The impact of vaccination on the epidemiology of infectious diseases

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• Recent events
• Changing world.
• Basic epidemiological principles.
• Criteria for eradication.
• Impact of mass vaccination on epidemiological pattern.
• Indirect effects.
• Influenza A (H5N1).
• Conclusions.
Vaccine producing nations and world population distribution
Geographical distribution of vaccine market share 2015-16 – post merger of GSK and Novartis vaccine businesses
Great success - Measles – England & Wales

FIGURE-18 Notifications and deaths from measles in England & Wales, 1940-2002. Source: registrar General’s Annual returns, ONS, Cfl

- Measles vaccine introduced
- MR mass vaccine campaign
- MMR vaccine introduced
- MMR 2nd dose

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Events - 2013-16

Measles epidemic in the UK - 2013

The media furore - started by a controversial paper published in the Lancet in 1998 (Wakefield et al) which raised fears about a link with autism (which has since been comprehensively discredited) - led to panic among parents.
Measles cases USA, January – May 2015
Malaria vaccine (RTS,S) candidate reduces disease over 4 years of follow-up in study of more than 15,000 infants and young children

October 2013 - Results from ongoing Phase III clinical trial
Further results from the Phase III efficacy trial of the RTS,S malaria vaccine candidate were presented on Tuesday, 8 October 2013, at the 6th Multilateral Initiative on Malaria (MIM) Pan-African Malaria Conference in Durban, South Africa. These latest results demonstrated that over 18 months of follow-up, RTS,S was shown to almost halve the number of malaria cases in young children (aged 5-17 months at first vaccination) and to reduce by around a quarter the malaria cases in infants (aged 6-12 weeks at first vaccination) in a study of 15,000 children and infants.

April 2015 - Lancet RTS,S Clinical Trials Partnership
Despite the falling efficacy over time, there is still a clear benefit from RTS,S/AS01. An average 1,363 cases of clinical malaria were prevented over 4 years of follow-up for every 1000 children vaccinated, and 1,774 cases in those who also received a booster shot. Over 3 years of follow-up, an average 558 cases were averted for every 1,000 infants vaccinated, and 983 cases in those also given a booster dose.”
Health and Economic Impact of Seasonal Influenza A vaccination programme in England

Vaccine 30 May 2012 3459-62 Baguelin, Miller and Edmonds

Seasonal influenza vaccination impact was assessed with a transmission model. Vaccination substantially reduces disease burden. The current programme is cost-effective when the vaccine is well matched to strain circulating.

Conclusion
The 2012 seasonal influenza vaccination programme appears to substantially reduce disease burden and provides good value for money. 2014-15 flu vaccine much less efficacious due to poor matching.
Dengue vaccine approved 2016 – Sanofi-Pasteur

Analysing 31,000 participants in 10 countries across Asia and Latin America, each with endemic dengue, the overall result is an efficacy of 60.8% against symptomatic dengue in children and adolescents (9-16) who received three doses of the vaccine. The vaccine also showed a 95.5% effectiveness against severe dengue and an 80.3% reduction in the risk of hospitalization. A safety analysis of the latest study also showed reporting rates similar to those found in the first phase III.
Licensed in 2016 for use in Asia & South America.
Ebola – 2013-15 outbreak - epidemiology

- Spread by direct contact with blood, bodily fluids or semen from infectious patient – or contaminated surfaces – no evidence of airborne transmission as yet – but this is a more transmissible strain than usual.
- Fever typically denotes infectiousness.
- Disease - Ebola Hemorrhagic Fever (EHF) or EVD
- Incubation period – 2-21 days (mean 8-10 days 2014; 12.7 days 2011 outbreak).
- Generation time – 10-12 days.
- Doubling time 4-5 days.
- $R_0$ is roughly 2-3.5 – each primary case generating 2 to 3 secondary cases over the first 35 weeks of the epidemic.
- Survival rate 47-50%
- Isolation of contacts – for 21 days post contact – use condoms for sexual partners.
Ebola vaccines

Ebola vaccine started trials in 2014 – all trials ended in 2015 due to too few cases

The first human trials of an Ebola vaccine candidate co-developed with the US National Institutes of Health (NIH) began in September 2014. The vaccine candidate was given to healthy volunteers in the US, UK, the Gambia, Uganda and Mali, as part of a series of safety trials of potential vaccines aimed at preventing Ebola, which has killed thousands of people in West Africa and led the World Health Organization (WHO) to declare a public health emergency of international concern. Phase III trials started in early 2015.

Moncef Slaoui from GSK - “Developing a new vaccine is complex with no guarantees of success and it’s still early days for our Ebola vaccine candidate. But we are encouraged by progress so far and will do the best we can, along with WHO and our partners, to speed up development and explore ways in which the vaccine could contribute to the control of this or future Ebola outbreaks.”
Ebola - current situation May 2016

• Epidemic began to decline rapidly in July 2015 - 26 confirmed cases in week ending 19th July 2015 compared with 30 cases the week before.

• Weekly incidence has stalled at between 20-30 cases since end of May 2015 – but now dropped to just a few isolated cases.

• Total of 28,000 cases and 12,000 deaths in three countries Guinea, Liberia and Sierra Leone plus sparks in other countries such as the USA, Nigeria, Mali, Senegal, Italy, Spain and the UK.

• Vaccine trials ended due to too few cases – but progress still being made in development of vaccines and trial design (ring vaccination).
Emergence of Zika virus infection epidemic in S America - association with microcephaly in infants born to infected mothers confirmed in Feb 2016
Zika virus – distribution map – past and present

Potential areas of risk in the USA
Concern over Yellow fever virus infection in Africa – WHO recommends setting up an emergency panel – April 2016
Genetic variation spectrum of pathogens

Relatively homogeneous

Measles virus  Bordetella  Dengue  Pneumococcal  HIV
Mumps virus  RSV  Rotavirus  Malaria
Rubella virus  HPV  HPV  Influenza A & B

Great heterogeneity

HIV-T virus

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Human evolution

Australopithecus ramidus
Australopithecus afarensis
Australopithecus africanus
Homo habilis
Homo erectus
Australopithecus robustus
Homo sapiens neandertalensis
Homo sapiens sapiens
Homo sapiens

Millions of Years Ago

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World population growth by continent: past and predicted

Population (billions)
Record of increasing travel over four male generations of the same family.

(A) Great-grandfather. (B) Grandfather. (C) Father. (D) Son. Each map shows in a simplified manner the individual’s ‘life-time tracks’ in a widening spatial context, with the linear scale increasing by a factor of 10 between each generation (Bradley, 1994 Geog. Ann. 76:91-104).

(A) Great-grandfather

(B) Grandfather

(C) Father

(D) Son
Air traffic flow – world picture - 2009
Hong Kong

Re-assortment of bird and human influenza viruses

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Africa</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Asia</td>
<td>2</td>
<td>10</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>Latin America</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>5</td>
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</table>

<table>
<thead>
<tr>
<th>More Developed Regions</th>
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<tbody>
<tr>
<td>Europe</td>
</tr>
<tr>
<td>Japan</td>
</tr>
<tr>
<td>North America</td>
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</table>
Surveillance - spatial dynamics of influenza A in France

French sentinel system for influenza case reporting.

Very rapid spread seen over a period of 4 reporting weeks.

http://www.b3e.jussieu.fr/sentiweb/en/sommaire.html
Daniel Bernoulli - 1700 to 1782

D. Bernoulli (1760) used a simple mathematical model to evaluate the effectiveness in reducing mortality of variolation to protect against smallpox.

Daniel Bernoulli was one of a number of early mathematicians who turned their skills to probability problems raised by gamblers - at the card tables in Monte Carlo! (e.g. C. Huyghens 1657).
Disease extinction likely by chance when number of infectives falls to very low numbers.

- so extinction more frequent as population size decreases and cycle amplitudes increase.
Critical community size

Minimum population size at which measles fadeouts (proportion of weeks with no cases) become rare.
Seasonality in transmission of measles – school holidays

![Graph showing incidence of measles over weeks with confidence bars and two lines: RCGP and Model.](image)
HIV-1 prevalence in Nairobi, Kenya 1981-1999 – stratified by risk group
Basic principles in Infectious Disease Epidemiology

• The key determinant of incidence and prevalence of infection is the basic reproductive number $R_0$.

• $R_0$ measures the average number of secondary cases generated by one primary case in a susceptible population.

• Many factors determine its magnitude, including those that influence the typical course of infection in the patient and those that determine transmission between people.
The key determinant of incidence and prevalence of infection is the basic reproductive number $R_0$.

Many factors determine its magnitude, including those that influence the typical course of infection in the patient and those that determine transmission between people.
The epidemic curve

Rate of new infections

- **establishment**
- **exponential growth**
- **endemicity**

Time

Random (stochastic) effects

Equilibrium, or recurrent epidemics

Exhaustion of susceptibles

**$y \propto e^{-\frac{(R_0-1)}{R_0} t}$**
Typical course of infection within the host

Estimation of average latent & infectious periods plus distributions
The typical course of infection

**SARS CoV**

- Days post onset of clinical symptoms
- Percentage of samples positive

- Nasopharyngeal aspirate
- Stool
- Urine

**Influenza A**

- Days post viral inoculation
- Viral load
- Symptom score

Experimental human influenza A/Texas/36/91 (H1N1) intranasal inoculation $10^5$ dose

Basic principles in Infectious Disease Epidemiology

- The magnitude of \( R_0 \) varies according to location and population - it is strongly influenced by birth rate, population density and behavioural factors.

- The magnitude of \( R_0 \) can be ascertained by cross sectional serological surveys.
What is Herd Immunity?

- The impact of the fraction immune in the community on the per capita rate of transmission of an infectious agent.
- The level of herd immunity can be measured by reference to the magnitude of reduction in the value of $R_o$. 
How can the degree of herd immunity and the magnitude of $R_0$ be assessed?

- Cross-sectional and longitudinal serological surveys.
- Serum and saliva (viral infections).
- Activated T cells (bacteria and protozoa)?
- Quantitative assays.
Scientific methods in the study of herd immunity

• **Immunological** and **Disease Surveillance** methods provide the empirical base for analysis and interpretation.

• **Mathematical & statistical** methods play an important role in the analysis of infectious disease transmission and control.

• They help to define both what needs to be measured, and how best to measure define epidemiological quantities.
Age-specific serology - measles

**Used to calculate the average age at infection, A, the average duration of maternal antibody protection, M, and the degree of herd immunity**
### Average age, $A$, at infection prior to immunisation

<table>
<thead>
<tr>
<th>Infection</th>
<th>Average age at infection, $A$</th>
<th>Location/time period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles virus</td>
<td>5-6 years</td>
<td>USA 1955-58</td>
</tr>
<tr>
<td></td>
<td>2-3 years</td>
<td>Bangkok, Thailand 1967</td>
</tr>
<tr>
<td>Rubella virus</td>
<td>9-10 years</td>
<td>Sweden 1965</td>
</tr>
<tr>
<td>Varicella virus</td>
<td>6-8 years</td>
<td>USA 1921-28</td>
</tr>
<tr>
<td>Polio virus</td>
<td>12-17 years</td>
<td>USA 1920-60</td>
</tr>
<tr>
<td>Mumps virus</td>
<td>7-8 years</td>
<td>England &amp; Wales 1975</td>
</tr>
<tr>
<td>Smallpox virus</td>
<td>10-15 years</td>
<td>Bangladesh 1940</td>
</tr>
</tbody>
</table>
## Estimates of the basic reproductive number, $R_o$

<table>
<thead>
<tr>
<th>Infection</th>
<th>Location</th>
<th>Time period</th>
<th>$R_o$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles</td>
<td>England</td>
<td>1947-50</td>
<td>13-15</td>
</tr>
<tr>
<td></td>
<td>Canada</td>
<td>1912-13</td>
<td>11-13</td>
</tr>
<tr>
<td>Varicella</td>
<td>USA</td>
<td>1943</td>
<td>7-8</td>
</tr>
<tr>
<td>Mumps</td>
<td>Netherlands</td>
<td>1970-80</td>
<td>11-14</td>
</tr>
<tr>
<td>Rubella</td>
<td>West Germany</td>
<td>1970-79</td>
<td>6-7</td>
</tr>
<tr>
<td>Polio</td>
<td>USA</td>
<td>1955</td>
<td>5-6</td>
</tr>
<tr>
<td>HIV-1</td>
<td>Nairobi, Kenya</td>
<td>1981-85</td>
<td>11-12</td>
</tr>
<tr>
<td></td>
<td>(sex workers)</td>
<td></td>
<td></td>
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<tr>
<td>Smallpox</td>
<td>Bangladesh</td>
<td>1940</td>
<td>4-6</td>
</tr>
<tr>
<td>Influenza A</td>
<td>England</td>
<td>2010</td>
<td>1-1.5</td>
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<tr>
<td>(H1N1)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Estimation of $R_0$ from past influenza A epidemics
Rapid SARS Virus Spread in Flats 7 and 8, Block E Amoy Garden, Hong Kong. 1st March 2003 – 292 people infected by one index case
The generation of secondary cases with vaccination

<table>
<thead>
<tr>
<th>Generation</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
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</thead>
<tbody>
<tr>
<td>Number Infected</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>$R$</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1.5</td>
<td>1.33</td>
<td>1.25</td>
<td>0.2</td>
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Vaccinated individuals
Vaccine efficacy

(Christensen & Bottiger, 1991; Clarkson & Fine, 1987; Ramsey et al., 1994)

**MEASLES**  90%-95%

**MUMPS**   72%-88%

**RUBELLA**  95%-98%
Mass vaccination

Fraction that must be vaccinated to block transmission (A=5 years) - measles

Vaccine efficacy changes with age due to presence of maternal antibodies

Maximum vaccine efficacy $Q$

$Q=1.0$

$Q=0.98$

$Q=0.97$
Age at vaccination - good and bad patterns

Good pattern - clustered around the optimal age

Poor pattern - spread to the right side of the optimal age
Percentage of children who had completed the primary course of measles or MMR vaccine at two years of age, Great Britain, 1980 - 2000

[Source: Department of Health, Statistics Division]

Adverse publicity in February 1998 created by a publication suggesting link between MMR, autism plus inflammatory bowel disease.
Predictions based on mathematical models of transmission and the impact of mass vaccination

1) Increase in average age at infection
2) Increase in the inter-epidemic period
3) Toughs in susceptibility in the herd immunity profile
4) Changes in the age distribution of infection and serious disease
5) Non-linear relationship between the incidence of infection and disease and vaccine uptake
Average age of infection - the impact of vaccination

Average age of infection prior to vaccination set at 5 years.

Average age of vaccination set at 2 years.
Vaccination - and the age distribution of infection

Measles - Gweru City, Zimbabwe
Vaccination since 1971

Proportion of cases in age class

Age group (months)
Impact of vaccination on serology

(a) Before immunization

(b) After immunization has begun

Vaccination

Proportion immune

Age  Adult

Proportion immune

Age  Adult

S1

S2

*
Herd immunity profile - across age classes and through time
(Anderson and May, 1982; Science 215:1053-60).

Measles - serology post the introduction of a cohort based vaccination programme
Age stratified & longitudinal serology for Rubella antibodies. Finland 1979-91

(Ukkonen et al, 1995)
Mass vaccination can increase the incidence of serious disease if the likelihood rises with age per case of infection (Anderson & May, 1983; *J. Hygiene* 90:259-325).

The case of rubella and congenital rubella syndrome.
Percentage gain from the **indirect** effects of herd immunity

![Graph showing percentage gain from indirect effects vs proportion of cohort vaccinated.](image)

**Critical vaccination coverage to block transmission,** $p_c$
Model design for individual based stochastic simulations

• High performance, object-oriented code. Intended to be scaleable to allow 000s of model simulations of 60 million population to be performed.
• Computationally intensive (>5GB memory use for 60 million).
• Three levels of population structure:
  - Household
  - Network (disease specific)
  - Spatial

• Flexible modelling of disease biology (arbitrary distributions, number of disease stages), and interventions (ring vaccination, mass vaccination, quarantine, anti-viral treatment, movement constraints).
Spatial kernels – mobile phone data – frequency versus – distanced moved per defined time unit

- Sum over daily legs
- Legs
- Daily Extent

Distance metres

Number of people
Ferguson et al, 2006 – Nature - on line April 27th 2006

Individual based stochastic simulation model with three scales of mixing – extensive sensitivity analysis and analysis of past influenza epidemics

200 days compressed into a few seconds
Conclusions

- Eradication difficult when $R_0$ large and population density plus net birth rate high.
- Heterogeneity in population density and vaccine coverage important.
- Carrier state important as are reservoir hosts (if involved).
- Mathematical & computational methods permit analytical & simulation studies of potential impact of different strategies.
- Cost benefit studies need to take account of indirect effects of mass vaccination on transmission.
- Vaccine coverage must be maintained at high levels to avoid the immigration of infectives stimulating epidemics in susceptible pockets.
- Multi-strain systems – Phase 4 monitoring - new strains replacing those targeted by a multi-valent vaccine in some cases.
- Need for new initiative to create vaccine manufacturing facility for novel pandemics/epidemics.
The End