity

• Role of mathematical models in vaccine policy

• Examples of resurgences – why did they happen?

• Protecting the older generation against influenza and pneumococcal disease through herd immunity
History and Theory

1906: Hamer introduced the theoretical basis of herd immunity.

He argued: “The ability to infect per measles case was a function of the number of susceptibles \( (S) \) in the population.”

Ability to infect = number of transmissions per case \( (C) \)

Basic concept leads to the **mass action equation**

\[
C_{t+1} = C_t S_t r \quad \text{where} \quad r \quad \text{is a disease-specific transmission parameter}
\]

1957: MacDonald introduced the concept of the “basic reproduction number” \( R_0 \) defined as:

The average number of secondary cases who contract an infection from a single primary case introduced into a totally susceptible population.
Basic reproduction number

$R_0 \equiv 3$

$N = 1$

$N = 3$

$N = 9$
Effective reproduction number $R_e$

- If the population is not fully susceptible, the average number of secondary cases is less than $R_0$. This is the effective reproduction number.
Effective reproduction number $R = 1$ if only 1 in 3 is susceptible

$R_0 = 3$
endemic equilibrium

If $R < 1$ disease dies out
Herd immunity threshold* and $R_0$

$H = 1 - 1/R_0$

(Assumes homogeneous mixing)

*Level of population immunity at which $R = 1$
## Basic reproductive rate ($R_0$)

<table>
<thead>
<tr>
<th>Infection</th>
<th>$R_0$</th>
<th>Effective vaccine coverage needed to stop transmission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphtheria</td>
<td>5 – 6</td>
<td>80 – 85%</td>
</tr>
<tr>
<td>Measles</td>
<td>15 – 17</td>
<td>92 – 95%</td>
</tr>
<tr>
<td>Mumps</td>
<td>10 – 12</td>
<td>90 – 92%</td>
</tr>
<tr>
<td>Rubella</td>
<td>7 – 8</td>
<td>85 – 87%</td>
</tr>
<tr>
<td>Smallpox</td>
<td>5 – 7</td>
<td>80 – 85%</td>
</tr>
</tbody>
</table>

Effective coverage = actual % vaccinated $\times$ vaccine efficacy against transmission

With $R=1$ what happens when there is an influx of new susceptibles e.g. by births or waning immunity?

$R_0 = 3$

Endemic equilibrium

$R$ becomes $>1$ and cases increase.
Epidemic threshold is number of susceptibles in population at which incidence starts to increase
Effect of vaccination: if effective coverage less than the herd immunity threshold, susceptibles accumulate but at a slower rate than in unvaccinated population.
Measles incidence in countries giving a single dose: *Italy (low coverage)* 1988-92

*Poland (high coverage)* 1984-90
Vaccination status of measles cases

Number of cases

Age of case (years)

Unvaccinated

Vaccinated

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Use of mathematical models to inform vaccine policy: some examples....
Vaccination strategies to control congenital rubella syndrome (CRS)

- **Selective vaccination of girls/women (UK)**
  - allows most to get natural immunity in childhood with less risk from possible waning immunity
  - No effect on herd immunity and exposure in pregnancy
  - Relies on direct protection of pregnant women

- **Mass vaccination of all children (US)**
  - Most women in future to rely on vaccine-induced immunity
  - Reduces risk of exposure in pregnancy
  - Relies on indirect protection of pregnant women
“under optimal conditions of uptake and efficacy the vaccination of pre-school boys and girls will give better results than the vaccination of 14 year old girls alone, but where conditions are less than optimal the second policy is preferable. “

“Low uptake or low efficacy can result in severe rebounds in the incidence of CRS and the medium-term results can be worse than if no vaccination had been provided”

WHO position on rubella vaccination WER 2011

“To avoid the potential of an increased risk of CRS, countries should achieve and maintain immunization coverage of 80% or greater”
Congenital Rubella Cases
UK, 1970-2006

Source: NCRSP & HPA CfI
Measles notifications & vaccine coverage

England and Wales 1950-2009

Notifications ('000s)

Year

0 200 400 600 800


Vaccine coverage (%)

Measles vaccine introduced

Measles vaccine introduced

MMR vaccine introduced

MR campaign

Source: Office for National Statistics and Department of Health
Proportion of children susceptible to measles, 1986/7 and 1991 England

% susceptible

Age Group (years)
UK measles-rubella vaccination campaign 1994

- Aimed to prevent a predicted measles epidemic
- First example of using a model prediction to prevent an epidemic
- **measles-rubella vaccine** was used to improve rubella control (not enough MMR available)
- Offered to all children aged 5-16 years
- 92% coverage achieved nationally
Examples of resurgences and their causes
Immunity to mumps before and 5 years after MMR introduction and notified and confirmed mumps Nov 1994 – Dec 2006

Proportion of sera negative for mumps antibody 1986/7 and 1993

Notified and confirmed mumps Nov 1994 – Dec 2006*
Pertussis resurgence: notifications England and Wales 1940 - 2013
Pertussis model predictions: cases < 1yr of age England and Wales

3. wP primary changed to aP primary at 2004 + aP pre-school booster at 2001
   Age Group =0 year, aP selected Scenarios
Protecting the older generation through vaccinating children
Weekly All-cause Mortality Surveillance
19 February 2015 – Week 8 report (up to week 7 data)

In week 7 2015, significant excess all-cause mortality by week of death was seen through the EuroMOMO algorithm in England in 65+ year olds. In the devolved administrations in week 7, significant excess all-cause mortality was also seen in Northern Ireland. Since week 40 2014, significant excess mortality has been seen in England from week 50 2014 onwards mainly in 65+ year olds, coinciding with circulating influenza and cold snaps, with suggestions impact is now decreasing.

Excess overall all-cause mortality, England and Wales

In week 6 2015, an estimated 12,039 all-cause deaths were registered in England and Wales (source: Office for National Statistics). This is less than the 12,900 estimated death registrations in week 5, but remains above the 95% upper limit of expected death registrations for the time of year as calculated by PHE (Figure 1). The sharp drop in number of deaths in week 52 corresponds to a week when there were bank holidays and fewer days when deaths were registered and so is likely to be artificial and result in subsequent increases in following weeks.

Excess all-cause mortality in subpopulations, UK

Since week 40 2014 up to week 7 2015 in England, excess mortality by date of death above the upper 2 z-score threshold was seen in England after correcting ONS disaggregate data for reporting delay with the standardised EuroMOMO algorithm 65+ year olds in weeks 50 to 7 2015, 15–64 year olds in weeks 51–2 and weeks 1, 2 and 4 in under five year olds (Figure 2, Table 1). This is consistent with raised impact of flu season and cold snap captured by other data sources.

Table 1: Excess mortality by age group, England

<table>
<thead>
<tr>
<th>Age group</th>
<th>Excess detected in week 7 2015?</th>
<th>Weeks with excess in 2014/15</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td></td>
<td>1-2.4</td>
</tr>
<tr>
<td>65-74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75+</td>
<td></td>
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</tbody>
</table>
EuroMOMO (mortality monitoring)
Children to be offered annual flu vaccine

Wednesday July 25, 2012

"Flu vaccines for all children," BBC News has reported.

The BBC’s story is based on a report by independent expert advisers, who have told the government that all children from the age of two to 17 should have an annual influenza vaccination.

The recommendations of the Joint Committee on Vaccination and Immunisation (JCVI) came as part of the government-funded National Childhood Immunisation Programme (NCIP) for 2012-13.

The JCVI made the following recommendations:

- Children aged 2 to 4 years
- Children aged 5 to 10 years
- Children aged 11 to 17 years
- Children with long-term health conditions
- Children in educational settings

These recommendations are based on the latest evidence and are designed to protect the health of children and reduce the spread of influenza in the community.

Flu vaccine for children will be given via a nasal spray.

Related articles

Does deadly diet drug work? (February 27 2015)

Over two hours screen child’s blood pressure (February 27 2015)

‘Game changer’ HIV drug cuts infection by 86% (February 25 2015)

Peanut butter for non-allers later allergies (February 25 2015)
Predicted cases and deaths prevented by adding annual flu vaccination of school children to current policy of vaccinating all 65+ year olds.

Baguelin et al Plos Med 2013
Annual incidence per 100,000 of invasive pneumococcal infection, E&W, by age group and year

- Inability to mount immune response to capsule
- Waning immunity
- Non-immune factors
Trends in IPD incidence by age and serotype grouping: E&W
From Waight et al in press
Corrected annual numbers of IPD cases, annual incidence rate (IR) and incidence rate ratios (IRR) in 65+ year olds pre PCV7 and 4 years post PCV13

<table>
<thead>
<tr>
<th></th>
<th>2000-06</th>
<th>IR</th>
<th>2013/14</th>
<th>IR</th>
<th>IRR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>3054</td>
<td>34.13</td>
<td>1841</td>
<td>20.58</td>
<td>0.60</td>
<td>0.56-0.64</td>
</tr>
<tr>
<td>PCV7</td>
<td>1601</td>
<td>17.89</td>
<td>47</td>
<td>0.53</td>
<td>0.03</td>
<td>0.02-0.04</td>
</tr>
<tr>
<td>PCV13-7</td>
<td>628</td>
<td>7.02</td>
<td>333</td>
<td>3.72</td>
<td>0.53</td>
<td>0.43-0.61</td>
</tr>
<tr>
<td>NVT</td>
<td>825</td>
<td>9.22</td>
<td>1461</td>
<td>16.33</td>
<td>1.77</td>
<td>1.62-1.95</td>
</tr>
</tbody>
</table>

Is there still a role for direct protection of 65+ year olds by vaccinating them with PCV to protect against CAP?
Impact of PCV 7 and PCV13 on VT IPD versus VT CAP (CAP data from Rodrigo et al in press 5 year longitudinal study)

<table>
<thead>
<tr>
<th>Incidence per 100,000</th>
<th>2008/9</th>
<th>2012/13</th>
<th>IRR-CAP</th>
<th>IRR-IPD for ≥ 65yrs over same period</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PCV7-type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-74</td>
<td>26.7</td>
<td>7.1</td>
<td>0.27</td>
<td>0.20</td>
</tr>
<tr>
<td>75-84</td>
<td>39.1</td>
<td>5.6</td>
<td>0.14</td>
<td>0.15</td>
</tr>
<tr>
<td>≥ 85</td>
<td>177.1</td>
<td>31.2</td>
<td>0.18</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>PCV13-7 type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65-74</td>
<td>23.2</td>
<td>12.5</td>
<td>0.54</td>
<td>0.56</td>
</tr>
<tr>
<td>75-84</td>
<td>44.7</td>
<td>22.3</td>
<td>0.50</td>
<td>0.62</td>
</tr>
<tr>
<td>≥ 85</td>
<td>104.2</td>
<td>20.8</td>
<td>0.20</td>
<td>0.62</td>
</tr>
</tbody>
</table>
Conclusions

• Important to understand potential herd immunity effects before introducing a vaccine
• Be prepared for resurgences due to temporary increases in number of susceptibles above the epidemic threshold
• A resurgence should not undermine confidence in the overall benefit of the vaccination programme
• Comparison of XS mortality data across EU should validate predicted herd immunity benefits for the elderly of vaccinating children
• Indirect effect of PCV in children on VT, IPD and CAP in 65+ yr olds is similar – what is the case for direct PCV vaccination of elderly?