Herd immunity/protection: Historical perspective

Paul Fine

Herd Immunity / Protection: an Important Indirect Benefit of Vaccination

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Definitions

- Herd immunity
- Herd protection
- Herd effects
- Indirect protection
- Community immunity

- Protection of non-immunes by the presence, prevalence and proximity of immunes ....
William Farr ….. saw it in 1840 !

“The smallpox would be disturbed, and sometimes arrested, by vaccination, which protected part of the population....”

Farr, W. Second Annual Report to the Registrar General, 1840
Topley and Wilson...thought about it in 1923
“Consideration of the results obtained during the past five years ... led us to believe that the question of immunity as an attribute of the herd should be studied as a separate problem, closely related to, but in many ways distinct from, the problem of immunity of an individual host.”

“... obvious problem to be solved .... Assuming a given total quantity of resistance against a specific ... parasite to be available among a considerable population, in what way should that resistance be distributed among the individuals at risk, so as best to ensure against the spread of the disease, of which the parasite in the causal agent ?”
The physical chemistry connection

“Mass action” (Hamer, 1906)

Incidence product of susceptibles times cases

\[ C_{t+1} = S_t \cdot C_t \cdot m \quad \text{or} \quad \frac{dy}{dt} = \beta \cdot x \cdot y \]

“Critical mass” = (Kermack + McKendrick, 1927)

Incidence declines if \( \frac{C_{t+1}}{C_t} < 1 \), i.e. if \( S_t < \frac{1}{m} \)

or if \( x < \frac{1}{\beta} \)

“Catalysis” (Muench, 1957)

Constant incidence rate by age
The Baltimore connection ....

Wade Hampton Frost + Lowell Reed
Responsible for epidemiology at Hopkins
.. and the eponymous model:
\[ C_{t+1} = S_t(1 - [1-p]^{C_t}) \]

Hedrich
Counted immunes and susceptibles

Langmuir
Studied epidemiology at Hopkins before setting up epidemiology programme at CDC
The proportion susceptible ("intact") to measles, under 15, fluctuated from 30 to 50% - i.e., epidemics stopped when < 30% susceptible.
Hubris, até.... (Public Health Reports, 1967)

From CDC / Atlanta:

“... of particular relevance are the meticulous studies of Hedrich....

....it is evident that when the level of immunity was higher than 55 percent, epidemics did not develop. This is an estimate of the threshold of herd immunity ....”
Needless to say…

Measles was not eradicated from the USA in 1967

But

the experience was a stimulus to important work
The first heterogeneous population microsimulation models

Community \((p_c, C_c)\)

School \((p_s, C_s)\)

Families \((p_f, C_f)\)

Risk of a child in this family =
\[
1 - (1 - p_c)^{C_c}(1 - p_s)^{C_s}(1 - p_f)^{C_f}
\]

*(child’s fate determined by Monte Carlo)*

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**Table 1: Summary of epidemic models**

<table>
<thead>
<tr>
<th>Model</th>
<th>Virology</th>
<th>Population structure</th>
<th>Method of spread</th>
<th>Length of periods</th>
<th>Vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Infection</td>
<td>Interference</td>
</tr>
<tr>
<td>I (4)*</td>
<td>Single agent</td>
<td>Unstructured (random mixing); (N = 400)</td>
<td></td>
<td>1 interval</td>
<td>None</td>
</tr>
<tr>
<td>II (2)</td>
<td>2 wild viruses</td>
<td>Structured: families, play groups, neighborhoods, school, (N = 100)</td>
<td></td>
<td>1 interval</td>
<td>None</td>
</tr>
<tr>
<td>III (G)</td>
<td>1 wild virus, 1 live-virus vaccine</td>
<td>Structured: families, play groups; (N = 900)</td>
<td>Contact</td>
<td>1 interval</td>
<td>None</td>
</tr>
<tr>
<td>IV</td>
<td>1 wild virus, 1 live-virus vaccine</td>
<td>Structured: families, play groups, neighborhoods, school, (N = 500)</td>
<td>Discrete random variable</td>
<td>Any schedule</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>V</td>
<td>Wild polio, vaccine polio, wild enteric</td>
<td>Structured: families, play groups; (N = 900)</td>
<td>Environmental contamination and contact</td>
<td>Any schedule</td>
<td>Asymptomatic</td>
</tr>
</tbody>
</table>

*Numbers in parentheses are references.*
The first heterogeneous population microsimulation models

These are Reed-Frost model “p”s, (probability of effective contacts), ie secondary attack rates
The first modelling on herd immunity
(based on microsimulation of heterogeneous population)

Concluded that: simple (e.g., single proportion) herd immunity thresholds are not appropriate for heterogeneous structured populations.
The first modelling on herd immunity
(based on microsimulation of heterogeneous population)

**Commentary**

HERD IMMUNITY: BASIC CONCEPT AND RELEVANCE TO PUBLIC HEALTH IMMUNIZATION PRACTICES

JOHN P. FOX, LILA ELVEBACK, WILLIAM SCOTT, LAEL GATEWOOD, AND EUGENE ACKERMAN

Specific immunization has long been a basic tool in medical practice and in local, state, national and international public health. However, the protection afforded by including the United States and major efforts are now in progress to eliminate disease from developing countries as West Africa (1).

**Addendum**

Since this paper was submitted, a particularly appropriate illustration of the thesis presented has come to attention. Scott (10) has described epidemic measles in Rhode Island in 1968 which was virtually confined to an “ethnic island” (Portuguese, chiefly recent immigrants) in a highly vaccinated general population. In this episode, the agent was introduced from Portugal via a three-year-old child who was developing disease as he arrived.

**Appendix**

The Reed-Frost model

A full discussion of this model is given elsewhere (6, 7). The basic description and definitions are given below.
Fox et al's 1971 conclusion:

“Free living populations of communities are made up of multiple and interlocking mixing groups, defined in such terms as families, family clusters, neighborhoods, playgroups, schools, places of work, ethnic and socioeconomic groups. These mixing groups are characterized by different contact rates and by differing numbers of susceptibles. The optimum immunization program is one which will reduce the supply of susceptibles in all subgroups. No matter how large the proportion of immunes in the total population, if some pockets of the community, such as low socio-economic neighborhoods, contain a large enough number of susceptibles among whom contacts are frequent, the epidemic potential in these neighborhoods will remain high. Success of a systematic immunization program requires knowledge of the age and subgroup distribution of the susceptibles and maximum effort to reduce their concentration throughout the community, rather than aiming to reach any specified overall proportion of the population.”
But those models needed estimates of “$p$”

= (probability of effective contact)

= (secondary attack rate)

for different contexts
Key methodological work on 2oAR, stimulated by Fox: #1

Error sources:

1. Subclinical infections

2. Community transmission (late co-primaries)
Key methodological work on 2°AR, stimulated by Fox: #2
(solved the problems raised by Kemper....)

Estimating "p", and the "community probability of transmission", by maximum likelihood, from frequency distribution of seropositives per household at end of epidemic
And, on the other side of the Atlantic ....
Herd immunity threshold


Threshold occurs when all but one \( (R_0 - 1) \) or the \( R_0 \) contacts of a case are immune: \( \text{ie} = \frac{(R_0 - 1)}{R_0} = 1 - 1/R_0 \)

From catalytic assumption:

\[
R_0 = 1 + \frac{L}{A}
\]

\( L \) = life expectancy
\( A \) = Average age at infection

("Transmission and control of arbovirus diseases" Society for Industrial and Applied Mathematics)
In the background... 1970s

- Smallpox eradication was proceeding ..... 
  - early emphasis implied threshold

“... eradication of smallpox from an endemic area can be accomplished by successfully vaccinating or revaccinating 80 % of the population within a period of four or five years , as has been demonstrated in several countries .” (12th World Health Assembly, 1959)

Note implication of $R_0 \approx 5$

- but shift to detection and containment - 1971
  - last case (ex Birmingham) in 1978

- Expanded programme of Immunization
  - started 1974
An interesting time.....
An obvious prediction ...

The greater the indirect protection the lower the risk (cumulative incidence) with increasing vaccine coverage.
An interesting observation ...

Decline in “risk” (cumulative incidence) in total population, with increase in vaccine coverage

But:

No apparent decline in “risk” among non-vaccinees

?!
Figure 4 (a) Measles incidence rate (sum of notifications in the 1974 cohort from 1974–9)/births in 1974) versus measles vaccine uptake rate (proportion of children born in 1974 who were vaccinated by the end of 1976) for Area Health Authorities (AHAs) in England.

(b) Measles incidence rate among susceptibles (now defined as (sum of notifications in the 1974 cohort from 1974–9)/(births in 1974—vaccinations given to 1974 cohort before the end of 1976)) versus measles vaccine uptake rate (as above) for AHAs in England.

89 of the total 90 AHAs were included in these analyses, the only exception being Avon for which vaccination statistics were not available.
Roy wrote to Paul (31 August 1982): “I very much share your confusion concerning why vaccination does not appear to have had any effect on the chance of an individual acquiring infection within a vaccinated community. I am rather coming to the belief that the mass action assumption is very false and that in reality the net rate of transmission plateaus rather rapidly as the density of susceptible rises. This is another way of saying that the homogeneous mixing assumption very incorrect since the number of contacts per unit of time is virtually constant for a large range of community sizes.”
An interesting correspondence

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Paul wrote to both (04/11/82): “I’m particularly delighted by your (our) different explanations for the finding illustrated in Figure 4. To make it complete, let me say that I disagree with both of you and favour the first of our suggested explanations - ie that it reflects ascertainment bias (correlation between notification efficiency and vaccine uptake on an area basis).”
Each theme developed, in the 80s and 90s ....

in particular with analytic methods for dealing with heterogeneity by age, and estimation of “$R_0$” from age structured data

and, independently, an increasing appreciation for the complexity of immunity and its population distribution ....

and, independently....

the decision to eradicate polio (1988)
An extraordinary milestone (1991)
An extraordinary milestone (1991) of an analytic approach

Observation:

750 pages, > 700 references, but **no** mention of:

- Frost, Reed, Fox,
- Kemper or Longini

(or their modelling !)
Some complications emerged

- Age shifts
  - rubella (George Knox, 1980)

- Freeloaders...
  - pertussis (UK 1974 et seq)

- Indirect protection isn’t immunity
  - long term responsibility implications

- Ethics of vaccinating some to protect others ...
  - school children in Japan (‘flu)
  - transmission blocking (malaria)
Herd immunity in the 21st Century

- **Observations**
  - powerful indirect effects eg of HiB, PCV...

- **Eradication programme experience**
  - it’s a lot more complicated than \( \frac{(1 - R_0)}{R_0} \)

- **Complex modelling**
  - Fox et al 1971’s approach on big computers

- **Direct measurement of indirect protection**
  - a new paradigm
Observations of herd effects ....

Diphtheria, UK

Haemophilus, UK

Influenza, Japan

'Flu vaccination of schoolchildren estimated to have prevented 1 adult death for every 420 vaccinations

Reichert et al NEJM 2001

More complicated than thresholds ....
The complexity of eradication ....

21 Jan 2008 - 20 Jan 2009

01 March - 31 August 2010

Routine, plus *monthly* campaigns of all under 5s, for five years....,

**but**

What’s the nature, proportion and distribution of “immunity “ ?
Return of the Fox et al. approach

“We model the spread of influenza in a population structured into households and schools....”

NB - the transmission parameter estimates refer back to Longini et al. ....
Direct measurement of indirect protection: Halloginigram analysis:

(Longini et al. PLoS 2007)
Direct measurement of indirect protection:

Hallogenigram analysis:

Provides a method to explain the observation which puzzled Bob and Roy and me .... 30 years ago

(Longini et al. PLoS 2007)
Conclusion

it's a history of
gobalisation of problems,
synthesis of methods,
and recognition of subtleties