SEASONALITY AND THE REQUIREMENTS FOR PERPETUATION AND ERADICATION OF VIRUSES IN POPULATIONS

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Perpetuation and persistence. Persistence of a virus in a population is a phenomenon distinct from persistence in a cell culture or in an individual animal, and the term "perpetuation" is used in this essay to maintain that distinction. Most viruses are capable of perpetuating in populations, regardless of the duration of infection in individual hosts. The ability of a virus to persist in an individual may, however, be critical for its perpetuation in certain populations, as discussed below.

Eradication is the converse of perpetuation and represents the ultimate method for control of an infectious disease. To determine the potential for eradication, it is necessary first to understand the requirements for perpetuation. Thus the subject is highly relevant to practical goals in public health and preventive medicine.

While we emphasize viral infections here, the principles governing perpetuation also apply to other microbial diseases, such as gonorrhea. Furthermore, eradication is a potential goal for agents such as tuberculosis, diphtheria, and pertussis.

Viruses in human populations: major ecologic patterns. The principal ecologic patterns of viruses in host populations are set forth in table 1, with particular reference to human infections. In the majority of instances, human viruses persist in only a single species and are transmitted directly from host to host. An infrequent variant of this pattern involves an intermediate insect vector, as with dengue. The other major pattern is that of the zoonotic viral infections, where the agent is maintained in another species, but may be transmitted to humans. In most such instances, man is a "dead end" host, although occasionally the agent may be subsequently maintained by human-to-human passage (urban yellow fever, perhaps influenza).
In this brief review, we will limit attention to the maintenance of a virus within a single naturally infected species. An implicit premise in the analysis which follows is that the long-lasting type-specific immunity conferred by viral infections (with possible odd exceptions) means that immune individuals can be considered permanently withdrawn from the susceptible population, as either potential cases or as potential new links in the infection chain.

Determinants of perpetuation. Descriptive epidemiologic studies, reviewed by Matumoto (4), have indicated a number of parameters which are important determinants of virus perpetuation. Discrete parameters which can be readily defined are listed in table 2. These parameters may be grouped into two composite factors which most directly affect transmission dynamics and perpetuation.

1) Population turnover per generation period. The number of new susceptibles introduced per generation period defines the theoretical limiting requirement for perpetuation. In a small population, if less than one new susceptible is introduced per generation period, a virus will almost certainly not perpetuate.

2) Transmissibility: The fraction of the susceptibles infected by each existing infection. This critical variable (5, 6) depends on biological, social, and physical factors which are generally impossible to sort out with precision. Although difficult to quantify its individual components, transmissibility clearly differs among viruses, as documented by the classical household studies of Hope Simpson (7). The variables, transmissibility and generation time will determine the rate of spread of an agent through a population, for a given set of population parameters. Paradoxically, an agent which spreads rapidly may exhaust susceptibles and disappear more quickly from a small population than a virus which spreads indolently. Among viruses endemic in a given population, those with higher transmissibility will have smaller pools of susceptibles.

Seasonal variation in transmissibility. Human virus infections differ widely in the extent of seasonal fluctuation in incidence, which is very dramatic for measles and poliomyelitis, but relatively modest for hepatitis B. Where seasonality is marked, it can play a major role in the size of the population required for perpetuation, as illustrated subsequently for measles. Among viruses which show great seasonal fluctuation, peak incidence may occur at different times of year. Thus, in the United States, measles peaks in early spring while poliomyelitis peaked in early fall. The mechanisms underlying
seasonality still remain essentially unexplained.

Core population. Populations are inhomogeneous in many respects, including the transmission of infectious agents. For some viruses, such as those which are sexually transmitted, the source of most infections can be attributed to a "core" group which is responsible for perpetuation. The same principle probably operates for other viruses, although the core population is less clearcut. Thus, infants may not have sufficient extrafamilial contacts to act as important transmitters, even though they are highly susceptible to many agents. In general, most viruses will depend for perpetuation on a core consisting of one or more subgroups of efficient transmitters (5, 6).

Perpetuation in small populations

Observations on the perpetuation of viruses in populations are scattered through the epidemiologic literature (4). No attempt has been made to compile these systematically. Instead, a few selected examples will be considered to illustrate the impact of some of the parameters noted above. Particular attention will be devoted to population size, population turnover, immunity levels, seasonal cycles, and to a comparison of viruses with differing patterns of pathogenesis.

Isolated human populations

Primitive human populations which have minimal contact with the outside world are occasionally available for serologic study. These populations provide a unique opportunity to determine the ability of viruses to perpetuate themselves in their natural host. The studies of Black et al. (9, 10) and others (8, 11–14) have delineated two principal patterns (table 3) for agents which have no extrahuman reservoir. Viruses which are eliminated following primary infection tend to cause abrupt outbreaks after introduction into the population and then die out until reintroduced. Viruses which are capable of persisting in individual hosts are able to perpetuate in small isolated groups. Epidemiologically, a distinction must be made between two kinds of persistent infection: those, like the herpesviruses, which are accompanied by long-term (if intermittent) shedding, and those where persistently infected individuals are not infectious, such as in measles or rubella panencephalitis.

Figure 1 shows the age distribution of neutralizing antibodies to poliovirus types 1, 2, and 3 in the isolated Eskimo village of Narssak (population 450) in southern Greenland, from a study by Paffenbarger and Bodian (13). The profiles are striking and show that type 1 virus had infected essentially the entire population 25 years previously, while type 2 virus had caused a similar wave of infections 15 years previously and type 3 had been present only one year prior to the collection of sera in 1952. Also, it is clear

Table 3

<table>
<thead>
<tr>
<th>Agents</th>
<th>Persist in individuals</th>
<th>Persist in small populations</th>
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<tr>
<td>Herpesviruses</td>
<td>+</td>
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<tr>
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<td>Kuru</td>
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<td>+</td>
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<td>Adenoviruses</td>
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<tr>
<td>Polyomaviruses</td>
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<td>+</td>
</tr>
<tr>
<td>Measles virus</td>
<td>+</td>
<td>~</td>
</tr>
<tr>
<td>Rubella virus</td>
<td>+</td>
<td>~</td>
</tr>
<tr>
<td>Creutzfeldt–Jacob</td>
<td>+</td>
<td>~</td>
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</table>
that following its intrusion and exhaustion of susceptibles, each virus had essentially disappeared from the population. (The type 1 antibodies at 15-24 years presumably represent cross-reactions due to infection with type 2 virus).

In contrast, hepatitis B (HB) produces a considerable proportion of persistent infections, particularly in primitive populations. Figure 2, from a study by Skinhøj (14) of Eskimos in southwest Greenland, shows that infections have occurred at all ages, with a gradual rise in cumulative incidence to 60 per cent by age 60.
presence of hepatitis B surface antigen (HBsAg) positives documents the mechanism of perpetuation.

Small animal populations

Animal populations differ radically from human populations in their relatively rapid rate of turnover, and this is a critical variable in virus perpetuation. Depending upon the circumstances, mean life expectancy in many animal populations ranges from 6-12 months, compared with a range of 30-70 years for humans. In contrast to these enormous differences, the kinetics of infection are similar in an individual human or animal host. For instance, the median incubation period (to rash) is about 14 days in smallpox and 10 days in mousepox. Thus, a human population of 1000 might commonly experience a turnover of one individual per smallpox generation period, while the same would be true for mousepox in a mouse population of about 35.

Differences in population turnover per generation period undoubtedly play an important role in the perpetuation of certain acute viral infections in wild animal populations. Thus, rabies can be maintained in the rather sparse fox population by moving back and forth between adjacent geographic areas. Infections with long incubation periods (such as progressive pneumonia and scrapie of sheep) may persist unrecognized because most animals are slaughtered prior to the onset of frank clinical signs.

Laboratory animal colonies have provided an opportunity to document the quantitative impact of population turnover. Observations in such colonies are of more than academic interest, since unwanted virus infections present an important practical problem which frequently confounds biomedical research (15–18).

Ectromelia. Ectromelia or mousepox (16) closely resembles variola in man. Infection is initiated either by entry through the skin or by inhalation, and in the systemic infection which follows, the liver and spleen are critically involved target organs and there is a generalized pox-like rash of the skin.

As in smallpox, infections can be fatal (depending upon many variables, including virus strain, and age and genotype of mouse), but recovered mice are solidly immune and have cleared virus from their tissues. Virus persistence, if it occurs, is at most a rare phenomenon, inadequate to perpetuate infection in a population (17). Ectromelia is a relatively infectious agent and a notorious cause of acute and devastating epizootics (18). When a few infected mice are placed in a larger group of susceptible animals, the virus spreads rapidly, and all mice are infected within 20 days or two incubation periods (figure 3). Many mice die, and all the survivors are immune.

In these circumstances, it would not be expected that ectromelia could be perpetuated in a small mouse population. However, a series of classical studies by Greenwood and his colleagues (19) and subsequently by Fenner (16, 17, 20–22), elegantly demonstrated that this virus was readily perpetuated in mouse populations of 100–200 animals.

Figure 4 summarizes one experiment, based on Greenwood's data, which have been interpreted and consolidated in the light of Fenner's subsequent publications (16, 17, 20–22). A mouse colony was established with 25 normal and 20 infected mice, three uninfected mice were added daily, and animals were only removed if they died. During the 30-month observation period shown, the total colony size gradually rose to a constant level of about 230 animals. At equilibrium, about 40 per cent of this population died and was replaced each month and the mean lifetime
of animals entering the colony was about 75 days. The infection was maintained throughout the existence of the colony and at equilibrium about one-fifth the mice were not yet infected, one-fifth were actively infected, and three-fifths were immune survivors. The mortality produced by acute infection was 50–60 per cent, typical for the Hampstead mouse passage strain. These observations indicate that, under the conditions of this experiment, turnover was about 25 mice per generation period, and this consideration makes perpetuation less surprising. Although the minimal population size in which ectromelia could perpetuate was not determined, Fenner (17) observed one persistently infected population which stabilized at 70 animals.

*Rat virus.* Rat virus is a parvovirus of rats which is mainly transmitted as an enteric infection. This agent was unwittingly maintained (23) in a juvenile colony of about 1000 animals of which 250 five-month-old animals were replaced monthly with 250 susceptible weanlings. Rat virus spread at a rate such that 50 per cent of animals were infected by age five months and the overall proportion immune averaged about 30 per cent. If the population had been permitted to remain for a normal life expectancy, it is likely that all animals would have converted to immunes; under such conditions the agent might have failed to perpetuate.

*Measles.* An interesting study (24) of the ecology of measles virus in rhesus monkeys indicated that animals in the wild were free of infection. Following capture, monkeys rapidly acquired infection during holding and shipment, so that all animals had been infected within eight weeks. The rapid turnover in the exporters' compounds in India, where monkeys were held for only a few days to a month, constantly introduced enough suscepti-
bles to perpetuate the virus. In contrast, measles infection could not be maintained in a stable rhesus colony.

PERPETUATION IN LARGE POPULATIONS: MEASLES

Descriptive epidemiologic data. To follow the pattern of virus infection in large populations, it is necessary to rely on reportable diseases which are clinically distinctive, and for which a high proportion of infections are clinically apparent. Measles is one of the few virus diseases which meets these criteria and its behavior in populations has been a recurrent subject of interest to epidemiologists (25–30). Even measles has its limitations as a subject for study, since only 10–55 per cent of cases are reported.

Although measles is an ubiquitous and highly infectious virus, its ability to perpetuate itself in human populations is surprisingly fragile. Bartlett, in his classical studies (25, 26), found that in urban populations of less than 500,000, measles would periodically disappear. As table 4 shows, in five cities of 200,000–300,000, the reported disease faded out for at least one month in 56 of the 100 years recorded. Black (27) compiled data on measles in island populations, which led to a similar estimate of critical population size.

Since a population of 300,000 might be expected to experience about 6000 cases of
measles in an average year, it is at first surprising that this would be insufficient to maintain the infection. The explanation becomes more apparent when the seasonal cycle of measles is examined (figure 5). Data from a large US city (Baltimore, Maryland) show that the seasonal cycle is very marked so that only about 1 per cent of the annual total occurs in the five low months (August–December). In the lowest month (August), less than 1/3000 of the annual total occurs per 12-day generation period. This is about two cases in a population of 300,000, and there is considerable statistical variation around this average. From this viewpoint, it is not implausible that periodic fade-outs would occur in populations below 500,000 (table 5).

It has been assumed in the foregoing that measles infects close to 100 per cent of the population, or that the average annual number of infections is equal to annual births. Figure 6 indicates that this is essentially correct, and that in one urban area (Baltimore, Maryland, 1900–1931) the average age of infection (t) was 5.7 years. Data of the kind in figure 6 suggest that the average size of the susceptible population (S) may be conveniently defined in terms of the equivalent number of annual birth cohorts. S is slightly less than t, since infants are not susceptible until they have lost maternal antibody, assumed here to occur at 0.7 years of age. In this example, the mean time a person is susceptible is 5.0 years and the average value of S is 5.0 annual birth cohorts.

Estimates of the size of the susceptible population, as a proportion of the total, are important because they determine both the maximum reduction which might be achieved by immunization, and the minimum number required for perpetuation. In turn, these estimates are important elements in projecting the po-
PERPETUATION AND ERADICATION OF VIRUSES

Seasonality and persistence. The foregoing observations suggest that the persistence of a short cycle infection in a large population is critically dependent upon the relationship between the generation time and incidence during the seasonal trough. Seasonality is clearly a key to understanding the requirements for perpetuation in large populations. Therefore, we have attempted to quantify the parameters which determine the seasonal cycle. To this end, we have developed a modified and simplified method for calculating seasonal variation in transmissibility. Application of this analysis to measles illustrates the method and shows

**Table 5**

<table>
<thead>
<tr>
<th>Population</th>
<th>Actual</th>
<th>Reported (30%)</th>
</tr>
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<tbody>
<tr>
<td>Average annual cases (birth rate 20/1000)</td>
<td>10,000</td>
<td>3000</td>
</tr>
<tr>
<td>Cases in trough month (0.1%)</td>
<td>10</td>
<td>2–3</td>
</tr>
<tr>
<td>Cases in trough generation (12 days)</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

FiguRE 5. Reported measles by month for Baltimore, Maryland, 1928–1961. The 16 high years ranged from 4400–18,600, and low years from 100–4300. It is estimated that about 35 per cent of cases were reported. Adapted from: Yorke and London (28).
Figure 6. Age-specific susceptibility to measles. Baltimore, Maryland, 1900–1931, based on age distribution of cases. Adapted from: Hedrich (29). United States, 1975, is a composite reconstruction based on measles immunization surveys and measles age distribution. Adapted from: CDC (46). The average age of acquisition of immunity (by infection or by immunization) is denoted by \( T \). The size of the susceptible population, expressed as the equivalent number of annual birth cohorts, is denoted as \( S \). See text for details.

The average number of cases (33,600 in two years or 46 daily) is also the daily gain in susceptibles. (Infant mortality is ignored.)

This procedure generates a periodic curve of the fluctuation in susceptibles around an average level (figure 7, middle panel). This average is independently estimated as described subsequently. The number of susceptibles \( S \) is expressed in terms of the equivalent number of annual birth cohorts, as described above. \( S \) may also be expressed as a per cent of the total population, if an annual birth rate is estimated. In figure 7, 3.6 years multiplied by two births per 100 person-years yields 7.2 per cent susceptible.

3) Transmissibility of measles varies by season, and is calculated as follows. The number of persons infected on day \( t \) can be taken to be \( C_{t+12} \), that is the cases with onset on day \( (t + 12) \), assuming a 12-day incubation period. Then

\[
\frac{C_{t+12}}{S_t}
\]

is the fraction of susceptibles infected on day \( t \). If \( C_t \) is the number of infectious individuals on day \( t \), assuming infectivity is confined to the day of onset of illness, then the fraction of the susceptibles infected per infectious individual is

\[
T_t = \frac{C_{t+12}}{S_t} \cdot \frac{1}{C_t}
\]

where \( T_t \) is transmissibility on day \( t \) (31). From the daily tabulations of \( C \) and \( S \), values of \( T \) can be computed and plotted (figure 7, bottom panel). (Transmission times are actually spread around the day of onset, but a correction for this spread has no significant influence on the plots in figure 7).

4) The average of susceptibles is set by trial-and-error, in which the two-year curve is generated using different average values of \( S \). The seasonal curves of \( T \) entering the population. If all persons eventually acquire measles, then the average daily number of cases (33,600 in two years or 46 daily) is also the daily gain in susceptibles. (Infant mortality is ignored.)

Computer accounting. To construct an estimate of seasonal variation in measles transmissibility, the problem is attacked in steps.

1) Between 1948 and 1964, measles in New York City (28, 30) exhibited a regular biennial cycle, alternating between years of high and low incidence. Using these data, an average two-year cycle of measles incidence is constructed. Monthly cases are spread by individual days to give a smooth curve (figure 7, top panel).

2) The number of susceptibles is tabulated on a daily basis, by a bookkeeping procedure which accounts for both losses and gains. Losses on a particular day are equivalent to the cases with onset one incubation period (taken as 12 days) later. Gains are the number of new susceptibles
Figure 7. Computer accounting of seasonal fluctuation in measles. The daily number of cases (top panel) has been used to generate the curves showing seasonal variation in number of susceptibles and in transmission rate. The high and low years are based on reported cases for New York City (28, 30), and it is assumed that 16,800 susceptibles enter the population annually, equivalent to a birthrate of 20 per 1000 in a population of 840,000. See text for details.
for high and low years are then superimposed, and a mean value of $S$ taken as that which minimizes the high-low differences in the seasonal configuration of $T$.

In the accounting shown in figure 7, the mean number of annual cohorts of susceptibles ($S$) is 3.6, less than Hedrich's (29) estimate of 5.0 years (figure 6). This is consistent with the concept of a "core" group of susceptibles who are potentially efficient transmitters, excluding infants under age two.

Observations on the model. Figure 7 sets forth the major parameters in the model over a biennial period, which then repeats indefinitely. Several points are noteworthy.

(a) Transmissibility ($T$) shows a rather small seasonal variation (about twofold), with somewhat greater variation during transitory seasonal extremes.

(b) Transmissibility is on the whole similar in the low and high years. (Close examination suggests that $T$ is actually slightly lower in the high year, an unexpected finding.) Thus, the model suggests that the larger number of cases in high incidence years is due to the accumulation of susceptibles at the beginning of the seasonal rise.

(c) The seasonal drop in low years occurs without a decrease in susceptibles and is ascribable to a reduction in transmissibility. In high years the case rate peaks earlier, following a drop in susceptibles. Subsequently, the early summer drop in transmissibility occurs, and the falling incidence begins to plummet. Thus, cyclic changes in $S$ and $T$ interplay in producing the familiar biennial cycle of endemic measles.

(d) An outbreak of measles can be constructed. At first, susceptibles are numerous and the number of cases is low but increasing. It may take a number of generations of growth in the case rate before susceptibles are affected substantially. Then susceptibles drop to some critical level where the case rate peaks. Temporarily, each infective is only replacing himself. The continuing drop in the level of susceptibles makes it less and less likely that an infective will transmit the infection, so the level of cases drops more and more steeply.

If the initial level of susceptibles was far above the critical level needed for one infective to infect one susceptible, then at the end of the outbreak the number of susceptibles will be far below that level. After a considerable interval, susceptibles will climb back to the critical level and will continue to climb since it will now take a long time before the level of infectives grows high enough to initiate a decline in susceptibles.

This picture ignores seasonal variation. Soper (32) incorrectly believed that this natural pattern of oscillation was sufficient to account for sustained fluctuation in incidence. Without a computer he could not tell what happens over a long time. Had he carried out his calculations over several cycles, he would have found the amplitude of oscillation slowly damping down to a constant endemic level (28, 30). We may think of the level of susceptibles as similar to a pendulum swinging back and forth past equilibrium. Seasonal variation gives the pendulum a shove every year and these regular shoves are required to keep the pendulum in motion.

(e) Bartlett (25, 26) based his theoretical analysis of measles fadeout on stochastic effects, excluding seasonal variation from consideration. We believe that stochastic effects play a role, but one which is secondary to seasonal variation in transmissibility. Construction of seasonal waves based on large populations, such as New York City (figure 7), minimizes stochastic effects and documents the reality of seasonality as a major underlying cycle. During the seasonal trough generated by this cycle, small numbers of cases occur and stochas-
tic effects can come into play, resulting in irregular and unpredictable fadeouts. It should be kept in mind that the foregoing analysis treats of the macro patterns seen in large populations. Enormous variations from these averages are seen in small subpopulations.

**Level of susceptibles and perpetuation.** If isolated large populations have a high level of susceptibles, a major epidemic may occur when infection is introduced, which reduces susceptibles to a very low level. During the extended period before susceptibles can accumulate, a fadeout is possible even in populations larger than Bartlett's critical 300,000. Hence, a situation of isolation is conducive to fadeout of an infectious agent (27).

The simulation model may be manipulated to examine the influence of different variables on perpetuation. An example is shown in figure 8, in which a single infection is introduced during the period of peak transmissibility (mid-January). If susceptibles are at a level of 6 per cent or higher, the virus persists and begins to move into the biennial cycle. With a relatively small reduction in susceptibles (to about 5 per cent), fadeout occurs during the first seasonal trough. This simulation is conducted with a number of cases roughly equivalent to those seen in a population of 840,000, and is, therefore, relevant to what might be expected in a city of moderate size, which has experienced a fadeout followed by reintroduction of measles. It indicates the difficulty in preventing measles above a critical level of susceptibles and the potential for control if immunization has reduced susceptibles below that level.

**Generation period and perpetuation.** The extent of seasonality for a particular agent is determined not only by cycles in transmissibility but also by the generation period. A given cycle in transmissibility will generate increasing degrees of seasonality as the generation period is reduced. Thus, if the transmissibility of measles drops markedly over a 60-day interval the effect is cumulated over five generation periods, that is, by the power

![Figure 8](http://aje.oxfordjournals.org/)

**Figure 8.** Computer simulation of measles, following introduction of one case at seasonal peak (January), to show effect of variation in the per cent of the population which is susceptible to measles at beginning of simulation. The simulation is based on a population of 840,000 with an annual birthrate of 20 per 1000, and uses the seasonally variable transmission rates shown in the prior figure. See text for details.
of 5. Applied to influenza, using an average generation period of three days, the same effect would be raised to a power of 20. If, for example, incidence drops by a factor of 0.7 per generation over a two-month period of low transmissibility, the resulting decrease in measles is $0.7^5$ (about sixfold) and in influenza is $0.7^{20}$ (over 1000-fold). For this reason, influenza might be unable to persist in any human population in the absence of antigenic variation.

Eradication: Public Health Implications of Virus Perpetuation

The recent dramatic successes in global smallpox control have demonstrated that eradication is an attainable objective for selected viral infections of man. The salient epidemiologic features of smallpox (3, 33) which made eradication possible were: 1) The relatively long incubation period (about 14 days) and relatively low infectiousness (requiring close direct contact) cause variola to spread slowly within or between rural communities. This made it practical to place emphasis on a search-and-containment strategy, in which local outbreaks were identified and aborted by intensive immunization around each focus. This strategy constituted a critical addition to ongoing mass vaccination programs. 2) The marked seasonality of smallpox meant that, even in epidemic areas, the number of cases was relatively low during the trough period. Exploitation of this phenomenon played a key role in achieving eradication in India and Bangladesh. 3) The high ratio of cases to infections (approaching unity) and the ready recognition of smallpox were also of great importance.

In light of this experience, it is of interest to examine the current status of several important viral infections of man, and the prospects for eradication at a continental if not a global level. Consideration is limited to the United States where copious data are available.

Poliomyelitis. The annual incidence of poliomyelitis in the United States is shown in figure 9, for 1951–1977 (34). Paralytic cases have been reduced from a level of 10,000–20,000 to 10–20, or about 1000-fold. The epidemiologic classification of cases for 1969–1977 is set forth in figure 10 (34, 35). Putting aside vaccine-associated cases and imported cases, it can be seen that the last domestic outbreak of poliomyelitis occurred in 1972. During the five years 1973–1977, there have been a total of only seven "endemic" cases (i.e., non-epidemic, non-imported) with no identified vaccine association, and the scattering of these seven in space and time makes it possible that they were related to the vaccine virus. Apparently indigenous natural poliomyelitis has been eradicated from the United States.

In searching for an explanation of the fadeout of wild poliovirus, an attempt has been made to estimate the reduction in the pool of susceptibles attained by oral poliovirus vaccination. Figure 11 sets forth the age-specific distribution of susceptibles in 1955, at the threshold of mass immunization. The 1955 estimates are based on the age-distribution of paralytic poliomyelitis (36) and involve several assumptions: (a) that most paralytic cases
were caused by type 1 poliovirus; (b) that the cumulative lifetime infection rate was 100 per cent; (c) that the age distribution of cases reflects the age distribution of infections (this may slightly overestimate the number of susceptibles); and (d) that maternal antibody conferred protection to age eight months (0.7 years). The 1955 data suggest that the susceptible pool (S) was about 11.2 annual birth cohorts or 22.4 per cent of the population.

The size of the susceptible population in 1977 is much harder to estimate, because of the lack of systematic serosurveys in the United States in recent years. The results of annual United States Immunization Surveys over the period 1965–1976 (34, 37) indicate a gradual increase in the proportion of children ages 0–14 who have not been immunized (5 per cent in 1965 and 8.8 per cent in 1976). This suggests that serosurveys throughout this period may be used to estimate the size of the susceptible population. Such surveys (38–41) have been based on small numbers and have not employed stratified random samples. Not surprisingly, the results vary considerably. One of the most

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**Figure 10.** Paralytic poliomyelitis by epidemiologic category, United States, 1969–1977. Adapted from: CDC (34, 35).

**Figure 11.** Estimated population susceptible to poliomyelitis (S), based on age distribution for United States in 1955. Adapted from: Hall (36).
recent and larger studies, conducted in England, is shown in table 6. A comparison of these surveys suggests an overall estimate, for children ages 0–14, of only 70–80 per cent with neutralizing antibody against type 1 poliovirus. In turn, this estimate implies a maximum reduction in susceptibles, between 1955 and 1976, of no more than threefold.

An apparent threefold reduction in susceptibles has led to a reduction in poliomyelitis of 1000-fold and brought the United States over the threshold of eradication. This remarkable achievement indicates that the pool of susceptibles has dropped below the level required for perpetuation of wild poliovirus. Such an unexpected development requires explanation. An examination of the seasonal cycle of poliomyelitis suggests a possible mechanism.

Figure 12 shows the seasonal cycle for poliomyelitis in the United States, based on pooled data for 1953–1955 (42). Poliomyelitis showed a marked seasonality, such that incidence during the seasonal trough was 30-fold below peak incidence. From this figure it can also be seen that the seasonality is due almost entirely to fluctuations in transmission rate (T) since the pool of susceptibles (S) is so large that it shows little change during the course of the year.

During the period 1955–1970, of declining poliomyelitis incidence, the infection retained its seasonality. The last year with enough natural cases for analysis was 1970 (figure 13). Although there were only 32 cases in 1970 (43), seasonality was still apparent. There was only one case during the period January–March, and again incidence dropped to zero in December. Since paralytic cases represent about 1 per cent of all infections, the 1970 data do not prove that the virus was unable to overwinter. However, when total infections for the entire United States drop to the order of 100 per month, it is plausible that the chain of infection might be entirely interrupted in major sections of the country.

The eradication of wild poliovirus from the United States has certain practical implications which deserve brief mention: (a) Importation becomes an important potential source of future poliomyelitis, and a requirement for adequate immunization of all entrants into the continental United States seems logical. Since Mexico is the major source of importations, all possible assistance should be provided to implement Mexican efforts at control. (b) It is important to maintain immunization levels to minimize the possibility that wild poliovirus could be re-established following the foreign introductions which are now occurring (figure 10).

**Measles.** Measles represents an infection which has been markedly reduced in the United States by immunization, but which is far from eradicated. Prior to live measles virus vaccine, about 450,000 cases were reported annually or 15 per cent of an estimated annual 3,000,000 cases. Following introduction of live measles vaccine in 1963, reported cases have decreased to 5–10 per cent of the pre-vaccine level. If, as seems likely, reporting of measles has improved pari passu with reduction in incidence, then measles may be well below 5 per cent of the pre-immunization level. However, during the last 10 years, the number of cases reported each year has remained at

<table>
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<th>Age group</th>
<th>No.</th>
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<th>Type 2</th>
<th>Type 3</th>
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<td>30–39</td>
<td>120</td>
<td>76</td>
<td>85</td>
<td>73</td>
</tr>
<tr>
<td>40+</td>
<td>403</td>
<td>73</td>
<td>73</td>
<td>59</td>
</tr>
</tbody>
</table>

* Adapted from: Codd and White (38).
**FIGURE 12.** Computer simulation of seasonal fluctuation in poliomyelitis, based on an average of total reported cases for United States, 1953 through 1955. Derived from data of CDC (42). The three panels show cases, susceptibles ($S_i$) and transmission rate ($T$). An incubation period of 10 days was used and $S$ was estimated from figure 11 (36). See figure 7 and text for details.
a plateau level, and the absence of a downward trend has markedly dampened (44, 45) earlier enthusiastic predictions of eventual eradication.

It is interesting to examine the possibility of measles eradication from the viewpoint of virus perpetuation. As a first step, it is necessary to estimate the size of the susceptible population prior to and after mass measles immunization. Figure 6 compares the age-specific distribution of susceptibles for a typical pre-vaccine period (Baltimore, 1900–1931) with estimates for the United States for 1975. To derive the 1975 curve, data (46) from the United States Immunization Survey was used to estimate the proportion of infants immunized at age 12–15 months; the age distribution of measles cases (46) in the unvaccinated was then applied to the residual susceptibles to complete the curve. The susceptible population is estimated at about 10 per cent prior to immunization compared to about 4.4 per cent currently.

If these estimates are applied to the population size requirements for measles perpetuation (table 7), it can be estimated that close to 50,000 susceptibles are required to maintain measles in a North American city. If the size of the susceptible pool is reduced by 50–60 per cent through immunization, the absolute number of susceptibles in a large city, such as New York, remains above the threshold for perpetuation. However, a city of moderate size, such as Baltimore, drops below the estimated threshold requirement for measles perpetuation. It is interesting that measles reports (table 8) indicate that measles continues to be constantly present in New York, as it was in Baltimore before mass measles immunization. However, since 1965 (data for 1968–1971 are shown) measles has been subject to periodic fadeouts in Baltimore. Parallel observations for Rhode Island were published by Scott (44), and similar predictions were published by Griffiths (45).

Thus the United States may be closer to measles eradication than is generally appreciated. If a renewed effort to eradicate measles were undertaken, this review suggests several components which should be included in such a plan: 1) The vigorous enforcement of measles immunization as a requirement for attendance in schools and in preschool day care centers

### Table 7

**Measles: hypothetical number of susceptibles before and after immunization program**

<table>
<thead>
<tr>
<th>Population</th>
<th>Susceptibles before immunization</th>
<th>Susceptibles after immunization</th>
</tr>
</thead>
<tbody>
<tr>
<td>9,000,000</td>
<td>900,000</td>
<td>400,000</td>
</tr>
<tr>
<td>900,000</td>
<td>90,000</td>
<td>40,000†</td>
</tr>
<tr>
<td>500,000</td>
<td>50,000</td>
<td>22,000†</td>
</tr>
<tr>
<td>300,000</td>
<td>30,000</td>
<td>13,000†</td>
</tr>
</tbody>
</table>

* Estimates of the number of susceptibles are based on data in figure 6.
† Predicted fadeouts.

### Table 8

**Perpetuation of measles before and after measles immunization program**

<table>
<thead>
<tr>
<th>Year</th>
<th>No. of reports in low month</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>New York</td>
</tr>
<tr>
<td>1958</td>
<td>47</td>
</tr>
<tr>
<td>1959</td>
<td>97</td>
</tr>
<tr>
<td>1960</td>
<td>43</td>
</tr>
<tr>
<td>1961</td>
<td>123</td>
</tr>
<tr>
<td>1968</td>
<td>11</td>
</tr>
<tr>
<td>1969</td>
<td>39</td>
</tr>
<tr>
<td>1970</td>
<td>31</td>
</tr>
<tr>
<td>1971</td>
<td>39</td>
</tr>
</tbody>
</table>

* Measles vaccine has been widely used in United States since 1963.
† Adapted from: Yorke and London (28).
and the like. This would reduce the potential "core" population to a minimum. 2) The application of a containment strategy where each school is considered a unit. The continued persistence of measles in spite of present day levels of immunity is probably explicable by the high transmis-
sion rates within such units. Therefore, when measles involves a school, the best strategy may be the identification of tangential schools at high risk of secondary spread and the vigorous immuni-
za-
stion of non-immunes within these adja-
cent units. 3) The seasonal trough should be exploited in two ways. Since only about 10 per cent of annual measles reports occur during the period August through November (46), this low season (plus the two preceding months) is the best time to quickly identify and cope with all new outbreaks. Furthermore, transmissibility is at a seasonal low during the same period, and this will favor a vigorous in-
tervention program. 4) Required measles immunization for all entrants into the United States would complement other elements in any containment program (44).

**Future prospects for eradication.** The principles discussed above can be used to speculate about the possible eradication of other human viral infections (table 9).

Rubella and mumps are two infections for which vaccines exist. For rubella, it is highly questionable whether an attempt to eradicate is preferable to a more fo-
cussed approach directed at women of child-bearing age. For mumps, it can be debated whether the cost of eradication would be justified by the potential benefits.

Of the viral infections for which vac-
cines will probably become available in the future, the most logical candidate for eradication (in the United States) is hepatitis A. Since the epidemiology of hepatitis A closely resembles that of poliomyelitis, eradication seems a realistic goal.

Hepatitis B also deserves consideration, since its ability to persist is offset by its very limited communicability. Three ob-
servations are relevant: 1) Personal habits and public sanitation have already had a marked impact on hepatitis B, as indicated by the much lower prevalence (47) of anti-HBs in developed than in de-
veloping countries (less than 10 per cent contrasted with up to 70 per cent). 2) In the United States, transmission of hepatitis B from a carrier to contacts is very restricted, since only about 30 per cent of intimate (household) contacts are infected (48). 3) Most (probably 90 per cent) hepatitis B infections are acquired after age six (49) when children are readily accessible for immunization programs. These considerations suggest that, if 90 per cent of infections could be prevented by school entry immunization, the cumulative reduction over several genera-
tions would be significant. However, further elucidation of the pathogenesis, immunology, and mode of transmission of hepatitis B is a necessary prerequisite for serious evaluation of the feasibility of eradication.

**Summary**

Perpetuation of a virus in a population is distinct from the ability to persist in a cell culture or individual host. Parameters which determine perpetuation in-clude: 1) the size of the population; 2) the turnover of the population; 3) the proportion of immunes in the population; 4) the transmissibility of the infection; and 5) the generation time between sequen-
tial infections. These parameters may be grouped into two composite factors which most directly affect transmission dynamics and perpetuation: (a) population turnover per generation period, and (b) transmissibility or the fraction of susceptibles infected per existing infection.

Perpetuation in small populations usually requires either the ability to persist in individuals or rapid population turnover. Conversely, human viruses which initiate only acute infections require larger populations to persist. Seasonal variation in transmissibility can greatly increase the minimum population size in which persistence is possible, and we argue that the population size of 500,000 for measles persistence (described by Bartlett) is primarily a consequence of seasonal variation. Computer modelling can be used to examine the effect of changes in parameters which determine the seasonal cycle of virus perpetuation and fadeout.

Finally, human infections are reviewed to indicate those which have been eradicated (smallpox), are on the threshold of eradication (poliomyelitis), are possibly eradicable (measles), or could be candidates for future efforts (hepatitis A and hepatitis B). In developing a strategy for eradication two points are of great potential utility: first, the seasonal trough should be exploited as a time for effective intervention; and, second, containment efforts should be directed at epidemiologically important population groupings such as schools.

References

42. Center for Disease Control: Poliomyelitis Surveillance Report No 56. Atlanta, 1956