Herd immunity/protection: Historical perspective

Hanuman and the mountain of herbs; Mysore painting

Paul Fine

Herd Immunity / Protection: an Important Indirect Benefit of Vaccination

Fondation Merieux

October 25-7 2010

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 !

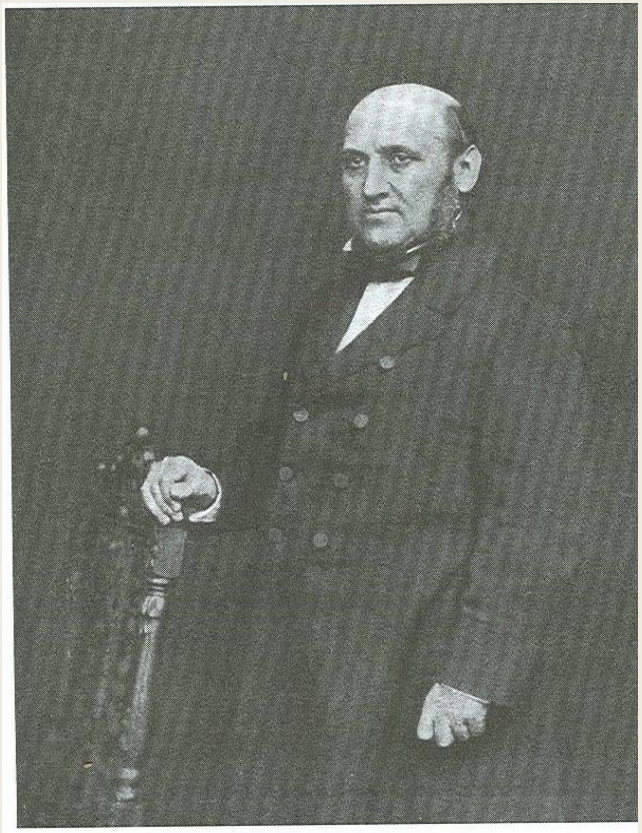


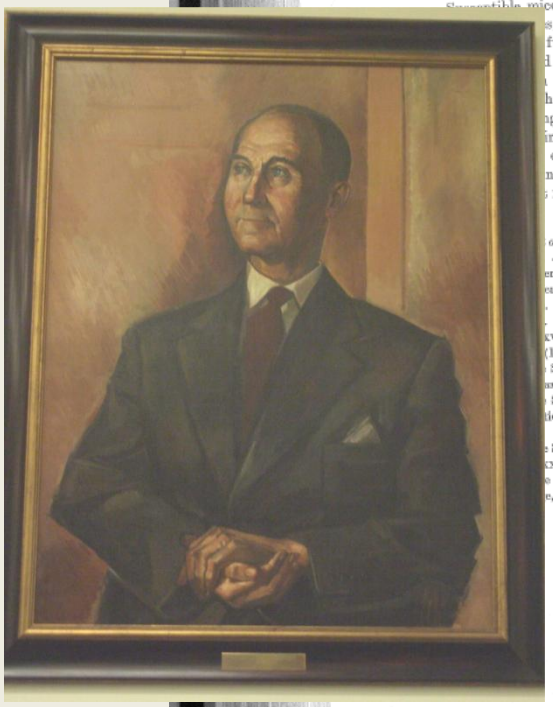
Figure 7.5. William Farr (1807–1883).

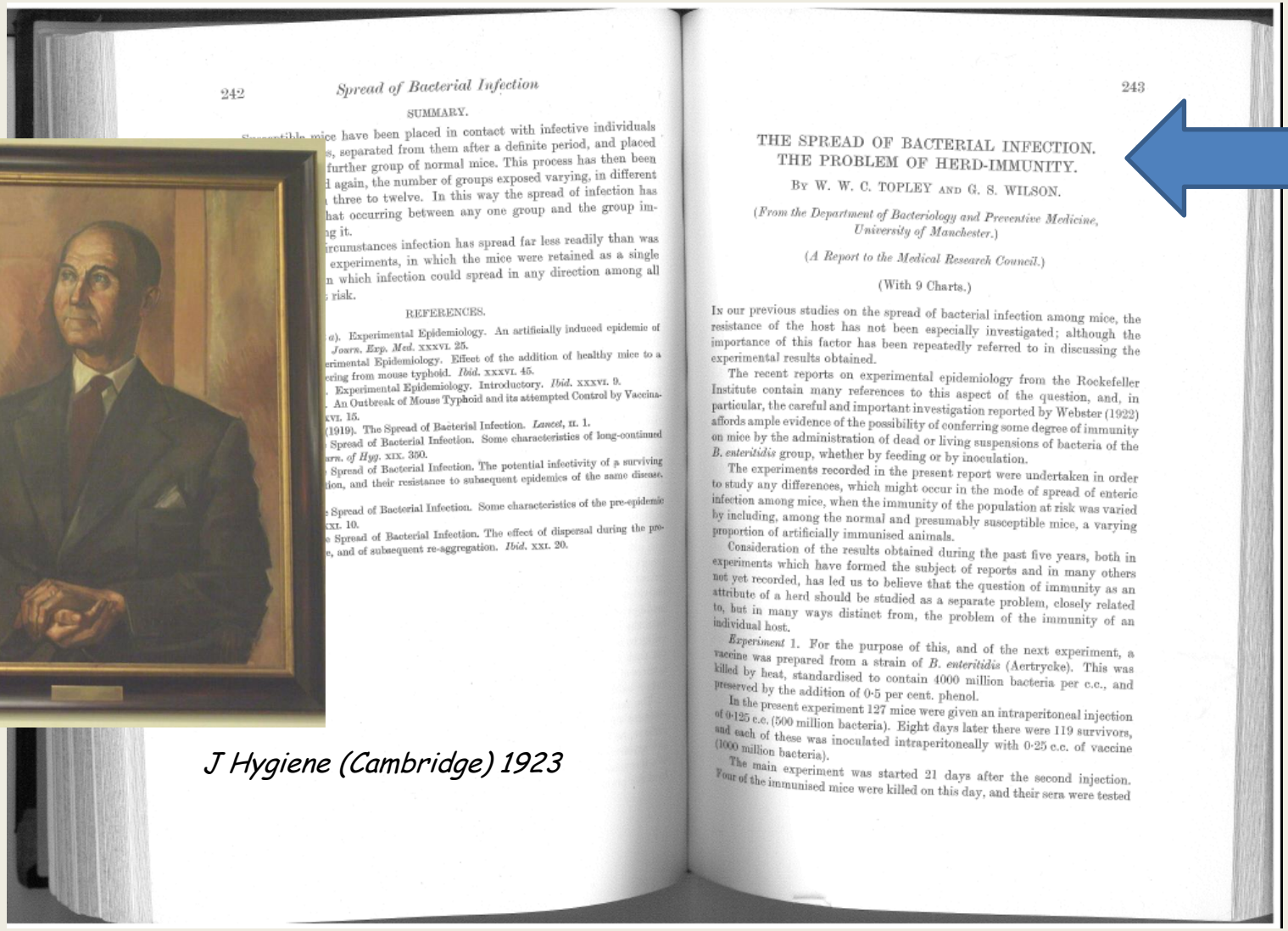
"The smallpox would be disturbed, and sometimes arrested, by vaccination , which protected part of the population...."

Farr, W. Second Annual Report to the Registrar General, 1840

Topley and Wilson

… thought about it in 1923





242 *Spread of Bacterial Infection*

SUMMARY.

…ceptible mice have been placed in contact with infective individuals …s, separated from them after a definite period, and placed … further group of normal mice. This process has then been …d again, the number of groups exposed varying, in different … three to twelve. In this way the spread of infection has …hat occurring between any one group and the group im… …g it.

…rcumstances infection has spread far less readily than was … experiments, in which the mice were retained as a single …n which infection could spread in any direction among all … risk.

REFERENCES.

…a). Experimental Epidemiology. An artificially induced epidemic of … *Journ. Exp. Med.* XXXVI. 25.

…erimental Epidemiology. Effect of the addition of healthy mice to a …ering from mouse typhoid. *Ibid.* XXXVI. 45.

… Experimental Epidemiology. Introductory. *Ibid.* XXXVI. 9.

… An Outbreak of Mouse Typhoid and its attempted Control by Vaccina… …XVI. 15.

…(1919). The Spread of Bacterial Infection. *Lancet*, II. 1.

… Spread of Bacterial Infection. Some characteristics of long-continued …*urn. of Hyg.* XIX. 350.

… Spread of Bacterial Infection. The potential infectivity of a surviving …tion, and their resistance to subsequent epidemics of the same disease.

… Spread of Bacterial Infection. Some characteristics of the pre-epidemic …XXI. 10.

… Spread of Bacterial Infection. The effect of dispersal during the pre… …e, and of subsequent re-aggregation. *Ibid.* XXI. 20.

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THE SPREAD OF BACTERIAL INFECTION.
THE PROBLEM OF HERD-IMMUNITY.

BY W. W. C. TOPLEY AND G. S. WILSON.

(*From the Department of Bacteriology and Preventive Medicine, University of Manchester.*)

(*A Report to the Medical Research Council.*)

(With 9 Charts.)

IN our previous studies on the spread of bacterial infection among mice, the resistance of the host has not been especially investigated; although the importance of this factor has been repeatedly referred to in discussing the experimental results obtained.

The recent reports on experimental epidemiology from the Rockefeller Institute contain many references to this aspect of the question, and, in particular, the careful and important investigation reported by Webster (1922) affords ample evidence of the possibility of conferring some degree of immunity on mice by the administration of dead or living suspensions of bacteria of the *B. enteritidis* group, whether by feeding or by inoculation.

The experiments recorded in the present report were undertaken in order to study any differences, which might occur in the mode of spread of enteric infection among mice, when the immunity of the population at risk was varied by including, among the normal and presumably susceptible mice, a varying proportion of artificially immunised animals.

Consideration of the results obtained during the past five years, both in experiments which have formed the subject of reports and in many others not yet recorded, has led us to believe that the question of immunity as an attribute of a herd should be studied as a separate problem, closely related to, but in many ways distinct from, the problem of the immunity of an individual host.

Experiment 1. For the purpose of this, and of the next experiment, a vaccine was prepared from a strain of *B. enteritidis* (Aertrycke). This was killed by heat, standardised to contain 4000 million bacteria per c.c., and preserved by the addition of 0·5 per cent. phenol.

In the present experiment 127 mice were given an intraperitoneal injection of 0·125 c.c. (500 million bacteria). Eight days later there were 119 survivors, and each of these was inoculated intraperitoneally with 0·25 c.c. of vaccine (1000 million bacteria).

The main experiment was started 21 days after the second injection. Four of the immunised mice were killed on this day, and their sera were tested

J Hygiene (Cambridge) 1923

From Topley and Wilson's 1923 paper

"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."

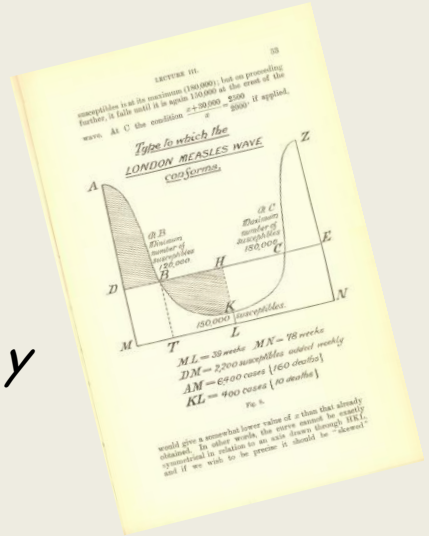
"... obvious problem to be solved .... Assuming a given total quantity of resistance against a specific ... parasite to be available among a considerable population, in what way should that resistance be distributed among the individuals at risk, so as best to ensure against the spread of the disease,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

The physical chemistry connection

"Mass action" (Hamer, 1906)

Incidence product of susceptibles times cases

$C_{t+1} = S_t \; C_t \; m$ or $dy/dt = \beta \; x \; y$



"Critical mass" = (Kermack + McKendrick, 1927)

Incidence declines if $C_{t+1} \; / \; C_t < 1$, ie if $S_t < 1/m$

or if $x < 1/\beta$

"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:

$$C_{t+1} = S_t(1 - [1-p]^{C_t})$$

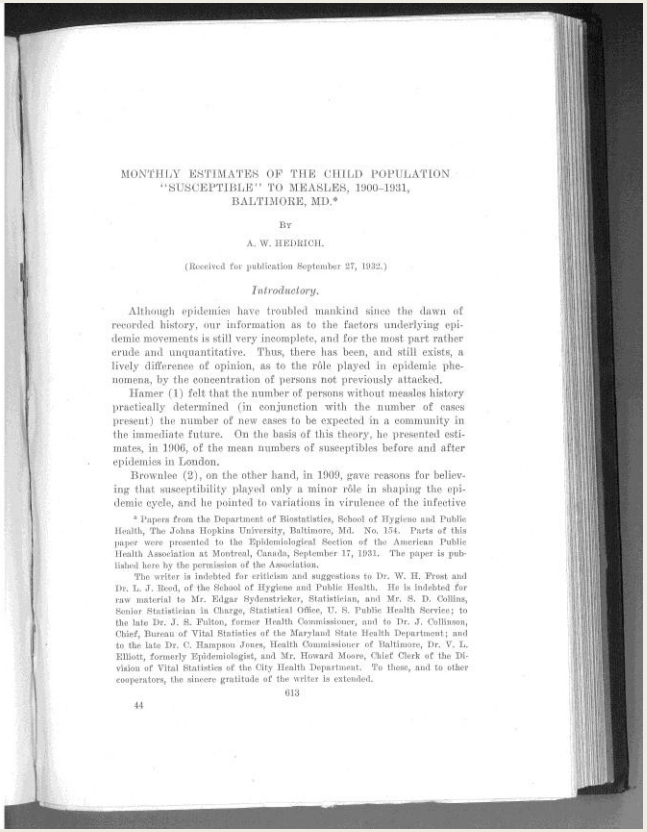
Hedrich

Counted immunes and susceptibles

Langmuir

Studied epidemiology at Hopkins before setting up epidemiology programme at CDC

The Hedrich paper (*Am J Hyg 1933*)



MONTHLY ESTIMATES OF THE CHILD POPULATION "SUSCEPTIBLE" TO MEASLES, 1900–1931, BALTIMORE, MD.*

By

A. W. HEDRICH.

(Received for publication September 27, 1932.)

Introductory.

Although epidemics have troubled mankind since the dawn of recorded history, our information as to the factors underlying epidemic movements is still very incomplete, and for the most part rather crude and unquantitative. Thus, there has been, and still exists, a lively difference of opinion, as to the rôle played in epidemic phenomena, by the concentration of persons not previously attacked.

Hamer (1) felt that the number of persons without measles history practically determined (in conjunction with the number of cases present) the number of new cases to be expected in a community in the immediate future. On the basis of this theory, he presented estimates, in 1906, of the mean numbers of susceptibles before and after epidemics in London.

Brownlee (2), on the other hand, in 1909, gave reasons for believing that susceptibility played only a minor rôle in shaping the epidemic cycle, and he pointed to variations in virulence of the infective

* Papers from the Department of Biostatistics, School of Hygiene and Public Health, The Johns Hopkins University, Baltimore, Md. No. 154. Parts of this paper were presented to the Epidemiological Section of the American Public Health Association at Montreal, Canada, September 17, 1931. The paper is published here by the permission of the Association.

The writer is indebted for criticism and suggestions to Dr. W. H. Frost and Dr. L. J. Reed, of the School of Hygiene and Public Health. He is indebted for raw material to Mr. Edgar Sydenstricker, Statistician, and Mr. S. D. Collins, Senior Statistician in Charge, Statistical Office, U. S. Public Health Service; to the late Dr. J. S. Fulton, former Health Commissioner, and to Dr. J. Cullimen, Chief, Bureau of Vital Statistics of the Maryland State Health Department; and to the late Dr. C. Hampson Jones, Health Commissioner of Baltimore, Dr. V. L. Elliott, formerly Epidemiologist, and Mr. Howard Moore, Chief Clerk of the Division of Vital Statistics of the City Health Department. To these, and to other cooperators, the sincere gratitude of the writer is extended.

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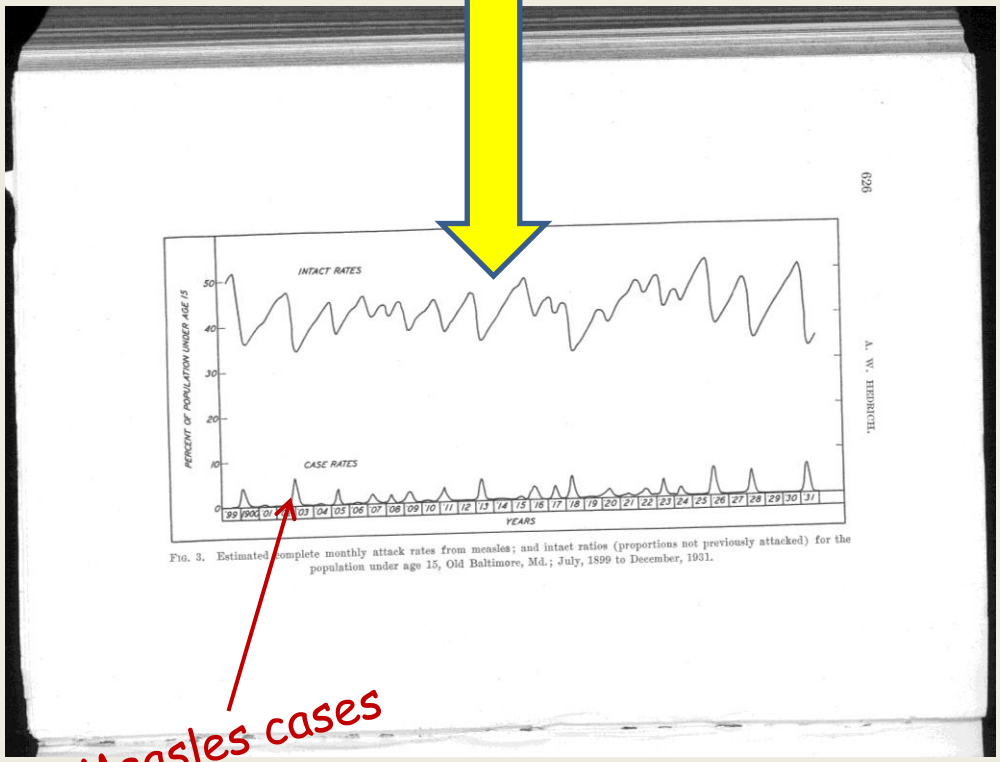
The proportion susceptible ("intact") to measles, under 15, fluctuated from 30 to 50 % - ie epidemics stopped when < 30 % susceptible



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A. W. HEDRICH.

FIG. 3. Estimated complete monthly attack rates from measles; and intact ratios (proportions not previously attacked) for the population under age 15, Old Baltimore, Md.; July, 1899 to December, 1931.

Measles cases

Hubris, até….

(Public Health Reports, 1967)

EPIDEMIOLOGIC BASIS FOR ERADICATION OF MEASLES IN 1967

David J. Sencer, M.D.
H. Bruce Dull, M.D.
Alexander D. Langmuir, M.D.

A STATEMENT BY THE PUBLIC HEALTH SERVICE

FOR CENTURIES the measles virus has maintained a remarkably stable ecological relationship with man. The clinical disease is a characteristic syndrome of notable constancy and only moderate severity. Complications are infrequent, and, with adequate medical care, fatality is rare. Susceptibility to the disease after the waning of

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Vol. 82, No. 3, March 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

AMERICAN JOURNAL OF EPIDEMIOLOGY
Vol. 93, No. 4

Printed in U.S.A.

STOCHASTIC TWO-AGENT EPIDEMIC SIMULATION MODELS FOR A COMMUNITY OF FAMILIES[1]

LILA ELVEBACK[2], EUGENE ACKERMAN[3], LAËL GATEWOOD[3] AND JOHN P. FOX[4]

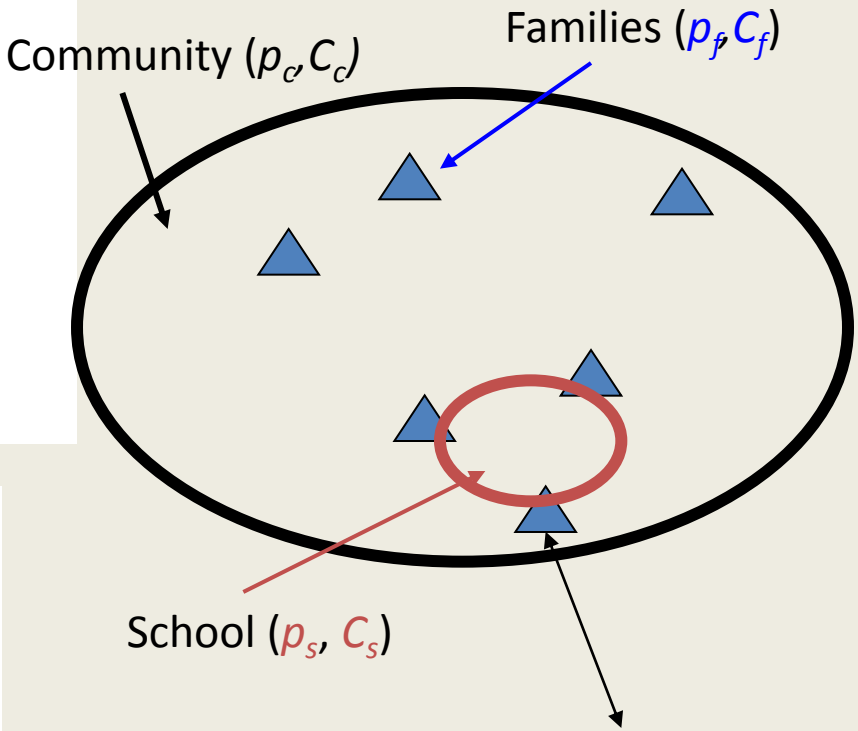
(Received for publication August 19, 1970)

Elveback, L. (Dept. Medical Statistics, Mayo Clinic, Rochester, Minnesota 55901), E. Ackerman, L. Gatewood and J. P. Fox. Stochastic two-agent epidemic simulation models for a community of families. *Amer J Epidem* 93: 267–280, 1971.—Two stochastic, discrete-time-interval simulation epidemic models which allow for competition and interference between a wild enteric virus and the live poliovirus vaccine are presented. The first is for a community of families in which each individual belongs to several mixing groups which depend on his age and which have different contact rates. The wild virus is taken to be one of the coxsackie

TABLE 1
Summary of epidemic models

Model	Viral agents	Population structure	Method of spread	Length of periods		Vaccination
				Infectivity	Interference	
I (4)*	Single agent	Unstructured (random mixing); N = 400	Contact	1 interval	None	None
II (2)	2 wild viruses			1 interval	1 interval	None
III (3)						
IV	1 wild virus, 1 live-virus vaccine	Structured: families, play groups, neighborhoods, school; N = 500		Discrete random variable	Assignable constant (3 intervals in examples)	Any schedule
V	Wild polio, vaccine polio, wild enteric	Structured: families, play groups; N = 500	Environmental contamination and contact			

* Numbers in parentheses are references.



Risk of a child in this family =

$$1 - (1 - p_c)^{Cc}(1 - p_s)^{Cs}(1 - p_f)^{Cf}$$

(child's fate determined by Monte Carlo)

The first heterogeneous population microsimulation models

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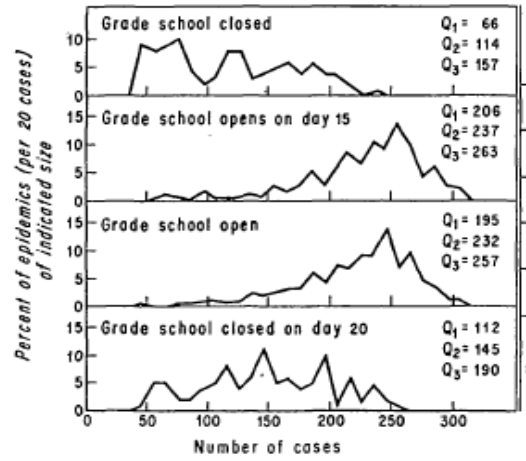
These are Reed-Frost model "*p*"s, (*probability of effective contacts*), ie secondary attack rates



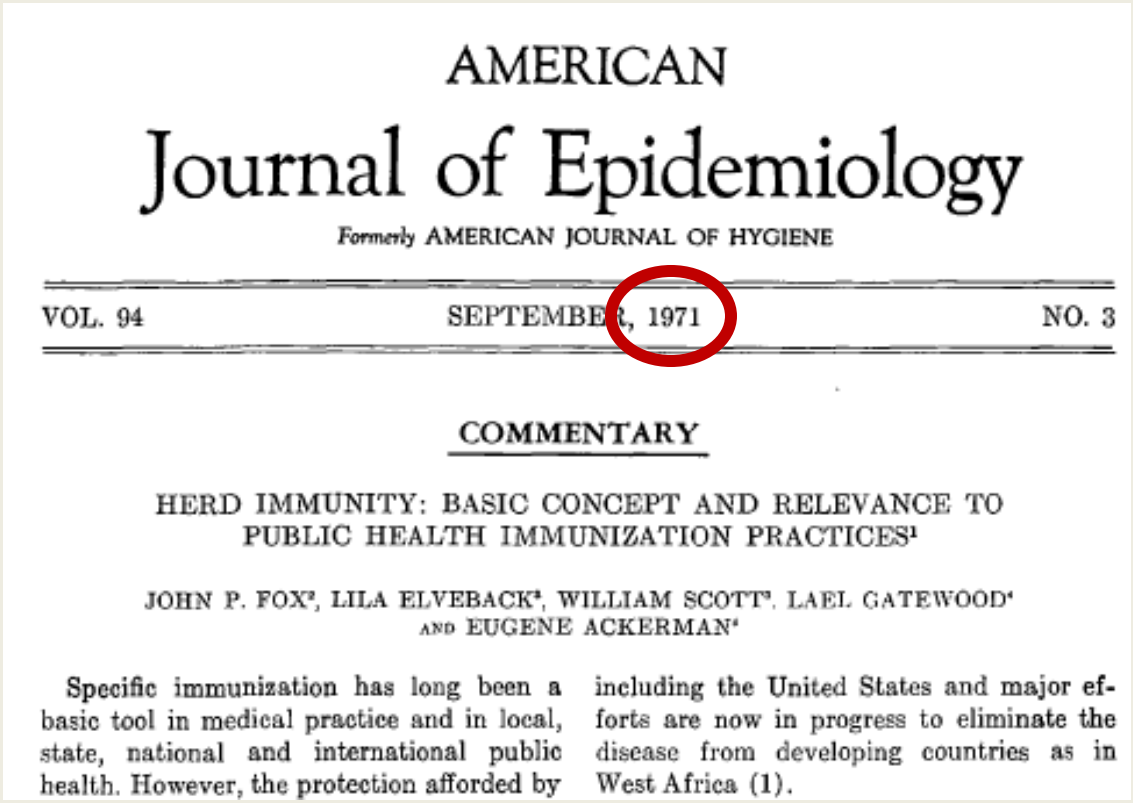
	Contact rates
	Cox
Family	.4
Playgroup	.1
Cluster	.007
Grade school	.001
Community	.00005

At day zero there are six cases in the population

FIGURE 1. School study using Model IV: Distributions of epidemic size with four schedules of school opening and closing. (Initially, six cases of coxsackievirus infection; no vaccination; 100 trial epidemics per set.) Quartiles of each distribution are shown on face of graph.

The first modelling on herd immunity

(based on microsimulation of heterogeneous population)



AMERICAN

Journal of Epidemiology

Formerly AMERICAN JOURNAL OF HYGIENE

VOL. 94 SEPTEMBER, 1971 NO. 3

COMMENTARY

HERD IMMUNITY: BASIC CONCEPT AND RELEVANCE TO PUBLIC HEALTH IMMUNIZATION PRACTICES[1]

JOHN P. FOX[2], LILA ELVEBACK[3], WILLIAM SCOTT[3], LAEL GATEWOOD[4] AND EUGENE ACKERMAN[4]

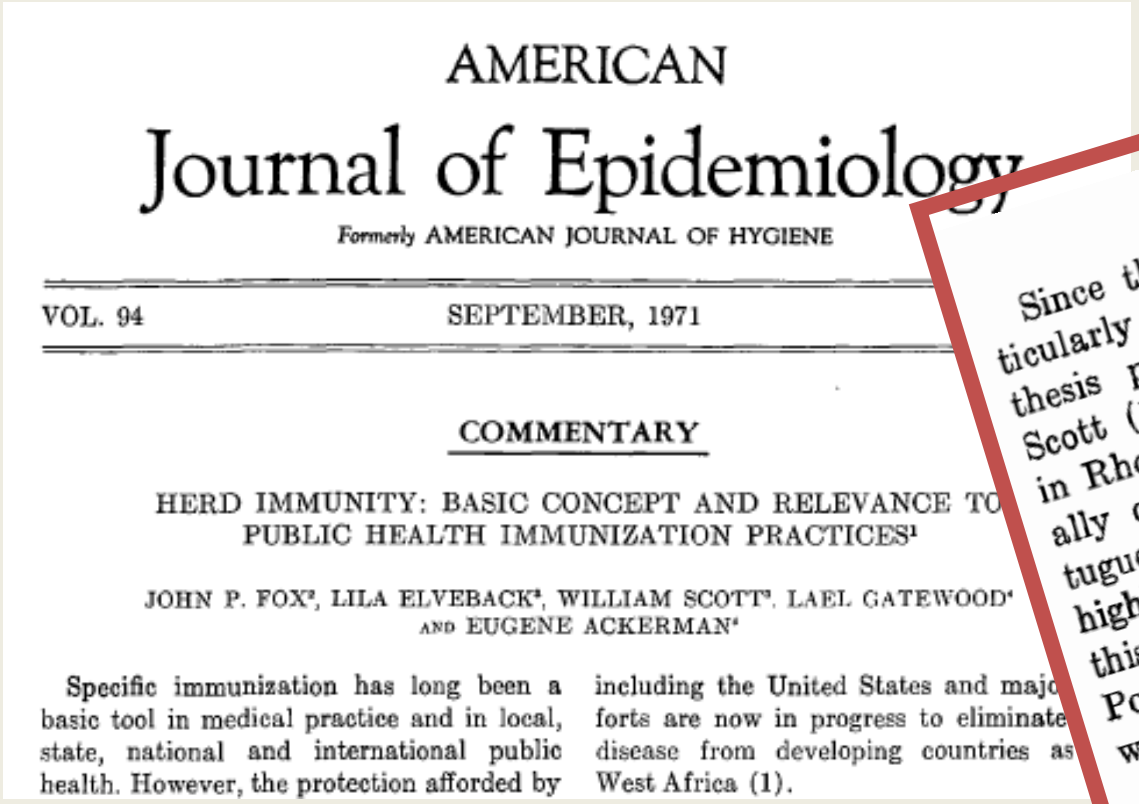
Specific immunization has long been a basic tool in medical practice and in local, state, national and international public health. However, the protection afforded by

including the United States and major efforts are now in progress to eliminate the disease from developing countries as in West Africa (1).

Concluded that: simple (eg single proportion) herd immunity thresholds are not appropriate for heterogeneous structured populations

The first modelling on herd immunity

(based on microsimulation of heterogeneous population)



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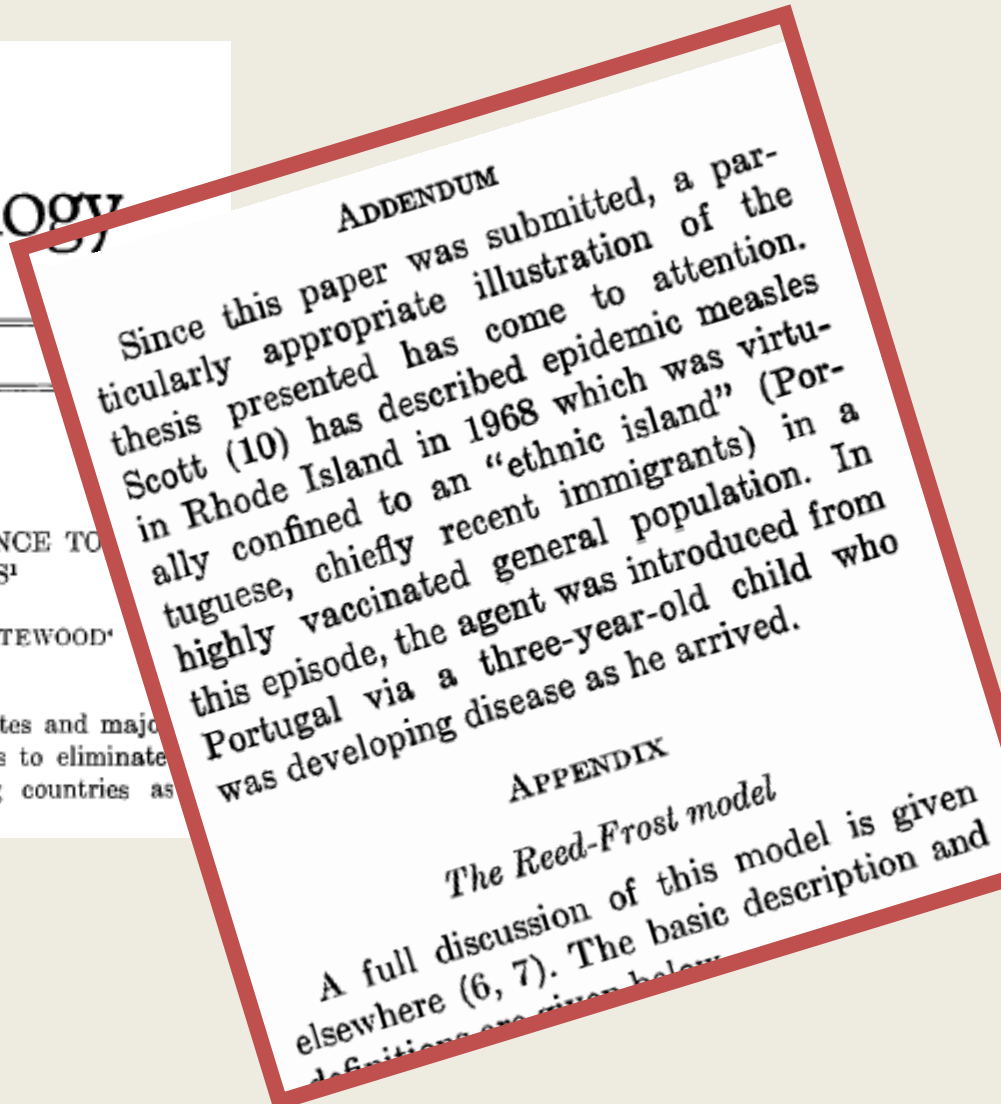


ADDENDUM

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

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

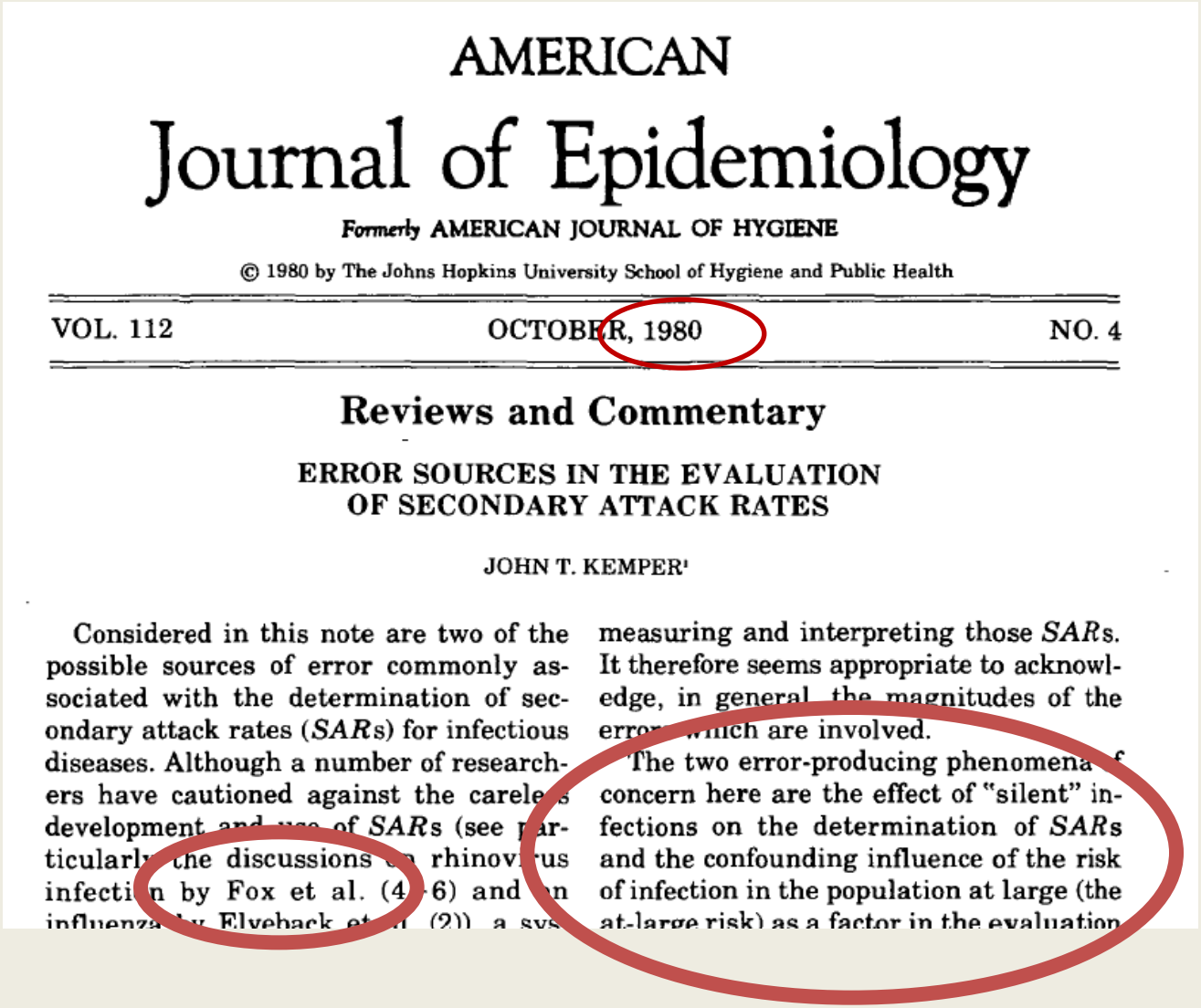
estimates of "*p*"

= (probability of effective contact)

= (secondary attack rate)

for different contexts

Key methodological work on 2°AR, stimulated by Fox: #1



AMERICAN

Journal of Epidemiology

Formerly AMERICAN JOURNAL OF HYGIENE

VOL. 112 OCTOBER, 1980 NO. 4

Reviews and Commentary

ERROR SOURCES IN THE EVALUATION OF SECONDARY ATTACK RATES

JOHN T. KEMPER[1]

Considered in this note are two of the possible sources of error commonly associated with the determination of secondary attack rates (*SAR*s) for infectious diseases. Although a number of researchers have cautioned against the careless development and use of *SAR*s (see particularly the discussions on rhinovirus infection by Fox et al. (4–6) and on influenza by Elveback et al. (2)), a sys-

measuring and interpreting those *SAR*s. It therefore seems appropriate to acknowledge, in general, the magnitudes of the errors which are involved.

The two error-producing phenomena of concern here are the effect of "silent" infections on the determination of *SAR*s and the confounding influence of the risk of infection in the population at large (the at-large risk) as a factor in the evaluation

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….)

AMERICAN JOURNAL OF EPIDEMIOLOGY
Vol. 115, No 5

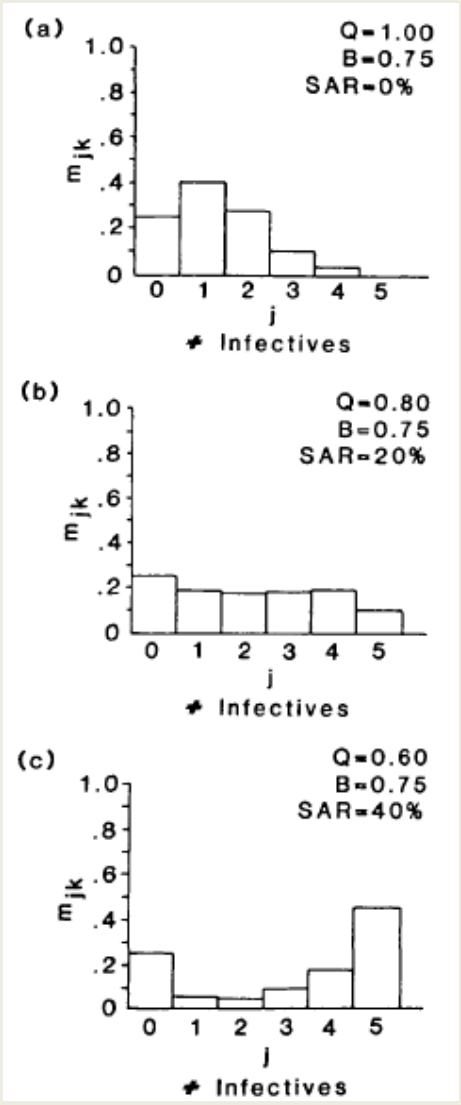
Printed in U.S.A.

ESTIMATING HOUSEHOLD AND COMMUNITY TRANSMISSION PARAMETERS FOR INFLUENZA

IRA M. LONGINI, JR.,[1] JAMES S. KOOPMAN,[1] ARNOLD S MONTO,[1] AND JOHN P. FOX[2]

Longini, I. M., Jr. (School of Public Health, University of Michigan, Ann Arbor, MI 48109), J. S. Koopman, A. S. Monto and J. P. Fox. Estimating household and community transmission parameters for influenza. *Am J Epidemiol* 1982; 115:736-51.

A maximum likelihood procedure is given for estimating houshold and community transmission parameters from observed influenza infection data. The estimator for the household transmission probability is an improvement over the classical secondary attack rate calculations because it factors out community-acquired infections from true secondary infections. The mathematical model used does not require the specification of infection onset times and, therefore, can be used with serologic data which detect asymptomatic



Estimated "*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

Macnamara (1955) .. CEG Smith (1970).. K Dietz (1975)

Threshold occurs when all but one $(R_0 - 1)$ or the R_0 contacts of a case are immune: ie = $(R_0 - 1) / R_0 = 1 - 1/ R_0$

("Transmission and control of arbovirus diseases" *Society for Industrial and Applied Mathematics*)

If $R_0 = 4$

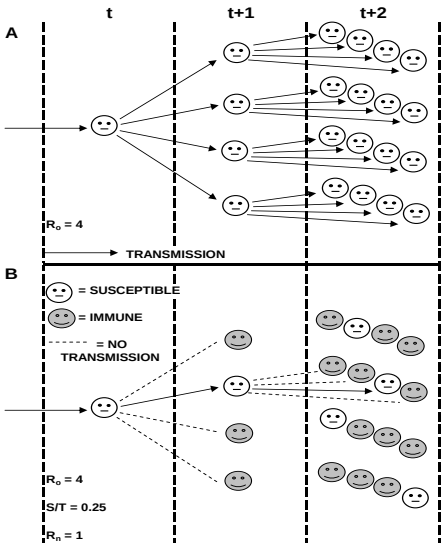


Figure 3 shows the effect of various immunity and/or vaccination prevalences on reproduction rates of infections (see also Table 7). Vaccination of say 70 per cent of a community is often

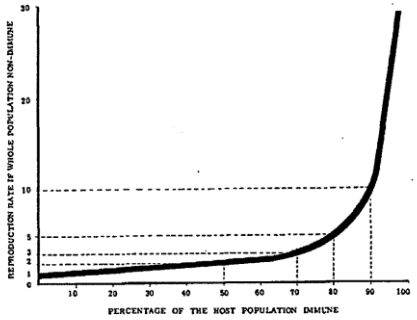


FIG. 3. Prevalences of immunity in vertebrate maintenance populations which will reduce to one various reproduction rates of infection.

suggested as the objective in an immunization campaign—this would reduce a reproduction rate of about three to unity. For reproduction rates over ten, more than 90 per cent of the community would have to be immunized. On the contrary a reproduction rate of two would require immunization of only rather more than 50 per cent.

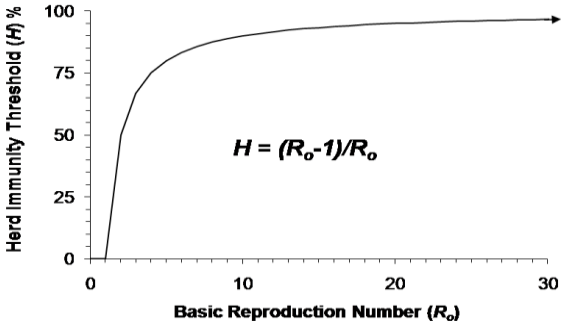
Unfortunately reproduction rates can rarely if ever be estimated with any accuracy because of the great complexity of the factors involved. However, from Macnamara's (1955) figures we might guess that if the epidemics stopped when 65–48 per cent of the population had become immune, the reproduction rates were between two and three (RR $\times 0{\cdot}54 < 1$, RR $\times 0{\cdot}35 < 1$).

From catalytic assumption:

$$R_0 = 1 + L / A$$

L = life expectancy

A = Average age at infection



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 .....

(Reprinted from Nature, Vol. 280, No. 5721, pp. 361-367, August 2 1979)
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Population biology of infectious diseases: Part I

Roy M. Anderson
Zoology Department and Centre for Environmental Technology, Imperial College, London University, London SW7, UK

Robert M. May
Biology Department, Princeton University, Princeton, New Jersey 08544

If the host population is taken to be a dynamic variable (rather ... assumed), a wider understanding of the population biology ... part of a two-part article, mathematical models are ... experiments, and used to explore the evolution... second part of the article, to be published ... indirectly transmitted infections, an...

SCIENCE

ANY contemporary ecolo... devoted to predato... embraces fo... math...

es
vin...
likes
of pre...
plant...
Park's
drastica...
Tribolium
outcome ...
studies of ...
sensitivity a...
insect *Hydro*
importance o...
lations of wil...
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sheep in North ...
infection by the h...
which then predis...
monia[4]. On a gran...
geographical distrib...
today is largely set b...
towards the end of the...
latitudes of Hilborn and
have a big influence on
authors[5,6,7,8,9,10] have argue...
cases as regulators of thei...

More broadly, it is likely
genicity of viral, bacterial, pa...
the nutritional state of the ho...
density-dependent regulation ...
parasites greatly amplifying the...
Such phenomena are largely
differences between age-specifi...

Reprint Series
26 February 1982, Volume 215, pp. 1053–1060

Directly Transmitted Infectious Diseases: Control by Vaccination

Roy M. ... and Robert M. May

Reprinted from Nature, Vol. 318, No. 6044, pp. 323-329, 28 November 1985
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Vaccination and herd immunity to infectious diseases

Roy M. Anderson & Robert M. May*
Department of Pure and Applied Biology, Imperial College, London University, London SW7 2BB, UK
*Biology Department, Princeton University, Princeton, New Jersey 08540, USA

An understanding of the relationship between the transmission dynamics of infectious agents and herd immunity provides a template for the design of effective control programmes based on mass immunization. Mathematical models of the spread and persistence of infection provide important insights into the problem of how best to protect the community against disease.

MUCH attention is now focused on the development and community-wide use of vaccines for the control of infectious diseases. This interest is a consequence of many factors; these include the worldwide eradication of smallpox by vaccination in the late 1970's[1], the current success of child immunization programmes for the control of measles, mumps, pertussis and rubella in the United States[2,3], the failure of frequent appeals by public health authorities in the United Kingdom to raise vaccination rates that are at present low by developed-country standards[4–6], the Expanded Programme on Immunization (EPI) of the World Health Organization (WHO) for the control of a variety of serious childhood viral and bacterial diseases in the developing world[6–8], and the rapid advances in molecular biology and biotechnology which promise new vaccines for the future[9–14]. The main thrust of research today is at the molecular level, where it is stimulated by the urgent need to develop vaccines for the major killing diseases of the Third World such as malaria[15–18] and to combat new infections such as the current epidemic of AIDS (acquired immune deficiency syndrome), caused by the recently isolated human T-lymphotropic virus (HTLV-III)[19–21].

The development of a safe, effective and cheap vaccine, however, is only a first step (albeit an essential one) towards community-wide control. Epidemiological, economic and motivational issues are at least as important as technological ones. A vaccine for measles (a very cost-effective immunization[22]) has been available since the late 1960s, yet the infection remains one of the world's major causes of child mortality[2,23]. Consistent with research on vaccine development, there is a need for an improved understanding of how best to use vaccines to protect the community as well as the individual. The persistence of infectious disease within a population requires the density of susceptible individuals to exceed a critical value such that, on average, each primary case of infection generates at least one secondary case. It is therefore not necessary to vaccinate everyone within a community to eliminate infection; the level of herd immunity must simply be sufficient to reduce the susceptible fraction below the critical point. The central epidemiological questions are thus: what proportion of the population should be vaccinated to achieve elimination (in a local programme), eradication (in a global programme) or a defined level of control? How is this affected by demographic factors (for example, birth rate)? What is the best age at which to immunize? How does mass immunization affect the age distribution of susceptible individuals, particularly in those classes most at risk from serious disease, and how important is genetic and spatial heterogeneity in susceptibility to infection (or response to immunization) to the creation of effective herd immunity[20–25]?

To answer these questions, we need to understand the interaction between the transmission dynamics of the disease agent and the level of naturally acquired (or artificially created) immunity to infection. This relationship is complex and depends on such factors as the precise course of infection within an individual, the demography of the host population, the duration of acquired immunity and maternally derived protection, age-related changes in the degree and intimacy of contacts among people, and the prevailing levels of genetic, spatial and behavioural heterogeneity in susceptibility/resistance to infection. Intuition built on many years of practical epidemiological experience often fails to predict the outcome of a particular vaccination programme. Mathematical models which clearly and accurately define the details of the association between disease agent and host (at the individual and population levels) can help to overcome such difficulties. This article reviews recent theoretical and empirical work on the transmission dynamics of infectious disease. Emphasis is placed on the relevance of such research to the design of disease control programmes based on vaccination.

General theory

Models for the transmission dynamics of directly transmitted viral and bacterial infections are typically compartmental in structure[26–28]. They represent changes, with respect to age, a, and time, t, in the populations of infants protected by maternally derived antibodies ($M(a,t)$), susceptible individuals ($X(a,t)$), infected individuals who are not yet infectious ($H(a,t)$), infectious people ($Y(a,t)$), and people who have recovered and are immune from subsequent infection ($Z(a,t)$). The total population is $N(a,t) = M(a,t) + X(a,t) + H(a,t) + Y(a,t) + Z(a,t)$.

The deterministic equations describing the flows from one class to another are of the general form[26,27]

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

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

$$\frac{\partial H(a,t)}{\partial t} + \frac{\partial H(a,t)}{\partial a} = \lambda(a,t)\,X(a,t) - [\mu(a)+\sigma]H(a,t) \qquad (1)$$

$$\frac{\partial Y(a,t)}{\partial t} + \frac{\partial Y(a,t)}{\partial a} = \sigma H(a,t) - [\mu(a)+\gamma]Y(a,t)$$

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

$$\frac{\partial N(a,t)}{\partial t} + \frac{\partial N(a,t)}{\partial a} = -\mu(a)\,N(a,t)$$

Here $\mu(a)$ denotes age-related human mortality, $1/\phi$ is the average duration of protection provided by maternal antibodies, $1/\sigma$ and $1/\gamma$ are the average incubation and infectious periods respectively, and $\psi(a,t)$ records the age- and time-specific vaccination schedule. Mortality explicitly associated with the

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Measles in England and Wales—I: An Analysis of Factors Underlying Seasonal Patterns

PAUL E M FINE* and JACQUELINE A CLARKSON*

Fine P E M [Ross Institute, London School of Hygiene and Tropical Medicine, Keppel Steet, London WC1E 7HT, United Kingdom] and Clarkson J A. Measles in England and Wales—I: An analysis of factors underlying seasonal patterns. *International Journal of Epid...*

Examination of weekly measles notifi... of major and minor epidemics before ... cycle of minor epidemics. Each year ... close to the opening of primary scho... underlying transmission parameter h... transmission parameter rises three ti... term and mid-term holidays. This pa... national vaccination began, indicatin... changed. The analysis further sugges... number of individuals susceptible to ...

Measles has long been a favourite ... logists. Its high incidence, worldw... clinical severity have merited its ... more important public health pro... and easily recognized clinical pic... wide availability of good data. Th... and deployment of measles vaccine ... urgency to studies of its epidemi... sense, the regularity of its clini... dramatic pattern of its recurrent e... measles a prototype for studies of t... infection. Indeed, it is probable that ... measles by Panum,[1] Hamer,[2] Hope ... contributed more to our understa... tagious processes than have any o... on any other disease.

The regular recurrence of epi... vaccinated populations is one of ... epidemiological features of measl... tend to occur in winter and sprin... appear to oscillate between temper... south of the equator. Though a ... incidence may occur yearly, there ... for large epidemics to occur at ... intervals in many populations of

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Measles in England and Wales—II: The Impact of the Measles Vaccination Programme on the Distribution of Immunity in the Population

PAUL E M FINE* and JACQUELINE A CLARKSON*

Fine P E M [Ross Institute, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom] and Clarkson J A. Measles in England and Wales—II: The impact of the Measles Vaccination Programme on the distribution of immunity in the population. *International Journal of Epidemiology* 1982, 11: 15–25.

Measles notification and va... dence and immunity levels ... nation experience is descri... of measles, and towards y... immunization programme ... complicated shift in the age ... now better protected, but s... trends are discussed with c... concluded that the number ... public health implications ... measles has remained rela... gramme. Though consisten... not been demonstrated be... measles control, it is impor... the findings.

Though vaccination of in... simple preventive measure... grammes are interventio... logical systems and the o... far from simple.

Most routine childhood ... at disease control—the re... level of public health imp... elimination. The obvious ... programmes of recent ye... eradication efforts in the ... The strategy of control is ... children by immunizing th... natural infection in the co... with such control policie... siderable proportion of ch... tection and enter the popul... be infected by, and in turn

* Ross Institute, London School ... Keppel Street, London WC1E 7H...

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Measles in England and Wales—III: Assessing Published Predictions of the Impact of Vaccination on Incidence

PAUL E M FINE and JACQUELINE A CLARKSON

Fine P E M (Ross Institute, London School of Hygiene and Tropical Medicine, London WC1E 7HT, UK) and Clarkson J A. Measles in England and Wales—III: Assessing published predictions of the impact of vaccination on incidence. *International Journal of Epidemiology* 1983, 12: 332–339.

Published predictions of the impact which different levels of vaccination should save on measles incidence are discussed in the context of observed data on vaccine uptake and measles incidence in England and Wales. Discrepancies are noted between prediction and observation with regard to the effect of vaccination on epidemic periodicity, epidemic size, age distribution of cases, and the disappearance of measles from communities. These errors are attributable to failures to recognize the implications of seasonal trends in incidence, age dependence of risk, and the non-homogeneity of human populations. Predictive models are useful hypotheses, but should be assessed critically against observation.

Over the past 20 years, many countries have introduced measles vaccine into their national childhood vaccination programmes. With the exception of the United States,[1] Canada[2] and Sweden,[3] all of which have openly declared an intent to eliminate measles virus transmission within their borders, the goals of these national measles vaccination programmes have been vaguely defined as efforts in measles control—attempts to reduce morbidity, mortality and economic losses attributable to measles. One reason for a reticence to stipulate precise goals for such programmes has been an uncertainty as to the relationship between different vaccination policies and the level of control achieved.

Insofar as a vaccination programme is liable to affect several aspects of incidence (ie its magnitude, age distribution and periodic epidemic pattern) prediction of the precise impact of any vaccination policy is a complicated problem. We might, however, reduce it to a simple diagrammatic relationship as shown in Figure 1. On the horizontal axis is an idealized measure of 'vaccine uptake', defined as the proportion of infants born into a population who are *effectively* vaccinated (ie immunized). The vertical axis presents the total expected cumulative incidence rate among all these children over time, eg the proportion expected to contract measles by age 15. The solid line D represents the conservative assumption that vaccine protects only recipient children, and that 95% of unimmunized children contract measles before age 15. Under this assumption the vaccine has no indirect effect of protecting unvaccinated children. We have reason to believe that the actual relationship should be rather different from this. Given that measles transmission requires contact with an infectious case, it is to

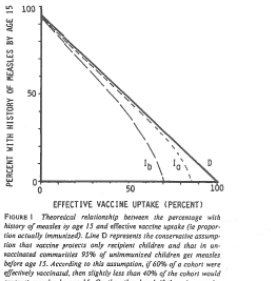

FIGURE 1 *Theoretical relationship between the percentage with history of measles by age 15 and effective vaccine uptake (ie proportion actually immunized). Line D represents the conservative assumption that vaccine protects only recipient children and that in unvaccinated communities 95% of unimmunized children get measles before age 15. According to this assumption, if 60% of a cohort were effectively vaccinated, then slightly less than 40% of the cohort would contract measles by age 15. On the other hand, if there is some indirect protection, and if transmission can be broken by reducing the number susceptible to below a critical population size, then lines I_0 and I_D show predicted relationships for large and/or dense populations (I_0) and for small or less dense populations (I_D).*

be expected that as the proportion immunized in the population increases, so does the probability that some individuals will escape ever meeting an infectious case. The distance of the actual line below D represents this indirect effect of vaccination — the protection of some unimmunized children by the presence of vaccinated peers.

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An obvious prediction …

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Measles in England and Wales—III: Assessing Published Predictions of the Impact of Vaccination on Incidence

PAUL E M FINE and JACQUELINE A CLARKSON

Fine P E M (Ross Institute, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK) and Clarkson J A. Measles in England and Wales—III: Assessing published predictions of the impact of vaccination on incidence. *International Journal of Epidemiology* 1983, **12**: 332–339.

Published predictions of the impact which different levels of vaccination should have on measles incidence are discussed in the context of observed data on vaccine uptake and measles incidence in England and Wales. Discrepancies are noted between prediction and observation with regard to the effect of vaccination on epidemic periodicity, epidemic size, age distribution of cases, and the disappearance of measles from communities. These errors are attributable to failures to recognize the implications of seasonal trends in incidence, age dependence of risk, and the non-homogeneity of human populations. Predictive models are useful hypotheses, but should be assessed critically against observation.

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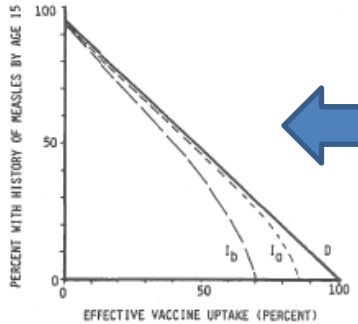

FIGURE 1 *Theoretical relationship between the percentage with history of measles by age 15 and effective vaccine uptake (ie proportion actually immunized). Line D represents the conservative assumption that vaccine protects only recipient children and that in unvaccinated communities 95% of unimmunized children get measles before age 15. According to this assumption, if 60% of a cohort were effectively vaccinated, then slightly less than 40% of the cohort would contract measles by age 15. On the other hand, if there is some indirect protection, and if transmission can be broken by reducing the number susceptible to below a critical population size, then lines Ia and Ib show predicted relationships for large and/or dense populations (Ia) and for small or less dense population (Ib).*

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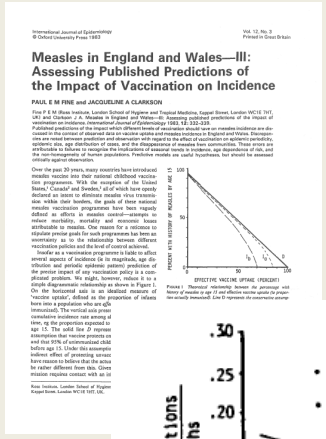
The greater the indirect protection the lower the risk (cumulative incidence) with increasing vaccine coverage

An interesting observation …



Measles in England and Wales—III: Assessing Published Predictions of the Impact of Vaccination on Incidence

PAUL E M FINE and JACQUELINE A CLARKSON

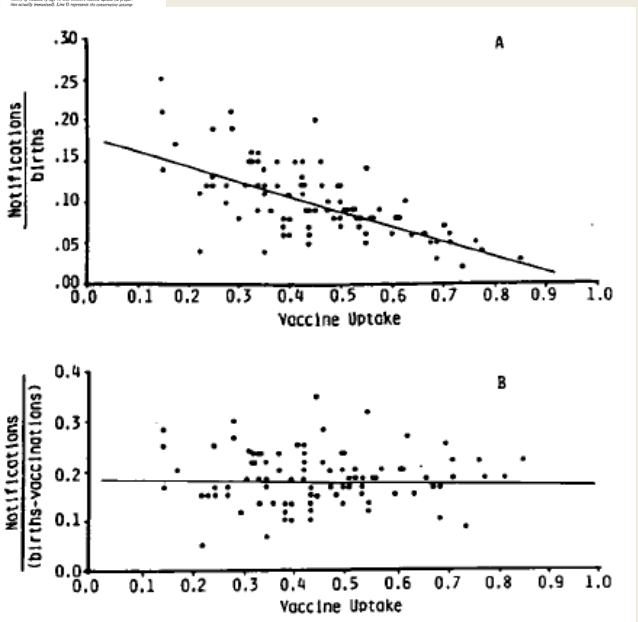


FIGURE 4 *(a) Measles incidence rate (sum of notifications in the 1974 cohort from 1974–9/births in 1974) versus measles vaccine uptake rate (proportion of children born in 1974 who were vaccinated by the end of 1976) for Area Health Authorities (AHAs) in England.*

(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.

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

But:

No apparent decline in "risk" among non-vaccinees

? !

An interesting correspondence

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Measles in England and Wales—III: Assessing Published Predictions of the Impact of Vaccination on Incidence

PAUL E M FINE and JACQUELINE A CLARKSON

Fine P E M (Ross Institute, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK) and Clarkson J A. Measles in England and Wales—III: Assessing published predictions of the impact of vaccination on incidence. *International Journal of Epidemiology* 1983; 12: 322–329.

Published predictions of the impact which different levels of vaccination should have on measles incidence are discussed in relation to observations in England and Wales. It is concluded that the major discrepancies which exist between these predictions and observation with regard to the effect of vaccination on epidemic periodicity, epidemic size, age distribution of cases, and the disappearance of measles from communities. These errors are due to the failure of models to incorporate the kinds of seasonal trends in incidence, age dependence of risk, and the non-homogeneity of human populations. Predictive models are useful hypotheses, but should be assessed critically against observation.

Over the past 30 years, many countries have introduced measles vaccine into their national childhood vaccination programmes. With the exception of the United States,[1] Canada[2] and Sweden,[3] all of which have openly declared an intent to eliminate measles virus transmission within their borders, the goals of these national measles vaccination programmes have been vaguely defined as efforts in measles control—attempts to reduce morbidity, mortality and economic losses attributable to measles. One reason for a reticence to stipulate precise goals for such programmes has been an uncertainty as to the relationship between different levels of vaccination and the impact on incidence.

Insofar as a vaccination programme is liable to affect several aspects of incidence (ie its magnitude, age distribution and periodic epidemic pattern) prediction of the precise impact of any vaccination policy is a complicated problem. We might, however, reduce it to a simple diagrammatic relationship as shown in Figure 1. On the horizontal axis is an idealized measure of "vaccine uptake", defined as the proportion of infants born into a population who are q[illegible] immunized). The vertical axis presents a measure of incidence, for example, the proportion expected to [illegible] age 15. The solid line D represents [illegible] assumption that vaccine protects only [illegible] and that 95% of unimmunized children [illegible] before age 15. Under this assumption [illegible] indirect effect of protecting unvaccinated [illegible] have reason to believe that the actual [illegible] be rather different from this. Given [illegible] measles contact with an [illegible]

Ross Institute, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK.

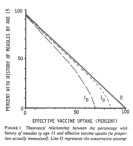


FIGURE 1 *Theoretical relationship between the percentage with history of measles at age 15 and effective vaccine uptake (in proportion actually immunized). Line D represents the conservative assumption*

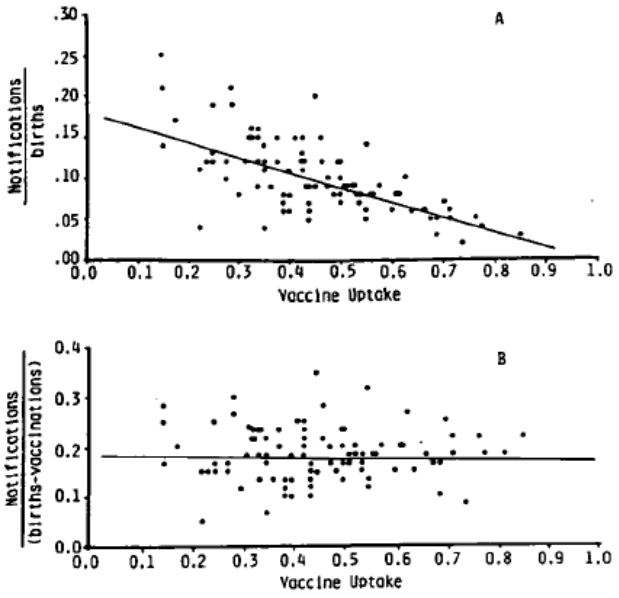
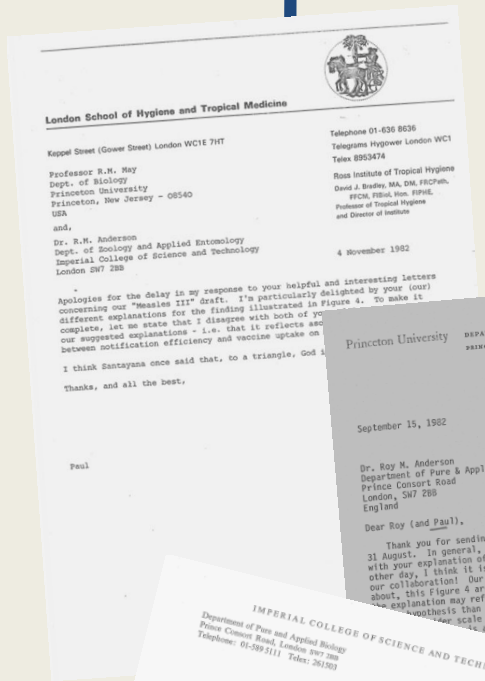


FIGURE 4 *(a) Measles incidence rate (sum of notifications in the 1974 cohort from 1974–9/births in 1974) versus measles vaccine uptake rate (proportion of children born in 1974 who were vaccinated by the end of 1976) for Area Health Authorities (AHAs) in England.*

(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.



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Ross Institute of Tropical Hygiene
David J. Bradley, MA, DM, FRCPath, FFCM, FIBiol, Hon. FIPHE.
Professor of Tropical Hygiene and Director of Institute

and,

Dr. R.M. Anderson
Dept. of Zoology and Applied Entomology
Imperial College of Science and Technology
London SW7 2BB

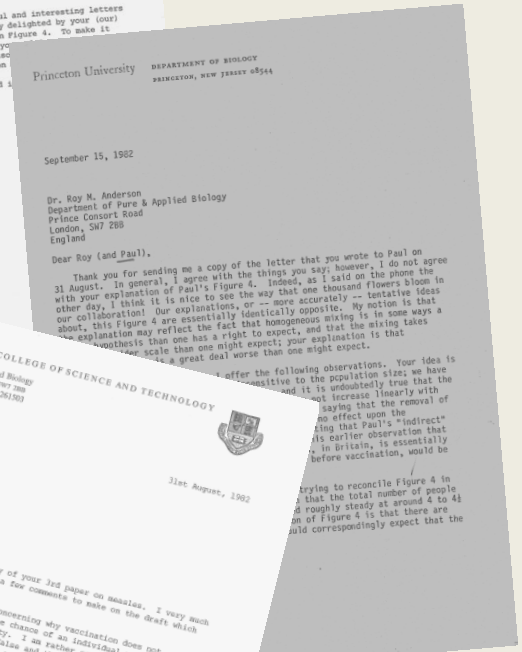
4 November 1982

Apologies for the delay in my response to your helpful and interesting letters concerning our "Measles III" draft. I'm particularly delighted by your (our) different explanations for the finding illustrated in Figure 4. To make it complete, let me state that I disagree with both of yo[illegible] complete, let me state that it reflects ass[illegible] our suggested explanations - i.e. that it reflects [illegible] between notification efficiency and vaccine uptake on [illegible]

I think Santayana once said that, to a triangle, God i[illegible]

Thanks, and all the best,

Paul



Princeton University DEPARTMENT OF BIOLOGY PRINCETON, NEW JERSEY 08544

September 15, 1982

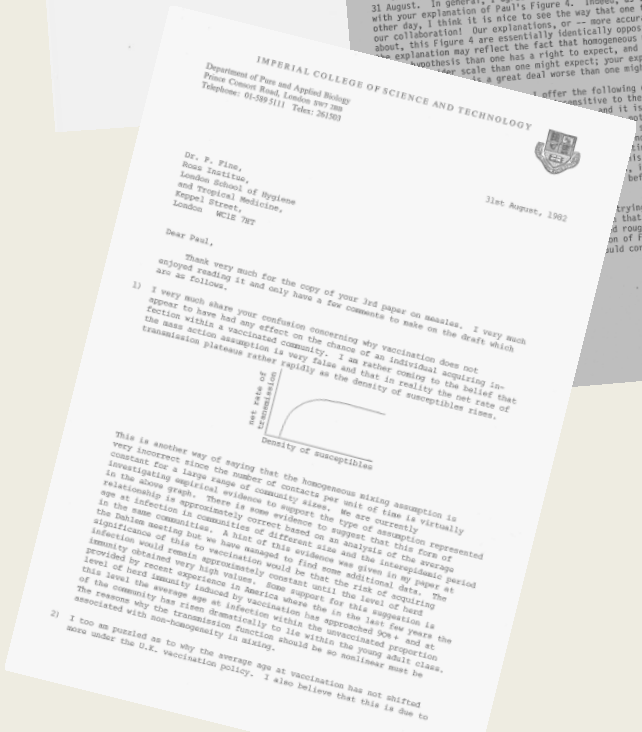
Dr. Roy M. Anderson
Department of Pure & Applied Biology
Prince Consort Road
London, SW7 2BB
England

Dear Roy (and Paul),

Thank you for sending me a copy of the letter that you wrote to Paul on 31 August. In general, I agree with the things you say; however, I do not agree with your explanation of Paul's Figure 4. Indeed, as I said on the phone the other day, I think it is nice to see the way that one thousand flowers bloom in our collaboration! Our explanations, or -- more accurately -- tentative ideas about, this Figure 4 are essentially identically opposite. My motion is that our explanation may reflect the fact that homogeneous mixing is in some ways a [illegible]othesis than one has a right to expect, and that the mixing takes [illegible]ear scale than one might expect; your explanation is that [illegible]s a great deal worse than one might expect.

[illegible]offer the following observations. Your idea is [illegible]nsitive to the population size; we have [illegible]nd it is undoubtedly true that the [illegible]ct increase linearly with [illegible]saying that the removal of [illegible]o effect upon the [illegible]ting that Paul's "indirect" [illegible]is earlier observation that [illegible], in Britain, is essentially [illegible]before vaccination, would be

[illegible]trying to reconcile Figure 4 in [illegible] that the total number of people [illegible]s roughly steady at around 4 to 4½ [illegible]n of Figure 4 is that there are [illegible]uld correspondingly expect that the



IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY

Department of Pure and Applied Biology
Prince Consort Road, London SW7 2BB
Telephone: 01-589 5111 Telex: 261503

Dr. P. Fine,
Ross Institute,
London School of Hygiene
and Tropical Medicine,
Keppel Street,
London WC1E 7HT

31st August, 1982

Dear Paul,

Thank very much for the copy of your 3rd paper on measles. I very much enjoyed reading it and only have a few comments to make on the draft which are as follows.

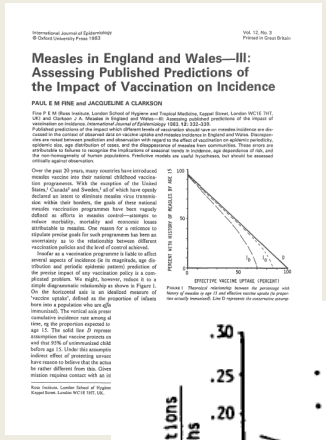
1) I very much share your confusion concerning why vaccination does not appear to have had any effect on the chance of an individual acquiring infection within a vaccinated community. I am rather coming to the belief that the mass action assumption is very false and that in reality the net rate of transmission plateaus rather rapidly as the density of susceptibles rises.

This is another way of saying that the homogeneous mixing assumption is very incorrect since the number of contacts per unit of time is virtually constant for a large range of community sizes. We are currently virtually investigating empirical evidence to support the type of assumption represented in the above graph. There is some evidence to support this assumption in the same communities. A list of different aims and analysis of the form of relationship is given in my paper at the Dahlem meeting but we have managed to find some additional data. The age at infection is approximately constant until the risk of acquiring infection would remain approximately constant over the interepidemic period provided by recent experience in America where the in the last few years the immunity obtained very high values. Some support for this level of herd level of herd immunity induced by vaccination within the unvaccinated proportion of the community has risen dramatically within the unvaccinated proportion of the community has risen dramatically within the young adult class. The reasons why the transmission function should be so nonlinear must be associated with non-homogeneity in mixing.

2) I too am puzzled as to why the average age at vaccination has not shifted more under the U.K. vaccination policy. I also believe that this is due to

An interesting correspondence

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."



Measles in England and Wales—III: Assessing Published Predictions of the Impact of Vaccination on Incidence

PAUL E M FINE and JACQUELINE A CLARKSON

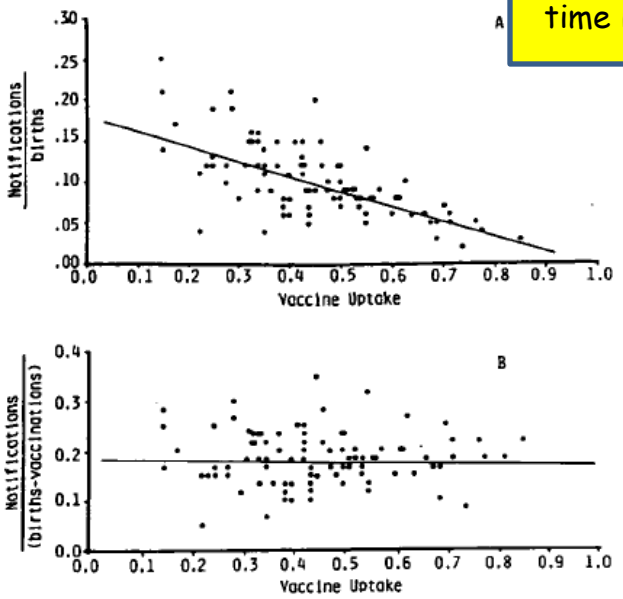


FIGURE 4 *(a) Measles incidence rate (sum of notifications in the 1974 cohort from 1974–9/births in 1974) versus measles vaccine uptake rate (proportion of children born in 1974 who were vaccinated by the end of 1976) for Area Health Authorities (AHAs) in England.*

(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.

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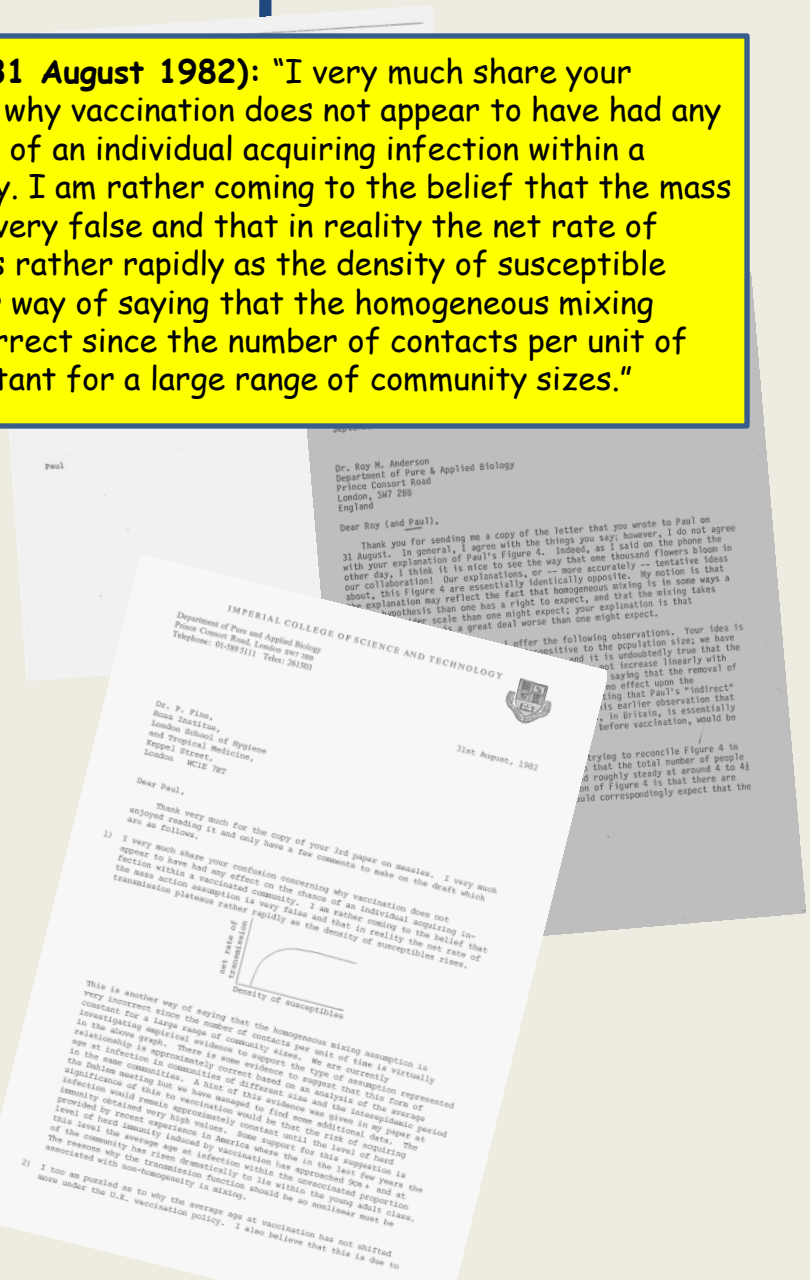

Dr. Roy M. Anderson
Department of Pure & Applied Biology
Prince Consort Road
London, SW7 2BB
England

Dear Roy (and Paul),

Thank you for sending me a copy of the letter that you wrote to Paul on 31 August. In general, I agree with the things you say; however, I do not agree with your explanation of Paul's Figure 4. Indeed, as I said on the phone the other day, I think it is nice to see the way that one thousand flowers bloom in our collaboration! Our explanations, or -- more accurately -- tentative ideas about, this Figure 4 are essentially identically opposite. My notion is that explanation may reflect the fact that homogeneous mixing is in some ways a [illegible] hypothesis than one has a right to expect, and that the mixing takes [illegible] scale than one might expect; your explanation is that [illegible] a great deal worse than one might expect.

IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY

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Telephone: 01-589 5111 Telex: 261503

31st August, 1982

Dr. P. Fine,
Ross Institute,
London School of Hygiene
and Tropical Medicine,
Keppel Street,
London WC1E 7HT

Dear Paul,

Thank very much for the copy of your 3rd paper on measles. I very much enjoyed reading it and only have a few comments to make on the draft which are as follows.

1) 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 susceptibles rises.

This is another way of saying that the homogeneous mixing assumption is very incorrect since the number of contacts per unit of time is virtually constant for a large range of community sizes. We are currently investigating empirical evidence to support the type of assumption represented in the above graph. There is some evidence to support this form of relationship is. There is some evidence that the interepidemic period age at infection approximately constant but the risk of acquiring infection would remain approximately constant until the level of herd immunity obtained very high values. Some support for this assumption is provided by recent experience in America where the in the last few years the significant decline in [illegible] has approached 50% and at the community has risen dramatically within the unvaccinated proportion level of herd immunity induced by vaccination has approached 50% + and at this level the average age at infection has increased by a factor of 2 or 3. The reasons why the transmission function should be so nonlinear must be associated with non-homogeneity in mixing.

2) I too am puzzled as to why the average age at vaccination has not shifted more under the U.K. vaccination policy. I also believe that this is due to

An interesting correspondence

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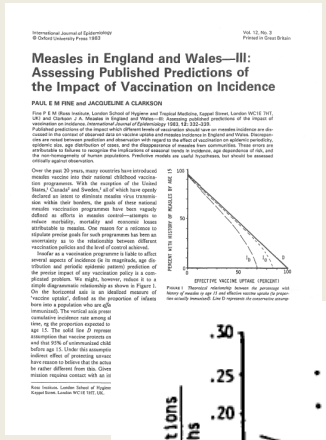


Measles in England and Wales—III: Assessing Published Predictions of the Impact of Vaccination on Incidence

PAUL E M FINE and JACQUELINE A CLARKSON

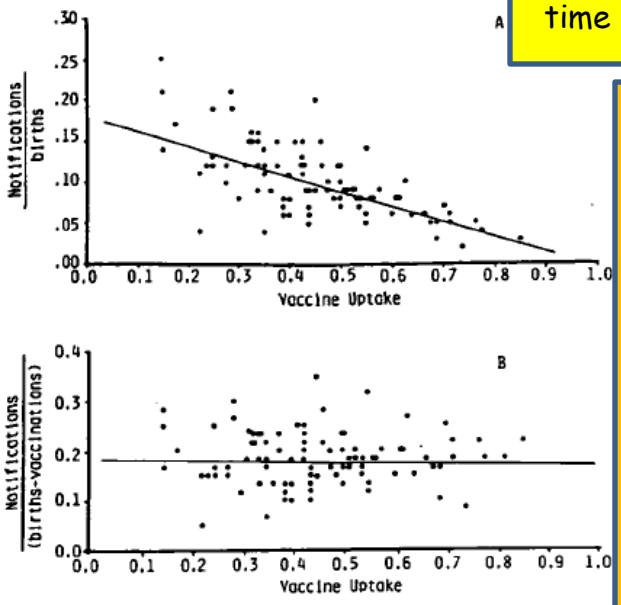
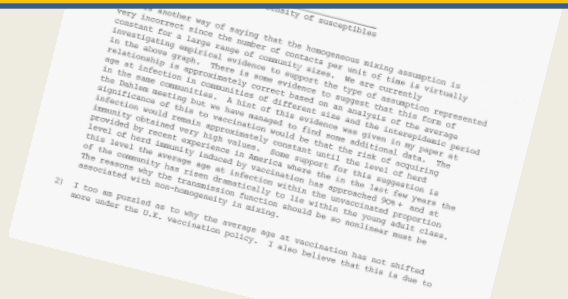


FIGURE 4 *(a) Measles incidence rate (sum of notifications in the 1974 cohort from 1974–9/births in 1974) versus measles vaccine uptake rate (proportion of children born in 1974 who were vaccinated by the end of 1976) for Area Health Authorities (AHAs) in England.*

(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.



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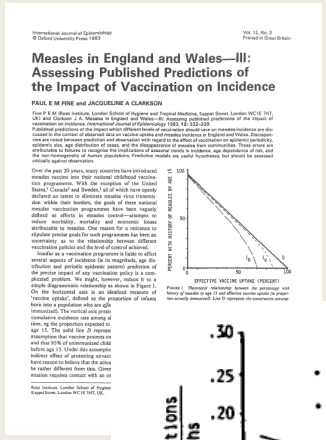

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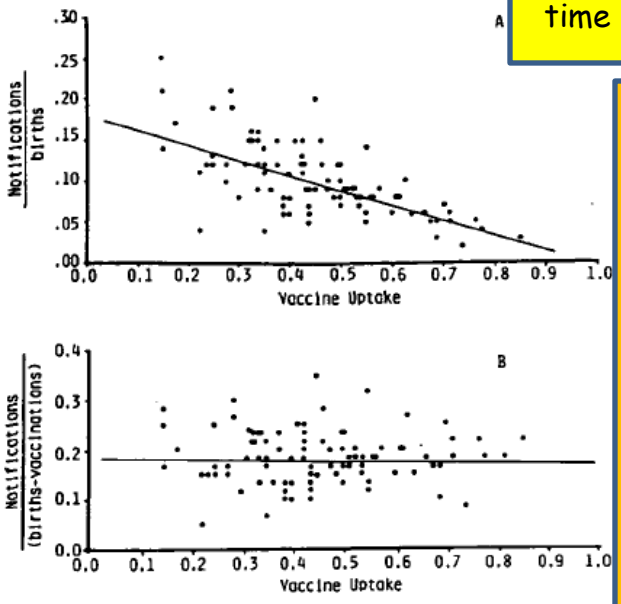

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Paul wrote to both (04/11/82): "I'm particularly delighted by your (our) different explanations for the finding illustrated in Figure 4. To make it complete, let me say that I disagree with both of you and favour the first of our suggested explanations – 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 ….

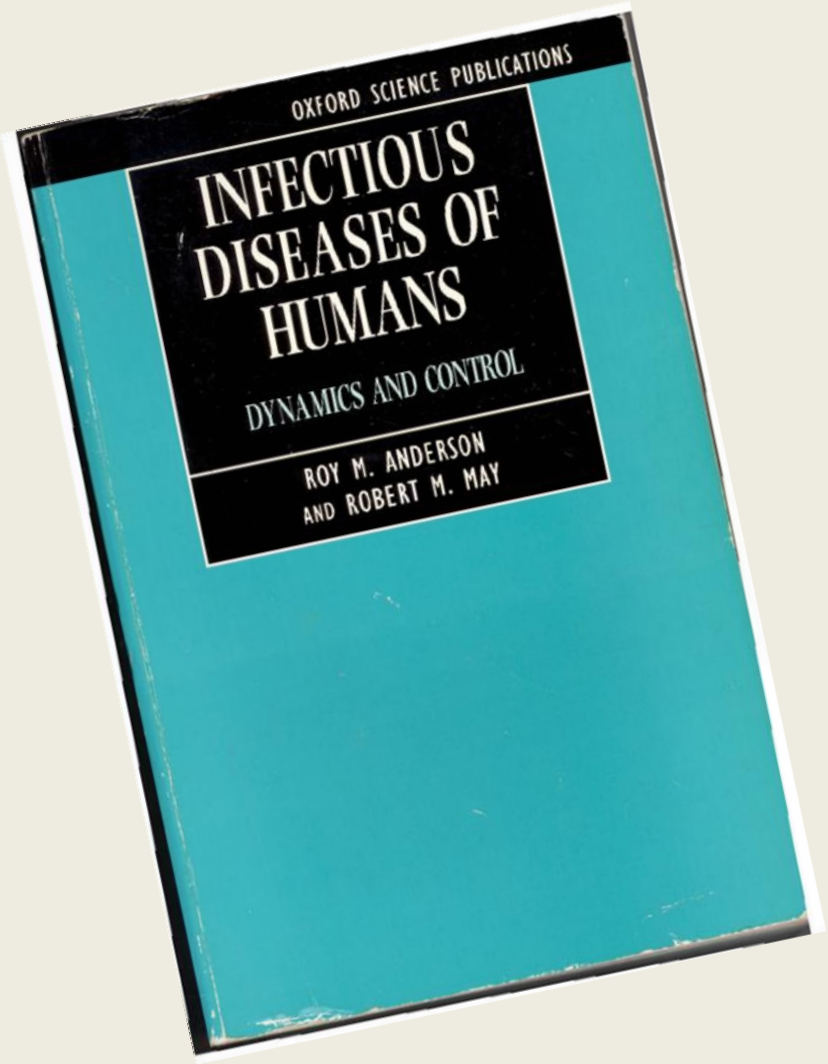
in particular with analytic methods for dealing with heterogeneity by age, and estimation of "R_0" from age structured data

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

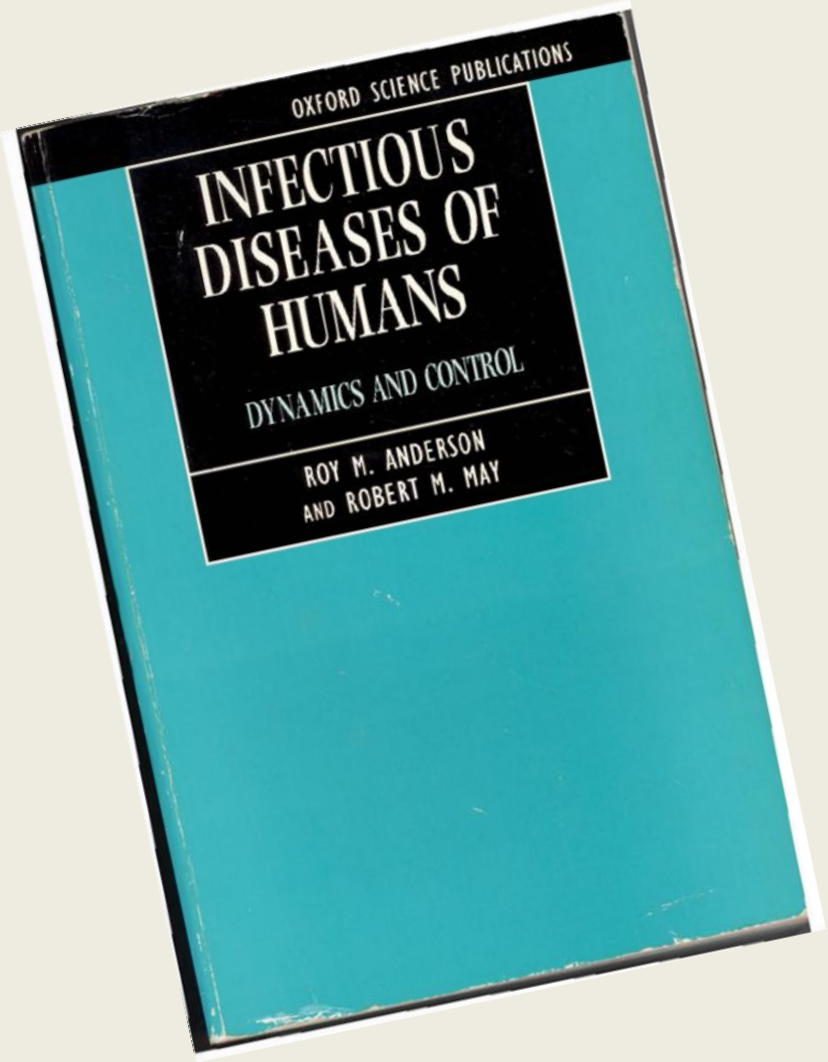
and, independently….

the decision to eradicate polio (1988)

An extraordinary milestone (1991)



An extraordinary milestone (1991) of an analytic approach



Observation:

750 pages, > 700 references,

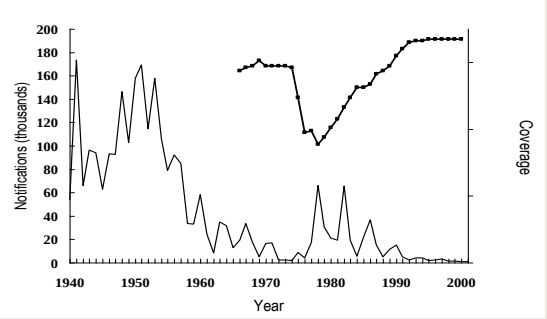
but **no** mention of:

Frost, Reed, Fox,
Kemper or Longini

(or their modelling !)

Some complications emerged

- Age shifts
  - rubella (George Knox, 1980)
- Freeloaders…
  - pertussis (UK 1974 et seq)



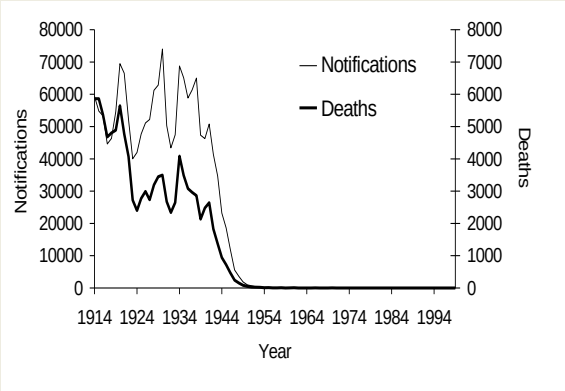
- Indirect protection isn't immunity
  - long term responsibility implications
- Ethics of vaccinating some to protect others …
  - school children in Japan ('flu)
  - transmission blocking (malaria)

Herd immunity in the 21st Century

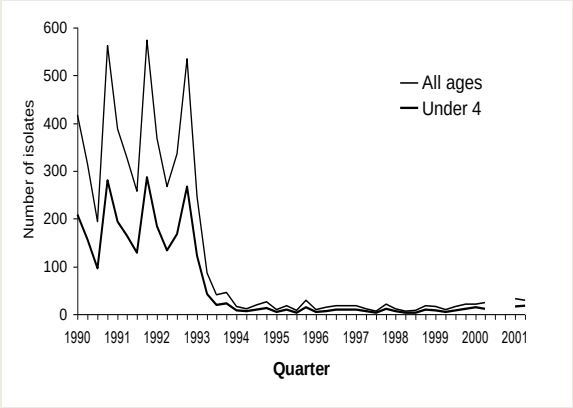
- **Observations**
  - powerful indirect effects eg of HiB, PCV…
- **Eradication programme experience**
  - it's a lot more complicated than $(1 - R_0) / R_0$
- **Complex modelling**
  - Fox et al 1971's approach on big computers
- **Direct measurement of indirect protection**
  - a new paradigm

Observations of herd effects ….

Diphtheria, UK



Haemophilus, UK



Influenza, Japan

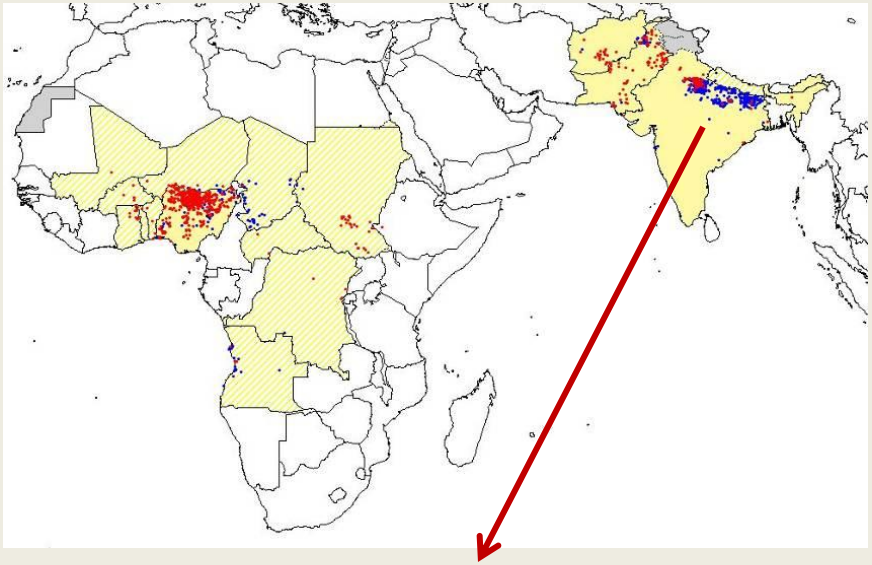
'Flu vaccination of schoolchildren estimated to have prevented 1 adult death for every 420 vaccinations

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

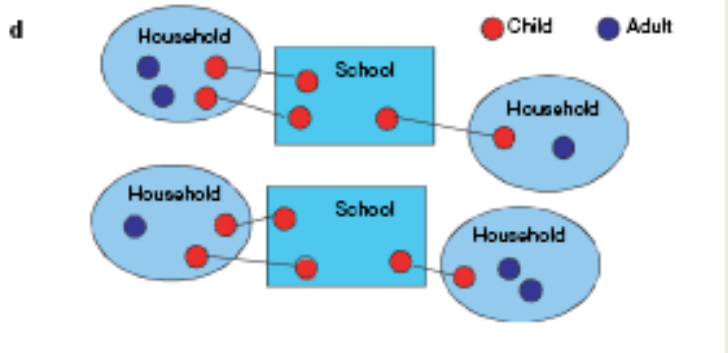
What's the nature, proportion and distribution of "immunity " ?

Return of the Fox *et al* approach

Estimating the impact of school closure on influenza transmission from Sentinel data

Simon Cauchemez[1], Alain-Jacques Valleron[2,3,4], Pierre-Yves Boëlle[2,3,4], Antoine Flahault[2,3,5] & Neil M. Ferguson[1]

(Nature, 2008)

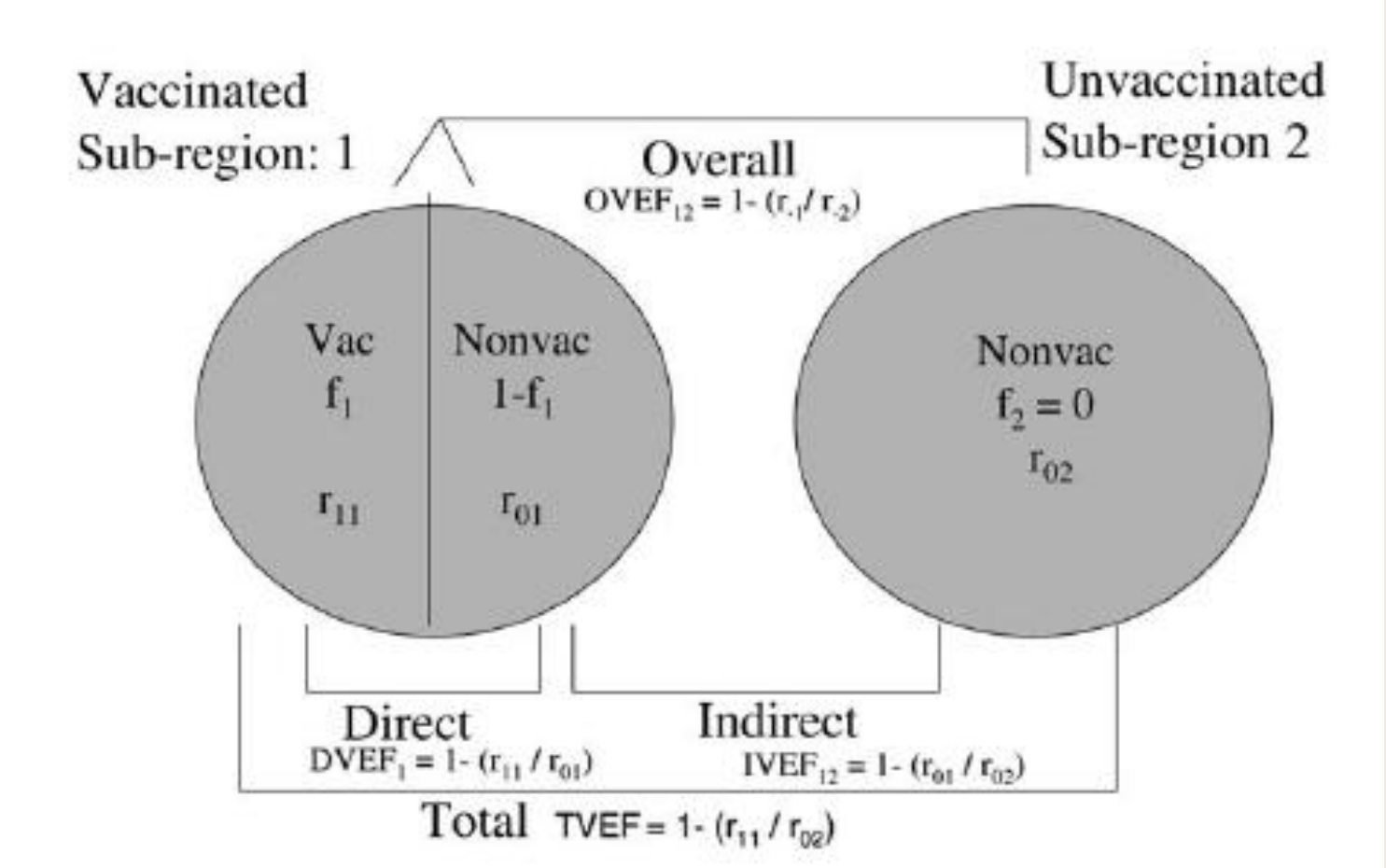


"We model the spread of influenza in a population structured into households and schools…."

NB – the transmission parameter estimates refer back to Longini et al …..

Direct measurement of indirect protection:

Halloginigram analysis:



(Longini et al. PLoS 2007)

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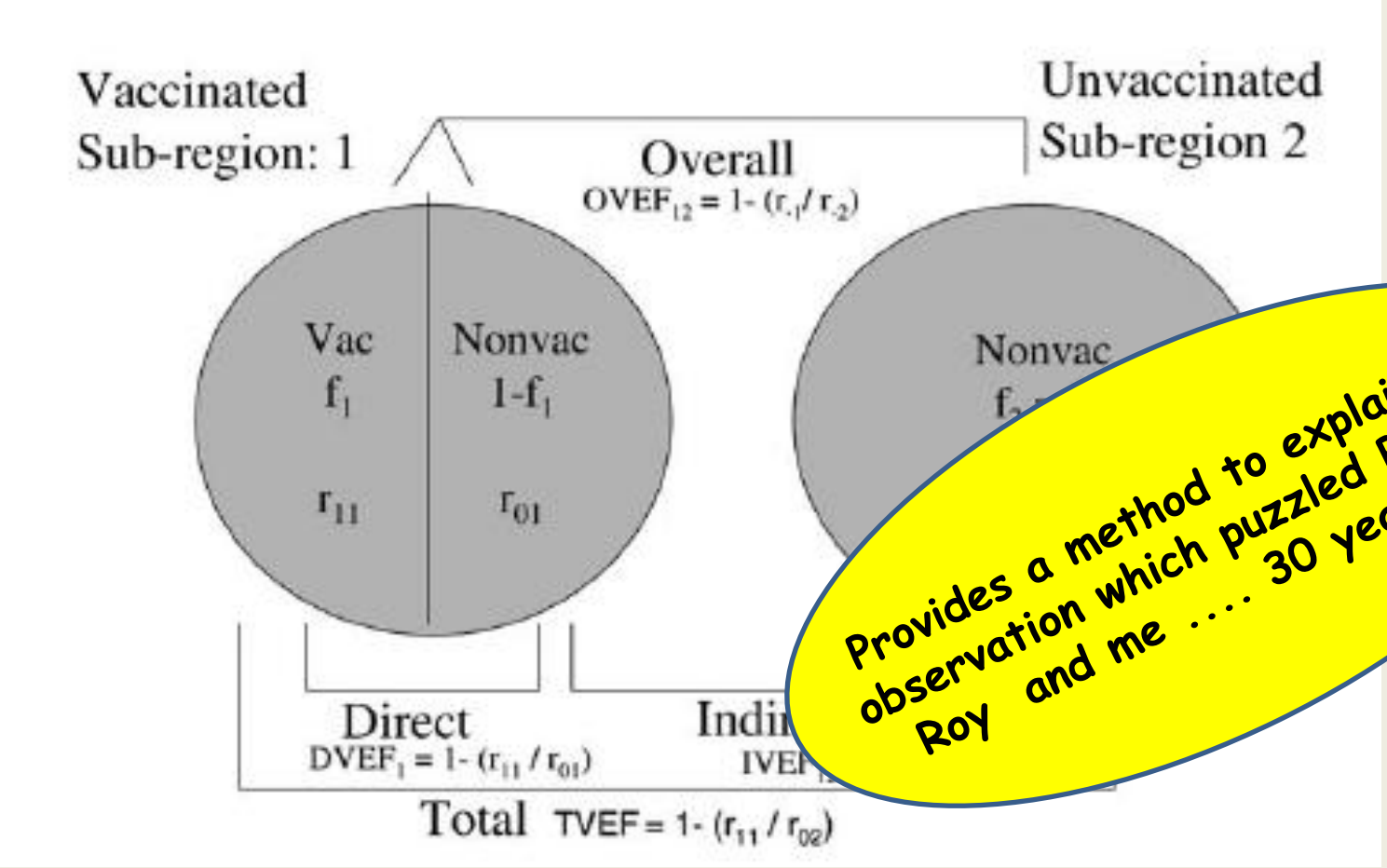

Provides a method to explain the observation which puzzled Bob and Roy and me .... 30 years ago

(Longini et al. PLoS 2007)

Conclusion

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