POPULATION BIOLOGY OF INFECTIOUS DISEASES

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The Population biology of infectious diseases breaks roughly into two main classes - those diseases causing immunity and those not causing immunity. These classes correspond (again roughly) to microparasitic infections and macroparasitic infections.

I don't intend to become too technical in this discussion but will aim to show how some simple mathematical models can be very powerful. In this paper I will discuss mainly micro-parasitic infections and in particular the construction and effects of vaccination programmes. However to start I want to describe briefly the other major category.

MACROPARASITES

Examples of diseases: Hookworm, Schistosomiasis

These are widespread and serious diseases. Approximately 200 million people suffer from schistosomiasis.

In general macroparasites have quite long generation times, and direct multiplication within the host is either absent or occurs at quite a low rate. The immune response elicited generally depends on the number of parasites present in a given host and tends to be of relatively short duration. Macroparasitic infections therefore tend to be of a persistent nature with hosts being continually reinfected. The pathogenicity of the infection is related to the worm burden. Typically, theoretical work had taken the worm burden to be Poisson distributed. However recent field trials have indicated that a much more realistic model for some infections, e.g. Hookworm, is to take the worm burden to be distributed according to the

negative Binomial distribution.

This distribution is more highly exaggerated, for example less than 10% of the population harbours 80% of the parasites.

Distribution	Probability Generating Function
Poisson	$\pi(z) = e^{-\mu(1-z)}$
Negative Binomial	$\pi(z) = [1 + \frac{\mu}{k}(1-z)]^{-k}$

This has major implications for control strategy since an obvious thing to do is to try and identify those people with a high worm burden and treat them. This is being attempted at the moment in two villages in Burma for Hookworm.

An interesting question concerns the reason for this aggregation of the worm burden. One speculation is that there is a genetic predisposition to high worm density.

MICROPARASITIC INFECTIONS

These are caused by most viruses, most bacteria and many protozoans.

They are characterized by small size, short generation times, extremely high rates of direct reproduction within the host and a tendency to induce immunity to reinfection in those hosts that survive the initial onslaught. The duration of infection is typically short in relation to the lifespan of the host and therefore is of a transient nature. However there are many exceptions.

Some examples are given in the Table on the following page:

	Incubation Period (days)	Duration of Infectiousness (days)	Pathogenicity
Measles	9-12	5-7	Low-High
Smallpox	12-14	10	High
Rubella	17-20	14	Low
Mumps	10-20	7	Low
Whooping Cough	7-10	14+	Medium
Polio	5-20	Long	Medium
Herpex Simplex Virus	5-8	Long	Very Low

All these examples induce lifelong immunity. However this need not be the case - typhoid is an example.

The reason why the pathogenicity of measles varies from low to high is that in developing countries measles can kill 30% of those who obtain it. Smallpox has been eradicated but we will see that it is an interesting example to consider when studying the present controversy regarding vaccination programmes for Whooping Cough.

Rubella (German measles) and Mumps will illustrate another aspect of the effects of a vaccination programme, which is, that vaccination increases the average age at which the infection is obtained. This is of particular concern for these two infections. Mumps in adolescent and adult males can cause intense discomfort. In women, rubella, which is normally a mild infectionaccompanied by a fever may cause serious diseases in offspring if the infection is acquired during the first three months of pregnancy; infants born with congenital rubella syndrome may suffer deafness and neurological and other disorders.

The first result I want to obtain is a connection between the force of infection λ and the average age A at which infection is obtained. The result is:

$$\lambda = \frac{1}{A}$$

where

λ = force of infection - percapita rate of acquiring infection; the probability to acquire infection in unit time.

A = average age of infection.

To obtain this we use a compartment model. Divide the host population into discrete classes, at age a and at time t, let

$X(a,t)$ = number susceptible,

$Y(a,t)$ = number infectious,

$Z(a,t)$ = number recovered and immune, at age a at time t.

The basic partial differential equations for this system are

$$\frac{\partial X}{\partial t} + \frac{\partial X}{\partial a} = -[\lambda(t) + \mu(a)]X(a,t)$$

$$\frac{\partial Y}{\partial t} + \frac{\partial Y}{\partial a} = \lambda X - [\alpha(a) + \mu(a) + \nu]Y(a,t)$$

$$\frac{\partial Z}{\partial t} + \frac{\partial Z}{\partial a} = \nu Y - \mu(a)X(a,t)$$

with initial and boundary conditions

$t=0$ specify $Z(a,0)$, $Y(a,0)$, $Z(a,0)$

$a=0$ specify $X(0,t) = B$, $Y(0,t) = X(0,t) = 0$

$\lambda(t)$ = force of infection

$\mu(a)$ = age specific death rate

$\alpha(a)$ = disease induced death rate

ν = recovery rate (constant).

<u>Observations:</u> This compartment model can be modified in many ways. Some of these are as follows:

(1) A latent class (infected but not yet infectious) may be added.

(2) Maternal antibodies may protect for first three to nine months so infants are born into new protected class and lose immunity in the first year.

(3) Immunity may be lost, not lifelong, as above.

(4) We have assumed a constant recovery rate ν but recovery may be after some defined interval or some more general statistical recovery.

(5) The assumption of homogeneous mixing assumes that we can average out all local details - school, family etc. This allows us to write

$$\lambda(t) = \beta\int_0^\infty Y(a,t)da.$$

These, or similar differential equations are often the starting point for the analysis. However I now want to restrict attention to the equilibrium situation with the assumptions that

(a) Births and deaths exactly balance - justified usually by stating that population densities remain roughly constant on the time scale appropriate to the pathology of most diseases. This is clearly not a reasonable assumption for many countries.

(b) $\alpha = 0$; infection does not cause significant number of deaths. Again this is not a reasonable assumption for some diseases in the developing countries.

Under equilibrium the partial differential equations reduce to

$$\frac{dX}{da} = -(\lambda + \mu(a)X(a))$$

$$\frac{dX}{da} = \lambda x - (\nu + \mu(a)Y(a))$$

$$\frac{dZ}{da} = \nu Y - \mu(a)Z(a)$$

$$N(a) = X(a) + Y(a) + Z(a)$$

$$X(0) = N(0);\ Y(0) = Z(0) = 0.$$

Then

$$X(a) = N(0)\phi(a)\exp(-\lambda a)$$

$$N(a) = N(0)\phi(a),$$

where

$$\phi(a) = \exp(-\int_0^a \mu(s)ds).$$

The fraction of people of age a who are susceptible is

$$x(a) = \frac{X(a)}{N(a)} = \exp(-\lambda)$$

Therefore the average age of infection

$$\equiv \frac{\int_0^\infty a\lambda x(a)da}{\int_0^\infty \lambda x(a)da} = \frac{1}{\lambda}$$

So

$$A = \frac{1}{\lambda}.$$

This relates the 'observable' A with the more abstract λ - provided we treat λ as independent of age. This is frequently done in mathematical work but usually is not true. From $\lambda A = 1$ we conclude that the lower the force of infection the greater the age at which infection is obtained. Therefore weakening this force of infection, e.g. by vaccination, increases this average age which is of concern for infections such as rubella.

We now need two further concepts. The basic reproduction rate R_0 is the number of secondary cases produced, on average, when everyone is susceptible. R_0 combines the biology of the infection with social and behavioural factors influencing contact rates.

The effective reproductive rate, R, when X out of N are susceptible is, assuming homogeneous mixing, given by $R=R_0X/N$.

It is the number of secondary cases produced on average when X out of N are susceptible.

However at equilibrium we must have R = 1, therefore

$$(R_o \frac{X}{N})_{eq.} = 1$$

which implies

$$R_o = (\frac{N}{X})_{eq.}$$

Now

$$N = \int_0^\infty N(a)da, \qquad X = \int_0^\infty X(a)da$$

To find N,X we need to specify $\mu(a)$ the age specific death rate. I will take this as all who have lived to age L when they die.

There are obvious alternatives, e.g. taking $\mu(a)$ to be a constant. Then from the expressions previously obtained for N(a), X(a) we obtain

$$R_o = \frac{L}{A} \text{ if L is much greater than A.}$$

Note: if $\mu(a)$ is taken as a constant then

$$R_o = 1 + \frac{L}{A}.$$

Examples: Before immunization began in the U.S. and U.K., children typically caught measles and whooping cough around 4 - 5 years. If we take L = 70 then

R_o = 13 - 15 for measles and whooping cough.

For rubella A is 9 - 10 years giving

R_o = 7 - 8 for rubella.

Effects of Vaccination

Mass vaccination as a means of controlling diseases has two main effects. Most obviously there is the direct effect that those effectively immunized are protected against infection. The second and indirect effect which is less obvious

arises because a susceptible individual has less chance of acquiring the infection in a partially vaccinated community than in an unvaccinated population; there are fewer people around him to give him the disease, thus it is not necessary to immunize everyone to eradicate the infection. The crucial factor is the effective reproductive rate R of the disease. If $R \geq 1$, i.e. if each infected individual infects one or more persons before he shakes off the disease then the infection will persist. But if $R < 1$ the disease will die out even if there are susceptible people in the community.

Let us suppose a proportion p are vaccinated at age b. Then we can find the new equilibrium for the previous system of differential equations. From this we can calculate the new force of infection, which will depend on p. Eradication of the disease corresponds to the force of infection going to zero. To achieve this it is then seen that the critical proportion requiring to be vaccinated is given by

$$P \text{ critical} > 1 - \frac{1 - \frac{b}{A}}{R_o - \frac{b}{A}}$$

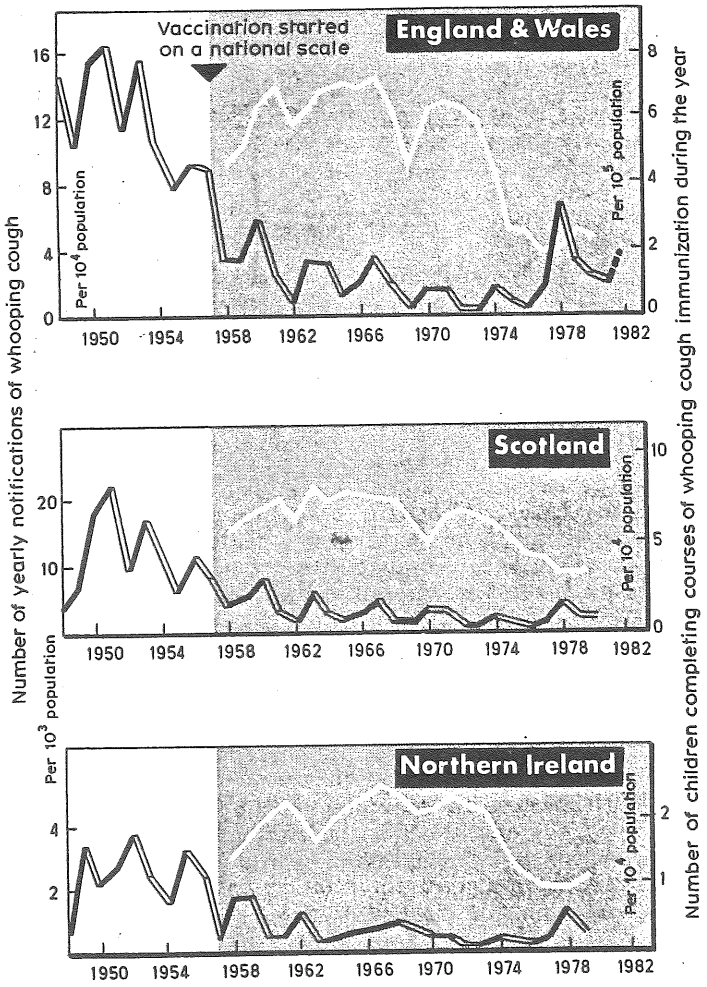
If b = 0, i.e. vaccination occurs at birth then

$$P \text{ critical} > 1 - \frac{1}{R_o}$$

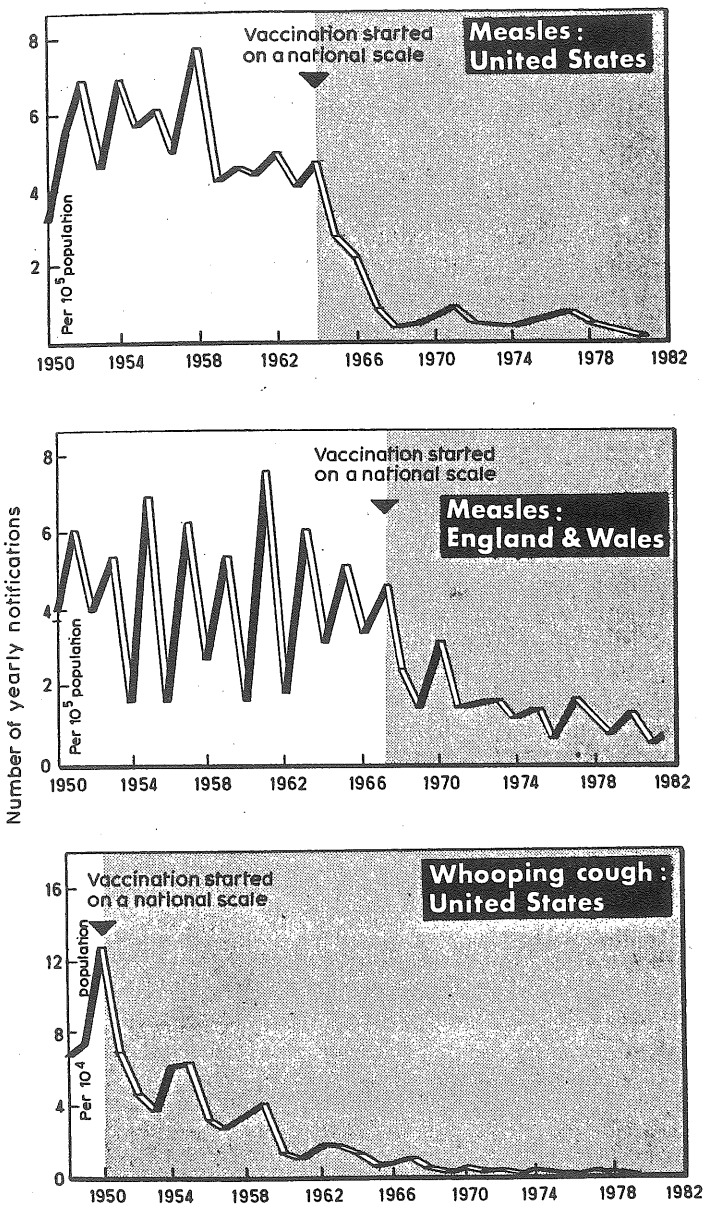
For measles and whooping cough we need 93% approximately. For polio and diptheria the situation is a little better since we require 80% and 85% respectively. If vaccination occurs at age 2 then we need approximately 95% coverage to eradicate measles and whooping cough.

These figures are depressingly high, but in the U.S. where indigenous measles has virtually disappeared more than 95% of children are currently vaccinated before reaching school age. This is the result of the childhood immunization initiative which began in 1977 (although widespread vaccination began much earlier). The goal is supported by laws which require docum-

Examples of trends in the numbers of reported cases of whooping cough (pertussis) and measles in Britain and the United States. The three graphs below show the trends in the United Kingdom of reported pertussis cases and the numbers of children vaccinated annually. The graphs to the right denote the reported cases of measles in the United States and England and Wales, plus pertussis in the United States



From *New Scientist*, 18 November, 1982



From *New Scientist*, 18 November, 1982

entary proof that a child has been vaccinated by the time it enters first grade; all 50 states had enforced this law by January 1982. Currently more than 95% of children in the U.S. are vaccinated against measles and pertussis (Whooping cough) before they enter school.

In the U.K. immunization is not enforced by law and high levels of vaccine coverage have proved difficult to achieve. Over the past decade levels of vaccination of children against diptheria, polio and measles have remained approximately constant - around 80% for diptheria and polio and around 50% for measles. In the case of whooping cough, as a result of the much publicised debate on the safety of the vaccine during the mid-1970s, vaccination fell from 80% in 1970 to less than 40% in 1981.

The controversy continues today and the current whooping cough epidemic is a direct result of the low levels of vaccination. It is interesting to compare this situation with that of smallpox.

In the U.K. from 1951 to 1970 there were roughly 100 deaths from smallpox vaccination and approximately 37 from smallpox itself, and in the U.S. the centre for disease control estimated that it would require 15 importations per year to produce the same mortality currently associated with smallpox vaccinations in the U.S. As a result vaccination against smallpox was discontinued both in the U.S. and U.K. in 1971.

The risk benefit analysis for whooping cough vaccine is considerably more complex than it was for smallpox. For one thing whooping cough has never been close to eradication in developing countries the way smallpox was in the 1960s. For another the range of neurological illnesses associated with whooping cough vaccination is clinically indistinguishable from that occurring in children who have not been immunized. In smallpox, by contrast, any disease produced by the vaccine can be clearly distinguished from the natural disease. Estimation

of the risk of vaccination must therefore come from large and statistically well designed studies that aim to distinguish neurological damage caused by the vaccine from the background of similar cases that arise in infancy and early childhood caused by bacterial and viral infections, congenital diseases and other processes that appear to be poorly understood.

The three year National Childhood encephalopathy study in the U.K. examined the records of every child below three years of age admitted to hospitals in Britain with neurological illness between June 1976 and July 1979. The study concluded that both pertussis and measles vaccines can indeed cause acute neurological reactions but that in both cases these are rare events. The study estimated the risk of persistent neurological damage one year after vaccination to be 1 in 310,000 immunizations.

The 1977-79 epidemic in Britain was responsible for 36 deaths and 17 cases of brain damage. Others suffer from continuing illness. The lower level illness associated with the disease should not be underestimated. The illness is protracted and debilitating, usually lasting 10 to 12 weeks and led to 5000 hospital admissions.

Based on the National Childhood encephalopathy study and a birth rate of 1.2%, i.e. 600,000 births, we can estimate that 6 cases of brain damage might be expected each year if every child completes the full course of 3 injections.

The consequences of the 1977-1979 epidemic were much worse.

Inter-Epidemic Period

From the graph one can see variation in the patterns of incidence. The models I have described also exhibit this behaviour. The incidence varies both from season to season and over longer periods. The seasonal trend is in part deter-

mined by patterns of social behaviour such as timing of school holidays. The best known examples of longer term fluctuations, taking place on time scales greater than one year, are the two to three year cycles in measles and the three to four year cycles in whooping cough. Indeed many directly transmitted viral infections such as measles, and bacterial infections such as whooping cough, typically follow such a pattern of recurrent epidemic largely because the susceptible population varies. First the number of susceptible people decreases as immunity is acquired by recovering from infection and then the number of susceptibles increases slowly as children are born.

This can be explained by the model we have proposed. In the partial differential equations we integrate out the age variable a to obtain a system of ordinary differential equations in which we will take the death rate to be constant. We obtain

$$\frac{dX}{dt} = \mu N - (\lambda + \mu)X(t)$$

$$\frac{dY}{dt} = \lambda X - (\nu + \mu)Y(t)$$

$$\frac{dZ}{dt} = \nu Y - \mu Z(t)$$

$$\frac{dN}{dt} = 0 \quad N = X(t) + Y(t) + Z(t)$$

Assuming birth rate = death rate.

Then we can analyse the equilibrium and stability behaviour of the solutions, to obtain damped periodic solutions with period

$$T = 2\pi\sqrt{A\tau}$$

where A = average age on infection

τ = average interval between an individual acquiring infection and passing it on to the next infectee.

Examples:

	A years	years	T years
Measles	4-5	1/25	2-3
Whooping Cough	4-5	1/14	3-4
Rubella	9-10	1/17	5

The tendency for the incidence of disease to oscillate in a regular manner raises a further problem in assessing the benefits of mass immunization. If vaccination coverage is high the non-seasonal epidemics will be small and it will be difficult to distinguish epidemic from non-epidemic years.

Under low to moderate levels of vaccination however, there may still be more cases in an epidemic year than there were in non-epidemic years before vaccination.

Thus in any assessment of the risk of exposure to infection we must base our calculations on the average risk over the inter-epidemic period covering years of low and high risk.

Average Age of Infection

I wish now to discuss the effect of a vaccination programme to increase the average of infection. I will illustrate this with respect to rubella, which as I have mentioned, is normally a mild infection accompanied by a fever but can cause serious damage to offspring if acquired during the first three months of pregnancy.

In the U.S. boys and girls are vaccinated against rubella around the age of two years with the aim of creating sufficient levels of herd immunity to virtually eliminate rubella from the population. Currently more than 90% of children are vaccinated before entering school and the incidence of rubella has dropped to very low levels.

In the U.K. the aim is to facilitate the natural circulation of the virus in the population so that most girls have contracted rubella before they reach child-bearing age. Currently the vaccination coverage is 60-80%. The average age (before vaccination programmes began) at which children caught rubella was 9-10 years. If they are still susceptible in early childhood then girls and only girls are immunized at around 12 years of age. This policy has had little impact on the incidence of rubella as such but has reduced the number of cases of congenital rubella syndrome.

Recent theoretical research has yielded the satisfactory conclusion that Britain's policy is best for Britain (since high levels of vaccination cannot be achieved) while the U.S. policy is best for its circumstances.

The important thing in the U.S. policy is that the level of vaccination does not fall below 50% to 55% otherwise more cases of congenital rubella syndrome will be obtained - due to increased average age of infection.

Define

D_a = number of people acquiring infection between ages a_1 and a_2 at equilibrium after vaccination

D_b = number of people acquiring infection between ages a_1 and a_2 at equilibrium before vaccination.

$W(a_1,a_2) = D_a/D_b$

We wish to ensure that the ratio $W(a_1,a_2)$ is less than 1. From the theory we have developed it can be shown that

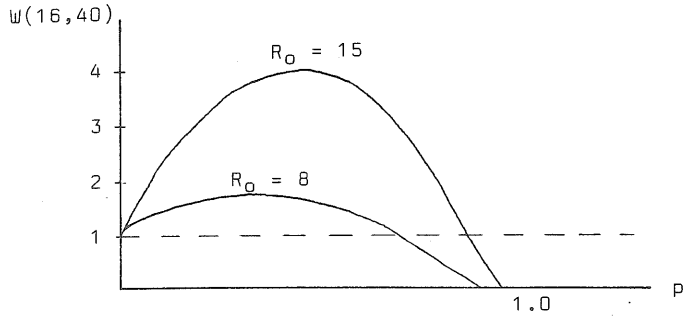
$$W(a_1,a_2) = (1 - p)\,\frac{e^{-\lambda_1 a_1} - e^{-\lambda_1 a_2}}{e^{-\lambda a_1} - e^{-\lambda a_2}}$$

where p = proportion vaccinated

λ_1 = force of infection at equilibrium after vaccination

λ = force of infection at equilibrium before vaccination.

We sketch below the graph of $W(16,40)$ for rubella and measles. The graphs illustrate that the number getting sick at older ages can increase if the coverage p is not approaching 1 whenever R_0 is large.



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