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CHAPTER 16

HERD IMMUNITY - CHANGING CONCEPTS

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In 1971, we discussed herd immunity and its relevance to immunization practices (1), using applications of the Reed-Frost epidemic model (2), and of a stochastic simulation model for a community of families (3) to illustrate the basic concepts. This presentation draws heavily on our previous discussion* but also will consider how these concepts of herd immunity relate to some important current immunization problems.

Herd immunity is an integral part of epidemic theory, as it applies to agents which spread by relatively direct means from host to host and induce significant post-infection immunity. Epidemics arise when such agents are introduced into populations containing susceptible individuals, who make sufficient contact with one another to permit transfer of infection from each newly infected host (new case) to, on the average, more than one susceptible host. The epidemic curve declines when, on the average, each new case infects less than one susceptible and the outbreak terminates as the proba-

*Tables 1 and 2, and related portions of the text, are abbreviated versions of material contained in (1) and are reproduced here with permission of the American Journal of Epidemiology.

bility of transmission from a new case approaches zero, typically well before the supply of susceptibles has been exhausted. In real life, the reasons for decline of transmission and termination of outbreaks are multiple and include seasonal changes in environmental factors (humidity and temperature) affecting agent viability outside the host and in host behavior (outdoor play versus indoor school) influencing the opportunity for effective contact between children, as well as progressive replacement of susceptibles with immunes which generates the "herd immunity" effect.

Popular understanding of herd immunity is essentially as described in a medical dictionary (4): herd immunity is "the resistance of a group to attack by a disease to which a large proportion of the members are immune, thus lessening the likelihood of a patient with a disease coming into contact with a susceptible individual". This definition implies that, if a large enough proportion of the population is immune, the agent can not be transmitted and the remaining susceptibles will be protected. In this light, the logical next question, for diseases preventable by vaccines is, "What proportion of the population must be immune to prevent an epidemic?" Both the question and the dictionary definition reflect incomplete understanding of the factors influencing the operation of herd immunity.

Most important is the failure to realize that the foregoing definition requires truly random mixing such as can be assumed only in a few small closed populations and which never occurs in open populations. Rather, as Bailey (5) notes, in describing epidemics in large populations: "We could hardly assume even a small town to be a single homogeneous mixing unit. Each individual is normally in close contact with only a small number of individuals, perhaps the order of 10 to 50. The observed figures are therefore pooled data for several epidemics occurring simultaneously in small groups of associates. In reality, such groups overlap and interact." Also, in a review of epidemic theory (6),Serfling traces back to 1906 recognition that "the progress of epidemics is regulated by the number of susceptibles and the rate of contact between infectious cases and susceptibles."

Illustrative Models

Borrowing from our previous discussion (1), two relatively simple models will identify and illustrate factors which favor or restrict spread of infection in populations containing many immunes. These will recognize (with Bailey) that

open populations consist of numerous definable but often interlocking subgroups differing in proportion of immunes and intimacy of contact, and show how variations in these population characteristics may affect (as put by Serfling) "the rate of contact between infectious cases and susceptibles" and so determine the occurrence of epidemic spread. In both models, we will deal exclusively with agents restricted to man and spread only by person-to-person contact. For simplicity, we also will assume that individuals are either susceptible or fully immune, that immunity is durable, and that the period of infectiousness is both short and relatively constant. Also, we will ignore possible withdrawal of infective cases from circulation because of illness, since, for many agents, infections are often silent or give rise to only mild disease or, as in measles, maximum infectivity preceeds illness onset. Because study of herd immunity focusses on spread of infection without regard to resulting illness, the word "case" throughout will refer to a person infectious for others (an infective). We will look first at a randomly mixing population in order to develop certain necessary tools and then move on to consider a more typical and complex population, made up of multiple and overlapping mixing groups.

The Reed-Frost Model: Truly random mixing requires that, within any time interval, the probability of contact is the same for every choice of two members of the population. A useful, simple and long familiar epidemic model for such a population is that of Reed and Frost (2). This employs discrete equal time intervals (days or weeks) which, for our purposes, will be taken as equal to the length of the period of infectivity. Thus, a person acquiring infection in the interval from t to t+1 (the first week) becomes a case and is infectious from t+1 to t+2 (the second week) and becomes immune at t+2 (beginning of the third week). The population (size N) is made up at time t of S_t (susceptibles) plus c_t (cases where, by convention, $c_0 = 1$) plus I_t (immunes). For purposes of this model, "adequate contact" is defined as that sufficient for transfer of infection from a case to a susceptible person. The contact rate, p, is the probability that any two persons in the population will make adequate contact during any interval. Thus, the contact rate summarizes both the infectivity of the agent and the relevant behavior of the population.

During any interval, the expected number of contacts for any person in the population, m, is the product of the contact rate, p, and the number of potential contacts, i.e., N (the total population) minus one. Expressed mathematically,

$m = p(N - 1)$. These contacts will be distributed between cases, susceptibles, and immunes in the proportions which each represent in the population during a given interval suc as time t to t+1. Also during this interval:
(1) The probability that a given susceptible will escape con tact with a particular case is $q = 1 - p$;
(2) The probability that he will escape contact with all c_t cases is q^{c_t}; and
(3) The probability that he will become infected (fail to escape contact with all c_t cases) is $1 - q^{c_t}$.

At the end of this interval, time t+1, the expected number o new cases, c_{t+1}, is simply the number of susceptibles at tim t, S_t, times the probability that a given susceptible will become infected ($1 - q^{c_t}$), or, again mathematically, $c_{t+1} = S_t(1 - q^{c_t})$. By repeated application of this equation for $t = 0, 1, 2, 3, \ldots$, the "expected epidemic" can be com-puted.

A simple first example involves a play group of 11 child ren made up of one case and 10 susceptibles, and examines what happens when the group is expanded by adding five im-munes. The central point of interest is the probability tha no spread will occur in the first interval. This requires that the case will make no contact with a susceptible, the probability of which is $(1 - p)^S$. If we hold the contact rate at .2, the case should make two contacts (both with sus ceptibles) when N = 11 and three contacts (two with suscepti bles and one with an immune) when N is increased to 16. In both instances, the probability of no spread is small and un changed at .107. However, if we hold constant the average number of contacts, m, (in this case to two), the contact rate when N = 16 is lowered to .133, and, since the two con-tacts, on the average, will include on 1.33 with susceptible the probability of no spread increases to .239 and the epi-demic potential decreases.

In the second example, illustrated in Table 1, we applie the Reed-Frost model to larger populations to illustrate the consequences of variation in important population character-istics identified in the headings of columns 2 - 7 in the table. Each of the six possible pairs of these characteris-tics were held constant (identified in the table by under-lining) while allowing others to vary. In four instances (Sets 1, 2, 4, and 6) the two designated characteristics

serve to determine a third characteristic which also remained constant. For each pair or set, the epidemic potential (reflected in probability of no spread) was determined under differing situations reflecting changes in one or more of the other characteristics; for each situation, 100 epidemics were simulated on the computer. Table 1 presents selected results for two different situations for each set.

TABLE 1. Epidemic potential and median epidemic size under various conditions in a randomly mixing population when one case is introduced

Set No.	Pop. Size N	% Immune N-S/N	No. Susceptible S_o	Contact Rate p	Average No. Contacts per Person: Total pN	Average No. Contacts per Person: With Susceptibles pS_o	Probability of no spread (P_{NS}) $(1-p)^{S_o}$	Computer simulation of 100 epidemics[a]: No. with one case	Computer simulation of 100 epidemics[a]: Median Size
1	400	0	400[b]	.005	2	2	.14	14	315
	10,000	96	400	.005	50	2	.14	14	315
2	2,000	96	80	.020	40	1.6	.20	18	40
	10,000	96	400	.004	40	1.6	.20	17	244
3	2,000	96	80	.005	10	0.4	.67	64	1
	10,000	96	400	.005	50	2.0	.14	13	315
4	5,000	96	200	.005	25	1.0	.37	41	2
	5,000	96	200	.010	50	2.0	.14	12	157
5	1,000	60	400	.004	4	1.6	.20	17	244
	2,000	80	400	.002	4	0.8	.45	45	1
6	2,000	80	400	.005	10	2.0	.14	13	315
	2,000	96	80	.005	10	0.4	.67	64	1

[a] Simulation using stochastic properties of the Reed-Frost model

[b] Underlining indicates pair of characteristics held constant

The important relations demonstrated are:
(1) the probability of no spread (P_{NS}) depends entirely on the expected number of contacts by the case with susceptibles (pS_o) during the first interval; when pS_o is constant, so is P_{NS} (Sets 1 and 2); when pS_o increases, P_{NS} declines (Sets 3 and 4); and when pS_o falls, P_{NS} rises (Sets 5 and 6).
(2) Although P_{NS} is constant when pS_o also is unchanged, the median epidemic size increases with the number of susceptibles (Set 2).
(3) P_{NS} and median epidemic size change with proportion immune, contact rate and population size only when their change

causes change in average number of contacts with susceptibles (Sets 3-6) or in number of susceptibles (Sets 2, 3, and 6).

In summary, the foregoing examples demonstrate that the number of susceptibles and the rate of contact between them completely determine epidemic potential in randomly mixing populations. Unless these change, changes in population size and, therefore, in proportion immune do not affect the probability of spread.

A community mixing model: A real life, free-living population is that of a typical U.S. city. This is made up of neighborhoods differing in population density and in respect to many important characteristics including ethnic, cultural, economic, educational and occupational. Superimposed are school districts, health care facilities, shopping and recreational centers, public transport systems, employment groups, etc. The complex mixing structure suggested in the foregoing affords innumerable potential paths for the spread of contact-transmitted agents, the relative importance of which depends on intimacy of contact and availability of susceptibles.

For commonly prevalent agents, the most important stratification by immune status is that by age. The proportion immune increases with age and, for highly infectious agents, will approach unity at some point in life. Using measles as an example, this may be in early adulthood in developed countries or, in developing countries such as West Africa, very early in childhood. However, within any community there may be pockets of susceptibles either because they have escaped prior epidemics or because they have not accepted available immunization. The importance of such unvaccinated groups in the U.S.A. is highlighted by the continuing occurrence within them of small outbreaks of measles and poliomyelitis.

The relative importance of mixing groups varies not only with their content of susceptibles but also with the intimacy of contact. The basic unit, social and epidemiologic, is the family or household within which the contact rate is high with little regard to age. The potential importance of this unit increases with its size and, in some countries or cultures, the effective household may be quite large, being made up of several related families living in one compound.

The importance of neighborhood varies from one society to another. Between-family contacts generally are higher for households in the same neighborhood. They are determined by the play habits of the children and the social habits of the older members, e.g., the "coffee klatch", and neighborhood parties and picnics. Common vocational, recreational or other

interests (including possessing children of like ages) lead to development of clusters of families between which intimacy of contact exceeds that with other neighborhood families.

Schools provide links between families and clusters of families by bringing together specific age subgroups of children from different families and immediate neighborhoods within a broad area of residence. The school bus, increasingly important in urban as well as in suburban and rural areas, serves as a particularly effective exposure chamber for spread of respiratory agents. Because susceptibility to many infectious agents is common, especially among younger school children, schools constitute potentially important paths for community spread and, whether or not school is open, may be of major importance to epidemic occurrence, e.g., influenza.

Preschool children manifest two highly relevant characteristics which combine to maximize their potential and often underestimated role in supporting agent spread within a population. These are a high probability of susceptibility and behavior resulting in unusually intimate contact. They are vulnerable to infections brought home by other family members and are important as introducers of infection into the home by virtue of contacts largely,but not exclusively, with their age peers in play groups, day care centers or, as infants accompanying their mothers, even in the market place (a mechanism particularly important to the epidemic occurrence of measles in West Africa).

To illustrate how some of the foregoing considerations operate, we presented an example using a model for a community of families in which opportunities for contact between susceptibles depend on various types of social mixing groups. The Reed-Frost model applies here only to within-subgroup mixing (family, play group, nursery school, etc.) but provides the basic framework of terms and definitions. As shown in Table 2, the example deals with 100 susceptible children and one child whose position among families, play groups and a nursery school is summarized in a footnote to the table. The 101 children may be regarded as part of the larger community of families, the total size of which and proportion immune need not be specified here, since the probabilities for contact between the susceptibles are determined by their memberships in the several mixing groups, each characterized by the contact rate shown in the table.

Table 2 presents observations resulting from four series of 100 computer simulated epidemics. These represent progressively increasing opportunities for contact between susceptibles beginning with only the low level of total

Table 2. Distribution by size of 100 simulated epidemics among 100 susceptible children in a community of families, play groups, and a nursery school[a]

Mixing Group	Within-Group Contact Rate	No. of epidemics with indicated numbers of cases						No. of cases	
		1	2	3	4-9	10-39	40-79	Median	Maximum
Community	.002	82	15	2	1	-	-	1	4
Community Families	.002 .005	22	18	34	25	1	-	3	16
Community Families Play Groups	.002 .005 .100	11	6	26	46	2	-	4	33
Community Families Play Groups Nursery School	.002 .005 .100 .100	23	4	-	-	-	73	45	73

[a] The 100 susceptible children and the initial case were in 62 families with 1 to 3 children (mean 1.6) and in 24 play groups with up to 10 children (mean 4.2). The case was in a 3-child family and a 5-child play group and did not attend nursery school although his 2 siblings were among the 40 susceptibles who did attend.

community mixing and increasing step wise as within-family, within-play group, and within-nursery school contacts are allowed. The corresponding decrease in proportion of epidemics which abort with less than four cases and the increase in median and maximum numbers of cases demonstrate that, given a fixed number of susceptibles, the epidemic potential increases as increasing contact between susceptibles is permitted, whether or not the proportion immune remains constant.

The final series, which included contacts made in the nursery school, illustrates a further point of interest, namely the bimodality typically resulting from contact rates which permit large epidemics but are not high enough to insure them. In this instance, introduction of a single case was followed by negligible spread in 27 per cent of trials. However, when three or more persons became infected, as in the remaining 73 per cent of trials, the epidemic inevitably caught fire and continued to more than 40 cases. Stated more generally, given a fixed number of susceptibles and within a range of rates of contact between them, there is a threshold number of cases (in this instance, three) which, if reached, insures significant continuation of epidemics.

The "three or more" phenomenon suggests another rather self-evident factor which may influence epidemic potential. Our examples so far have assumed the introduction of a single infective case. In real life, two or more cases may well be introduced into a community at about the same time, e.g., students from one school following their basketball team when

it plays on the home court of a rival school team. Obviously, increasing the number of introductory cases correspondingly increases the likelihood that the epidemic threshold will be exceeded.

Behavior of Common Contagious Diseases

We suggested, at the outset, in a very general way how herd immunity may contribute to the termination of naturally occurring outbreaks. Let us look briefly at two larger aspects of the behavior of common contagious agents in large populations, namely seasonal and cyclic variations over time and differences in risk of infection between specified subgroups of such populations.

Using data for disease reported over periods of 30 to 35 years in New York City and Baltimore, London and Yorke(7) employed a mathematical model to explore the factors which determine that mumps and chickenpox occur in regular annual undamped outbreaks whereas measles, although similarly seasonal, manifests biennial peaks. In this model, contact is defined as an encounter or exposure in which infection is transmitted and the contact rate is defined as the fraction of susceptibles contacted per infective per day. Although these differ from the corresponding definitions used in the Reed-Frost model, contact rate continues to reflect both the social behavior of members of the population and the ease with which the disease agent is transmitted, both of which factors may vary during the year. The remaining important components of the model are incubation period (from exposure to beginning of infectivity) and effective period of infectivity (terminated in this case by withdrawal by confinement to home), both of which are disease-specific, plus number of susceptibles available. The latter varies over time according to the difference between input of new susceptibles (births and immigration) and withdrawals (by infection with resulting immunity and emigration).

Using reported numbers of cases for each month over the period of available data (prior to the advent of measles vaccine) and different choices of periods of incubation and infectivity, mean monthly contact rates were calculated for use in stochastic simulation of the recurrent outbreaks. These rates were up to 2 times higher during fall and winter than during summer months. Use of the observed rates in the simulation model resulted in regular annual seasonal peaks for mumps and chickenpox and biennial epidemics of measles when a 12-13 day incubation period was employed. Both the incubation period and infectivity (contact rates) were

critical for measles; if the former were shortened to 10 days or the latter slightly increased, measles would die out locally and there would be no regular pattern. The model also indicated that persistence of the biennial patterns for measles, despite extensive use of vaccine and the related reduction in cases, reflects non-uniformity of use of the vaccine and the continuing transmission in the unvaccinated subgroups of the population.

Yorke and London (8) also noted that, for measles and mumps, early season contact rates during years of high incidence exceeded those during low incidence years and that for later season contact rates the relation was reversed. This phenomenon could be reproduced only using a model for a non-homogeneous population containing subgroups differing in social and other characteristics within which, for stochastic reasons, cases are non-uniformly distributed. In subgroups in which cases cluster, infectives become isolated among immunes, while other similar subgroups continue with many susceptibles. They pointed out that the tendency for cases to cluster relates inversely to agent infectivity, a factor of greater import in spread to casual acquaintances (as from another population subgroup) than in spread to close acquaintances (as within the same subgroup) between whom frequent contact occurs. Thus, highly infective measles is less likely to cluster than are less infective mumps and chickenpox.

Current Immunization Problems

Measles: The U.S. national experience with measles since the advent of effective vaccine is illuminating (9). From 1965 through 1972, the U.S. Immunization Survey revealed that the per cent vaccinated among 1-4 year children rose from 33 to 62% and among the 5-9 year age group from 19 to 71% but that the total proportions immune (including that due to natural infection) reached virtual plateaus of 66 and 81% respectively, in 1967. Because of this, the annual national incidence of measles has shown no consistent decrease since 1968. The usual seasonal pattern has persisted but disease has tended to occur among school age children (Mississippi, 1971, Massachusetts and New Hampshire, 1972) where immunity levels were below 70% and in islands of susceptibles, e.g., among a Portuguese "ethnic island" in Rhode Island in 1968 (10). A similar episode in Tampa, also in 1968, is of special interest since it followed a "highly successful" mass vaccination effort (26,200 children, representing 94% of the estimated number of susceptibles, vaccinated on a single Sunday in

January)(11). In March, a Viral Immunity Survey of a stratified random population sample revealed that, in reality, not quite 80% of the target age group had received vaccine and that the more than 20% remaining susceptibles were largely clustered sociogeographically so that susceptibility exceeded 70% in some areas. In late April measles hit these clusters.

Measles in Ibadan, West Africa, illustrates a different situation. Although some 90% of the population are immune, annual epidemics occur associated with significant mortality. Virtually all of the susceptibles and 94% of the cases (1968-69) were under 4 years of age(90% were under age 3)(12). Mass vaccination reaching 92% of the 0-3 year age group was followed by a major drop in incidence but, despite limited maintenance programs at 6-month intervals, a new epidemic occurred after an 18-month interval. This situation was simulated on a computer by MacDonald, who showed that mass campaigns (85% coverage) at 3- or 2-year intervals afforded only temporary suppression, whereas annual campaigns would lead to complete cessation of endemicity within 4 years and a continuing program of immunization of 75% of children on becoming 6 months of age would achieve this result within 7 months. Although the latter program was judged not feasible, both the model and actual experience suggest that properly timed annual vaccination programs with high coverage would keep the numbers of susceptibles below the threshold at which epidemics become highly probable.

Smallpox: Smallpox in West Africa provides something of a contrast to measles. Its lower effective transmission rate results in chains of transmission that can continue for long periods without coming to attention and in outbreaks which, if left unattended, do not "burn out" by themselves. Also, because of this lesser infectivity, 3-year cycles of mass vaccination have proved sufficient to keep the number of susceptibles low enough to make uncontrollable epidemics unlikely (13). However, even in the best conducted campaigns small groups are left unvaccinated in which slow transmission can occur, as in Abakalike in eastern Nigeria. Dispersed through this well-vaccinated community but socially segregated from the rest of the population were members of a small religious sect who refused vaccination and among whom transmission persisted for an extended period (14). In the face of such tenacity an additional strategy was adopted, using probability of exposure rather than of susceptibility as a guide to vaccination. Beginning in 1968, mass vaccination was supplemented by outbreak control as a "specific attack on transmission when the disease was at its low seasonal ebb" (15). Intensive search was begun for new cases and outbreaks

and each such focus was contained by intensive vaccination. Dubbed "eradication escalation", this new effort resulted in eradication of smallpox from 20 West and Central African countries as of May 1970.

Rubella: Turning to rubella, there is active controversy as to the strategy for vaccine usage. In Britain and other European countries, major reliance is on direct protection of potential mothers by immunization of post-pubertal females. In the U.S., vaccine campaigns have been directed at children under age 12 and especially young school children in an effort to provide indirect protection of vulnerable females in the childbearing years via herd immunity. Observations in closed populations, e.g., military recruits (16), or a child care center (17) demonstrated that, when outbreaks of rubella occur in such populations, no susceptibles escape infection. In the case of the military recruits the presence of 26 susceptibles was sufficient to permit an outbreak to occur, even though dispersed among 164 immunes (86%). Perhaps more relevant is the experience in open communities such as Casper, Wyoming (18), where a major rubella epidemic occurred in 1971 shortly after a vaccine campaign which had reached 52% of preschool and 83% of elementary school children (70% overall). Herd immunity completely failed to operate in the closed populations, and, at first glance, was not effective in Casper. However, analysis of the data indicates that virus dissemination in the target population (0-12-year-old children) was in fact greatly reduced since the clinical attack rate was only 1%. Although rubella virus spreads with ease among susceptible adolescents (causing a 15% clinical attack rate despite 70% prevalence of immunity),vaccination of the young children clearly reduced the size of the outbreak and, more importantly, the number of susceptible women of childbearing age who were exposed. In discussing the Casper experience, the authors (18) conclude that "childhood rubella immunization remains an important method of rubella prevention; however, because of the potential for outbreaks in older children, this procedure should be supplemented by other methods", the most important of which "is the identification and vaccination of susceptible non-pregnant women in the childbearing age". It seems apparent, thus, that prevention of rubella outbreaks would require a uniform and very high level of immunization (perhaps 95%) to achieve, which would require an expenditure of resources and effort disproportionate to the importance of the disease.

Influenza: Our final example relates to the pandemic of type A influenza predicted when the next major antigenic variant appears. With early recognition and recovery of the new

variant strain through the worldwide WHO surveillance program, appropriately specific vaccine should be available in many areas in advance of the pandemic wave. How can this vaccine be used most effectively? To explore this the previously described community mixing model was adapted to simulation of epidemics of influenza. Details of the model and of our results will appear elsewhere (19), but are briefly summarized here. The model community contains 1,000 persons, divided by age into preschool, school (including high school), young adults and older adults, residing in 254 families and linked via 50 family clusters, 30 play groups and one school. For each subgroup contact rates (Reed-Frost definition) are specified and the parameters employed allow for variability in relative susceptibility of individuals, in the lengths of the latent and infectious periods, in relative infectiousness for others as related to overt and silent infections, in the occurrence of illness given infection, in confinement to home (withdrawal from mixing groups) given illness as related to age and in response to vaccination.

A first step was fitting the model to observational data from previous pandemics, e.g., 1957 and 1968. It is important to note that, although a "new" type virus was invading highly susceptible populations in each case, the resulting initial epidemics were similar in overall attack rates but differed greatly in other respects. Asian virus (1957) caused rather explosive epidemics centering in schools and school-age children experienced by far the highest attack rates (20). Hong Kong virus (1968) caused less abrupt but more prolonged epidemics with less prominent involvement of schools and attack rates varied little with age (21). Assuming that the initial epidemics due to the anticipated new varient strain may follow either of the above patterns, we fit the model to each, largely on the basis of age-specific primary and secondary attack rates, the shape of the epidemic curves, and the time relationship of the peak incidence in the school and non-school population subgroups. Fitting involved choosing sets of attack rates and various parameter possibilities by trial and error coupled with value judgments made within the framework of present knowledge. Control strategies were evaluated on the basis of epidemics beginning as school reopens in January at which time 9 cases are present, all in school age children in the Asian model and 3 each in the school age, young adult and older adult groups in the Hong Kong model.

Present immunization strategy emphasizes protection of the population segment (over age 65 or with certain chronic illnesses) at greatest risk of influenza-related death. An

alternate or supplemental strategy would assign priority for vaccination to population subgroups in relation to their role in community spread of infection, relying on herd immunity to minimize exposure of persons otherwise unprotected. In our model, as in real life, the largest number of interfamily paths lead through schools and many paths involve preschool children in play groups and/or day-care centers. Hence, our control trials (100-200 simulated epidemics per situation) have centered on these two age groups. So far, more trials have been made with the Asian than the Hong Kong model. Nearly all were made with inactivated vaccine of the type currently manufactured which, over a 28-day period, induces increasingly effective resistance in 80% of vaccinees (20% failure rate). A few trials employed a live attenuated virus vaccine such as may be available before the next pandemic and which, as the combined effect of interference and immune response, induces increasingly effective resistance over only a 3-day period in 95% of vaccinees (5% failure rate). In all cases vaccine was given only to the proportions of children specified in each age group.

Table 3 illustrates the effect of 70% vaccination of school children at least 28 days before epidemics of the Asian

TABLE 3. Effect of vaccinating (killed vaccine) 70% of school children 28 days before epidemic on age-specific clinical attack rates (AR)

Age	Baseline AR		AR after Vaccine as % of Baseline	
	Asian	Hong Kong	Asian	Hong Kong
Preschool	.35	.35	52	55
School	.62	.36	33	23
Young Adults	.23	.32	45	53
Older Adults	.13	.32	39	50
All Ages	.35	.34	38	42

and Hong Kong types. Results are in terms of attack rates (age-specific and total) expressed as per cent of the rates generated in baseline epidemics (unmodified by vaccination). Reflecting the obviously great importance of school children in community spread, school vaccination proved highly effective with the Asian model. The maximum benefit was in the school-age group, but the attack rates overall and, of special interest, for older adults were reduced by more than 60%. Surprisingly, school vaccination was nearly as effective with the Hong Kong model with reduction of attack rates in the non-school groups, ranging from 45% in younger children to 50% in

older adults. Trials using only the Asian model looked at the proportion of school children vaccinated by 28 days pre-outbreak (vaccination of 90% resulted in an 80% reduction in rates overall and for older adults while 50% vaccination led to only a 45% reduction in the same rates), at extending vaccination to include preschool children (Figure 1), and finally, at 70% vaccination of school children with live vaccine (Figure 2). Not too surprisingly, inclusion of pre-

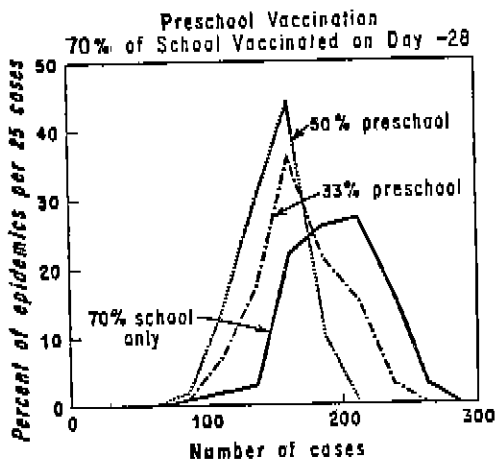

Figure 1. Asian influenza. The distribution of epidemic size for three schedules of vaccinations of 70% of school children plus 33 and 50% of preschool children 28 days before the beginning of the epidemic.

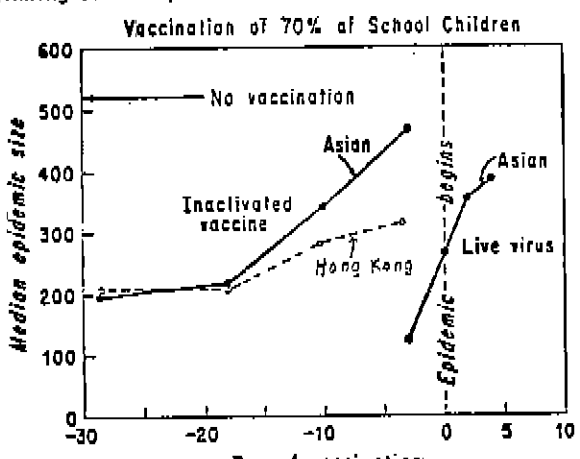

Figure 2. Median epidemic size for vaccination of 70% of school children as a function of time of vaccination and type of vaccine.

school children increases the proportion of epidemics with fewer than 200 cases while use of live virus vaccine was highly effective when delayed until 3 days before or even the day of the beginning of the epidemic. Figure 2 also shows results for both models using 70% school vaccination (killed vaccine) at shorter intervals (18, 10, and 3 days) before the epidemic begins. Delay to -10 and -3 days reduced vaccine effectiveness with both models but appreciably less with the Hong Kong model in which the epidemic builds up more slowly.

Discussion and Summary

This presentation has emphasized certain points. First, spread of a given contact-transmitted agent in a population is determined entirely by the number of susceptibles and the nature and frequency of their contacts with each other. Second, the concept that increasing the proportion of immunes correspondingly decreases the probability of spread of infection among susceptibles (as herd immunity is usually conceived) is valid only for populations in which completely random mixing occurs, a situation which, in real life, is approximated only in small closed populations. And third, populations of typical communities are non-homogeneous and are made up of many interlocking subgroups of differing size, proportion of susceptibles and intimacy of contact. These are defined by such terms as family, place of residence (neighborhood), play group, school attendance, and employment group and may be further characterized by such attributes as economic status, level of education and ethnic origin. This non-homogeneity of populations underlies the usual non-uniformity with which infections occur, as indicated by clustering of cases in various subgroups. It also is the reason why it is not possible to specify a proportion of immunes appreciably less than 100%, which is sufficient to prevent the occurrence of outbreaks. In general, systematic immunization programs should be accompanied by surveys to identify particularly susceptible population subgroups and should provide for special efforts to reach groups so identified. The goal, thus, becomes the maximum possible reduction in the number of susceptibles. Currently, in the United States such a goal is clearly appropriate for poliomyelitis and measles but, for differing reasons, may not be appropriate for rubella, smallpox and influenza.

Rubella is important only when it causes fetal infection. Sufficient reduction in overall dissemination of rubella virus to prevent fetal infection would require a uniform,

very high level of immunization, the cost of which would be disproportionate to the importance of the disease. Although immunization of preschool and grade-school children reduces the exposure of potentially pregnant women, community outbreaks continue to occur in adolescents. This suggests the advisability of an alternate or supplemental strategy emphasizing direct protection of females approaching childbearing age.

A strategy based on probability of exposure rather than on susceptibility to guide vaccination has become appropriate for smallpox throughout the world. This depends on continuing vigilance and intensive search to recognize cases (including introductions into disease-free countries) and containment of such foci by intensive vaccination. Such a strategy may become appropriate for measles (and possibly for poliomyelitis) when the frequency of disease reaches a very low level.

Pandemic influenza poses a special problem since the population will contain virtually no immunes to the new variant virus and appropriately specific vaccine presumably will be in short supply. Using a community mixing model adapted to computer simulation of influenza epidemics, we explored the effect of vaccination focussed on population subgroups (school and preschool children) most involved in community virus spread. The major reductions achieved in attack rates among the unvaccinated portions of the population (including older adults) argue strongly for this strategy to obtain maximum benefit from a limited supply of vaccine.

REFERENCES

1. Fox, J.P., Elveback, L., Scott, W., Gatewood, L., and Ackerman, E., Amer. J. Epidemiol., 94:179, 1971.
2. Abbey, H., Hum. Biol., 24:201, 1952.
3. Elveback, L., Fox, J.P., Ackerman, E., et al, Amer. J. Epidemiol., 93:267, 1971.
4. Dorland's Illustrated Medical Dictionary, W. B. Saunders Co., Philadelphia, 1965.
5. Bailey, N.T.J., The Mathematical Theory of Epidemics, Hafner Publishing Co., Darien, 1957.
6. Serfling, R.E., Hum. Biol., 24:145, 1952.
7. London, W.P., and Yorke, J.A., Amer. J. Epidemiol., 98: 453, 1973.
8. Yorke, J.A., and London, W.P., Amer. J. Epidemiol., 98: 469, 1973.

9. Measles Surveillance, Center for Disease Control Report No. 9, 1972 Summary, DHEW Publication No. (CDC) 74-8253, issued August 1973.
10. Scott, H.D., Amer. J. Epidemiol., 94:37, 1971.
11. Prather, E.C., Assessment of Immunization Levels, A Problem. Presented at SIMS Conference on Epidemiology, Alta, Utah, July 8-12, 1974.
12. Millar, J.D., Proceedings of Seminar on Smallpox Eradication and Measles Control in Western and Central Africa, May 13-20, 1969, Part II; SEP Report, Vol. IV, No. 2, CDC Smallpox Eradication Program, pp 165-176, January 30, 1970.
13. Millar, J.D., Proceedings of Seminar on Smallpox Eradication and Measles Control in Western and Central Africa, May 13-20, 1969, Part I; SEP Report, Vol. IV, No. 1, 7, 1970.
14. Foege, W.H. (Personal communication, 1971)
15. Millar, J.D., and Foege, W.H., J. Infec. Dis., 120:725, 1969.
16. Horstmann, D.M., Liebhaber, H., Le Bouvier, G.L., Rosenberg, D.A., and Halstead, S.B., N.Engl. J. Med., 283: 771, 1970.
17. Chang, T.-W., DesRosiers, S., and Weinstein, L., N. Engl. J. Med., 283:246, 1970.
18. Klock, L.E., and Rachelefsky, G.S., N. Engl. J. Med., 288:69, 1973.
19. Elveback, L., Fox, J.P., and Ackerman, E., To be submitted to the Amer. J. Epidemiol.
20. Dunn, F.L., Carey, D.E., Cohen, A., et al, Amer. J. Hyg., 70:351, 1959.
21. Davis, L.E., Caldwell, G.G., Lynch, R.E., et al, Amer. J. Epidemiol., 92:240, 1970.