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THE PROPAGATING RATE: A METHOD OF INTERPRETING
INFECTIOUS DISEASE INCIDENCE

by

Morris Chelsky, M.D.

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Doctoral Committee:

Professor Horace J. Dodge, Chairman
Associate Professor Norman S. Hayner
Associate Professor Albert V. Hennessy
Associate Professor Stanley H. Schuman
Associate Professor Michael E. Tarter

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Chapter I

INTRODUCTION

The incidence curve has long been among the most important instruments in formulating theory concerning the natural history of a disease. Nonetheless, the appearance of the incidence curve often suggests conclusions which seem to lack conformity with clinical and laboratory findings. For example, in temperate climates viral hepatitis is most prevalent in late fall and early winter and this suggests the importance of a respiratory type of transmission even though the clinical features and transmission studies of viral hepatitis are incongruous with such a conclusion. Measles incidence is highest in late winter and early spring, while the common cold maintains a high incidence throughout fall and winter. This suggests that for these similarly spread diseases the seasons for greater transmission correlate poorly. If one assumes on a logical basis that all droplet-borne diseases tend to greater transmission during fall and winter, one is challenged to explain the differences noted for the two incidence curves. The reconciliation of the appearance of the incidence curve with known facts or logic may lie in the manner in which the incidence curve is examined.

The purpose of this study is to seek out and develop improvements over the present methods of interpreting seasonal variation in disease incidence. An improvement in interpretation should enhance the usefulness of the incidence curve in research and public health practice. The basic approach will be the transforming of the incidence curve to what will be termed the "propagating rate" curve. The treatment of the transformed curve that follows will then vary according to the particular answer sought.

A. The Propagating Rate

To provide a measure of the degree of disease transmission from person-to-person the propagating rate is introduced and defined as the ratio of secondary cases to source cases.

In order to use reported incidence in computing the propagating rate, it is necessary to define source and secondary cases that serve as denominator and numerator, respectively. If the time axis is divided into intervals, each equal to the average incubation period of the disease, then the propagating rate for time interval i may be considered the quotient of the number of reported cases in time interval $i+1$ (the "secondary" cases) divided by the reported cases in time interval i (the "source" cases). Two assumptions have been made: 1) that cases reported in successive intervals of time are generally secondary to those reported in the preceding interval, when the interval equals the average incubation period of the disease; and 2) that the quality of reporting remains more or less stable. Since the propagating rate is a ratio, it is not the excellence of reporting but rather its stability that enables comparison on a seasonal basis.

A second approach in computing the propagating rate is to construct the incidence curve as a continuous smoothed-out curve. The incidence curve may be smoothed-out by use of a moving mean or by a computer type method for estimating density from a histogram, described by Tarter, Holcomb and Kronmal¹. The propagating rate may then be defined in terms of the height of the curve. If the height of the curve at time t is $h(t)$ and at time $t+k$ (where k is the average incubation period) is $h(t+k)$, the propagating rate at time t , $R(t) = h(t+k)/h(t)$. This second definition, though similar to the first, considers a continuous curve for the propagating rate, which can be constructed by the method described below.

Since $\log R(t) = \log h(t+k)/h(t) = \log h(t+k) - \log h(t)$, if the continuous incidence curve is plotted on semi-logarithmic paper, the propagating rate at time t can be evaluated by deducting the height of the log incidence curve at time t from the height of the curve at time $t+k$. Values of the propagating rate above the base line are greater than 1.0 and those below the base line are less than 1.0.

It should be noted that in both methods of computing the propagating rate it has been assumed, as is commonly done, that the interval between source and secondary cases approximates the average incubation period. The basis for this assumption is the observation that acute diseases communicable from man to man tend to be transmitted at or near the time of onset of clinical disease^{2,3}. Thus the interval between a source and secondary case would tend to equal the incubation period. With allowance made for oversimplification, the propagating rate yields a possibly useful method of measuring the level of disease propagation.

At this point it is well to examine the relationship of critical points on the incidence curve to those on the propagating rate curve. In Figure 1, the reported incidence of measles in the United States for 1965⁴ is plotted by weekly intervals on semi-logarithmic paper. (Incidence is plotted on a logarithmic scale with time plotted on an arithmetic scale.) Using a three week moving mean, a smoothed-out continuous curve of log incidence is then drawn. The propagating rates computed by the first method described above, using reported cases for each two week interval (the average incubation period) as a generation of cases, are also plotted and by use of a three week moving mean, a smoothed-out continuous curve is drawn. Comparison of the empirical resulting curves reveals a tendency for definite interrelationships between their respective critical points and these are listed as follows: 1) The minimum on the propagating rate curve is followed one generation (incubation) interval later by the point of inflection of the descending limb of the incidence curve. 2) The maximum on the propagating rate curve is followed one generation interval later by the point of inflection of the ascending limb of the incidence curve. 3) The minimum of the incidence curve occurs 1/2 generation interval after the ascending limb of the propagating rate curve attains the value 1.0. 4) The maximum of the incidence curve occurs 1/2 generation interval after the descending limb of the propagating rate curve attains the value 1.0. A mathematical argument for the above interrelationships between critical points on the incidence and propagating rate curves is included in the Appendix.

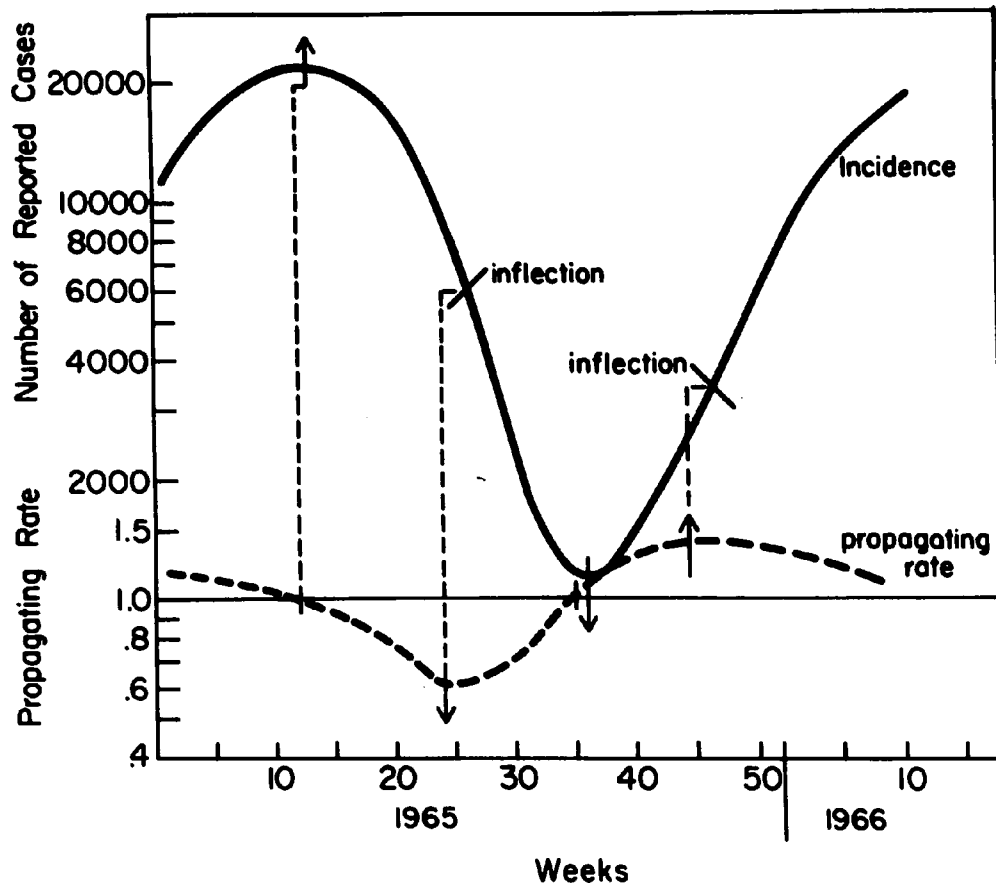


FIGURE 1
MEASLES, U.S.A., 1965
THE RELATIONSHIP OF THE INCIDENCE CURVE TO THE PROPAGATING RATE CURVE

B. Seasonal Variation in the Propagating Rate Curve Compared with that of the Incidence Curve

As an example of how seasonal changes in disease propagation may affect incidence, consider again the incidence and propagating rate curves of measles for 1965, as outlined in Figure 1.

In the first quarter of the year measles incidence is rising while the related portion of the propagating rate curve is falling. A continued rise in incidence despite a declining propagating rate will occur whenever the propagating rate remains greater than 1.0. As noted in the figure, the effect of the propagating rate on the incidence curve lags in time by approximately one incubation period (two weeks). Toward the end of the first quarter the declining propagating rate curve reaches the value 1.0 and this is followed after a lag of about one week by a cessation in the rise of the incidence curve; that is, the incidence curve reaches a maximum.

In the second quarter of the year the propagating rate curve continues its descent and reaches a minimum near the end of the period. The corresponding incidence curve shows both a decline and a decreasing slope. The incidence curve declines whenever the related propagating rate curve remains less than 1.0 and decreases its slope (decelerates) whenever the related propagating rate curve is decreasing in value. When the propagating rate curve reaches a minimum, since it is neither decreasing nor increasing in value, the corresponding point of the descending limb of the incidence curve that follows is a point of inflection. This point of inflection is the transition point between deceleration and acceleration of the incidence curve.

During the third quarter the propagating rate curve is rising. At first it is below 1.0 and therefore the corresponding incidence curve continues to decline, but with increasing slope (acceleration) since the propagating rate curve is increasing in value. About one week after the rising propagating rate attains the value 1.0, the incidence curve ceases its decline; that is, it reaches a minimum.

The propagating rate curve continues above 1.0 until the midpart of the fourth quarter when a maximum is reached. The corresponding section of the incidence curve thus both rises and increases its slope. The maximum of the propagating rate curve is followed two weeks later

by the point of inflection on the ascending limb of the incidence curve. This point of inflection is the transition point between acceleration and deceleration of the incidence curve. For the remainder of 1965 and during the first quarter of 1966 the propagating rate curve is declining but its value remains greater than 1.0. Consequently the corresponding incidence curve continues to climb but with a decreasing slope.

If the propagating rate is accepted as a measure of the level of disease propagation from man to man in a given community, then the following points may be drawn from the above illustration:

1. The onset of a decline in disease propagation may occur well in advance of the onset of a decline in disease incidence. For example, the decline in measles propagation began about the 44th week in 1965, yet incidence continued to rise for an additional 18 weeks before reaching a maximum.

2. The onset of a rise in disease propagation may occur long before the onset of a rise in disease incidence. In 1965, measles propagation began its increase about the 24th week, yet incidence continued to decline until the 36th week when it reached a minimum.

3. The effect of the level of propagation on resulting incidence is delayed in time by one generation, which has been assumed to approximate the mean incubation period of the disease.

When the above relationships between disease propagation and incidence are taken into account, it is understandable how two or more diseases, similarly transmitted from person to person, may simultaneously develop a rise in their respective levels of propagation and still differ widely in the time of onset of a rise in incidence.

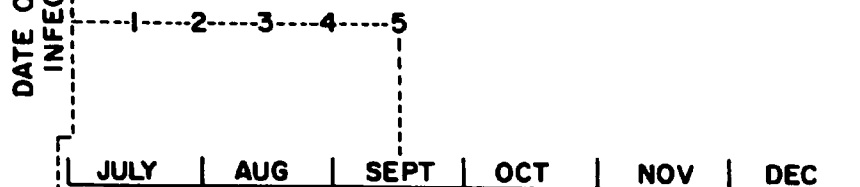
In addition to the propagating rate, the length of the incubation period also affects the slope, or rate of rise or fall, in the incidence curve. Figure 2 illustrates the hypothetical time of occurrence of the fifth generation of cases for three enteric spread diseases when infection of the first case occurs on July 1. Each generation of cases is separated by an interval approximating the mean incubation period of a particular disease. If the propagating

HYPOTHETICAL DATES OF ONSET OF THE FIFTH GENERATION OF CASES

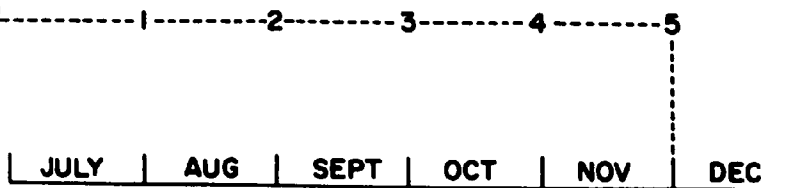
DIARRHEAL DISEASE (BASED ON 4-DAY INCUBATION PERIOD)



POLIOMYELITIS (BASED ON 15-DAY INCUBATION PERIOD)



INFECTIOUS HEPATITIS (BASED ON 30-DAY INCUBATION PERIOD)



* Date of onset OF FIFTH GENERATION

FIGURE 2
INFLUENCE OF THE INCUBATION PERIOD ON THE SEASONAL DISTRIBUTION
OF ENTERIC INFECTIONS

rate by generation of passage were the same for all three diseases, then for each disease an equal number of cases would develop after five generations of passage but the time span required for completion would differ widely.

In Figure 2, the times of occurrence for the fifth generation of cases coincide closely with the periods of highest incidence of these diseases in northern temperate climates. For diarrheal disease with its short incubation period, a high incidence is reached in mid-summer. A disease with an incubation period of two weeks, such as poliomyelitis, achieves a high incidence by early fall. Infectious hepatitis, however, with its much longer incubation period does not reach its fifth generation of passage until late fall. The above concept can be summarized by stating that the time required for a certain incidence level to be reached increases with the length of the incubation period.

C. Measuring Seasonal Variation in Disease Propagation for Diseases with a Short Incubation Period

For diseases with a very short incubation period such as influenza, streptococcal infection and many of the diarrheal diseases, certain difficulties arise in evaluating the levels of seasonal propagation by the methods described. Firstly, morbidity data are usually compiled by week, which may span several generations of passage of these diseases. Secondly, when the interval between successive generations is very small the propagating rate tends to approach the value 1 for any point in time. This is shown as follows:

Let k be the interval between successive generations and approach zero. Then, $R(t) = \lim_{k \rightarrow 0} \frac{h(t+k)}{h(t)} = \frac{h(t+0)}{h(t)} = 1$

When incidence is increasing, however, the corresponding propagating rates must be greater than 1; conversely, when incidence is decreasing, the corresponding propagating rates must be less than 1. Nonetheless, since propagating rates tend to be near 1 when the incubation period is very short, it is difficult to measure and plot the seasonal pattern of the propagating rates.

A suggested solution to the problem is the utilization of the relationship of critical points on the incidence curve to those on the propagating rate curve. It is first necessary to draw a smoothed-out continuous incidence curve on semi-logarithmic paper. The critical points, including the minimum, maximum and inflection points, are then located. The time of occurrence of the corresponding critical points on the propagating rate curve can then be located on the time axis. In Figure 3 the smoothed-out incidence curve for streptococcal sore throat and scarlet fever in the United States for 1966⁴ is drawn and the critical points located. The times of occurrence of the corresponding critical points on the propagating rate curve are represented diagrammatically (without correction for time lag since the incubation period is very small). The maximum and minimum of the propagating rate are shown as to time of occurrence but their relative heights are not evaluated. Locating the points in time when the propagating rate curve attains the base line value 1 enables delineation of the year into seasons of propagating rates above 1 and below 1.

For comparison, rubella with a two to three week incubation period is similarly represented in Figure 3. The smoothed-out incidence curve is drawn and the critical points located. The corresponding points for the propagating rate curve are shown occurring either two weeks prior to the inflection points or one week prior to the extrema of the incidence curve, thus approximating the lag between propagation and clinical disease.

It is observed in Figure 3 that the two diseases, both presumably spread by similar means, have different seasonal time spans for propagating rates above 1 or below 1 but their minimum propagating rates almost coincide in time of occurrence. This latter relationship is investigated more fully in the following chapter.

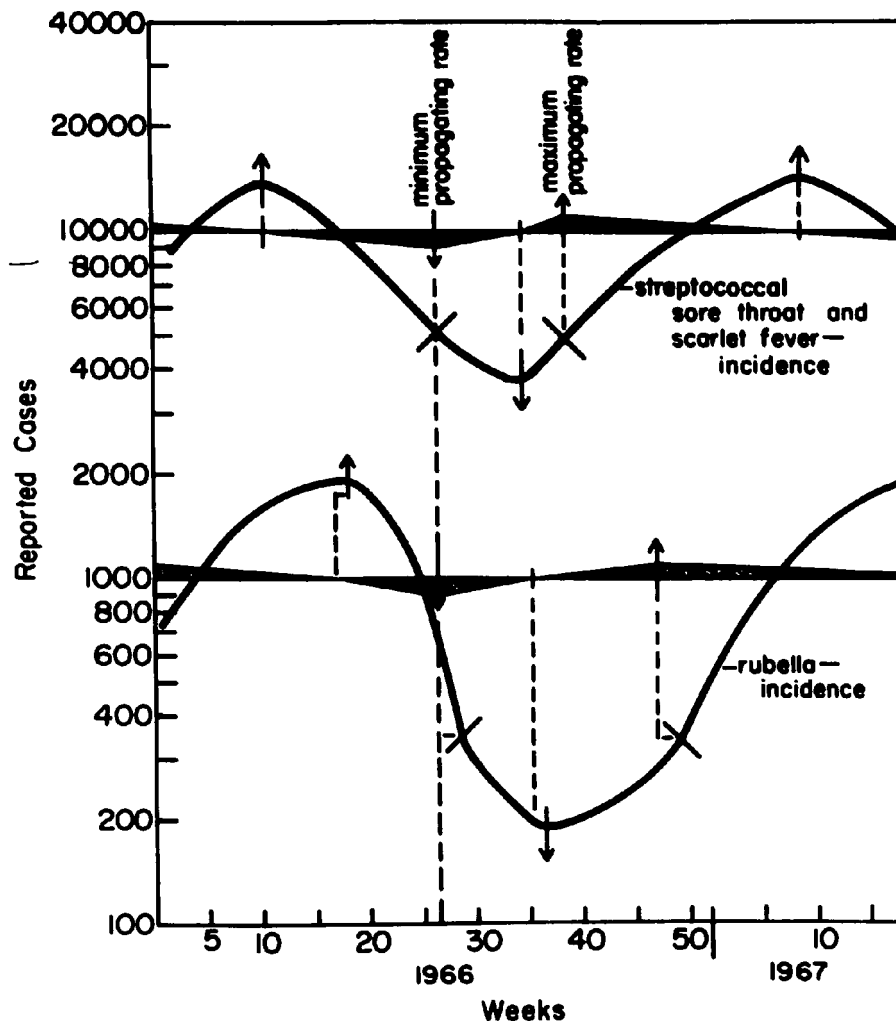


FIGURE 3
RESPIRATORY TRANSMITTED DISEASES, U.S.A., 1966
OUTLINE OF THE SEASONAL PATTERN OF PROPAGATION BASED ON THE TIME OF
OCCURRENCE OF CRITICAL POINTS ON THE INCIDENCE CURVE (I)

Chapter II

THE EFFECT OF MODE OF SPREAD ON THE SEASONAL PATTERN OF DISEASE PROPAGATION

If the seasonal pattern of propagation is determined in large part by the mode of spread, then diseases similarly spread could be expected to have similarities in their propagating rate curves. A comparison of the propagating rate patterns of diseases grouped according to mode of spread is made below.

A. Respiratory Transmitted Disease

Figures 3, 4 and 5 illustrate the findings pertaining to the propagating tendencies of acute respiratory transmitted diseases in the United States based on a review of the weekly Morbidity and Mortality Reports of the National Communicable Disease Center for the period 1952-1967⁴. By using the relationships of critical points on the incidence curve to points on the propagating rate curve, the seasonal pattern of propagation is shown diagrammatically in Figure 5 for streptococcal sore throat and scarlet fever, measles, rubella and meningococcal infections reported during the year 1966. The following relationships between the propagation patterns are noted in Figure 5.

1. There is a trend for the time of occurrence of minimum propagation to coincide closely for all four diseases, usually at about midpoint of the year. This same tendency has been observed with similar data for other years and for other acute respiratory transmitted diseases, provided that preventive measures that have been instituted have not sufficiently altered the natural seasonal pattern of incidence. For example, the tendency for the time of minimum propagation of diphtheria to coincide closely with that of measles can be demonstrated with data reported as recently as 1949, but as immunization against diphtheria became more complete and its incidence curve approached the base line with only minor elevations, the former propagation pattern disappeared.

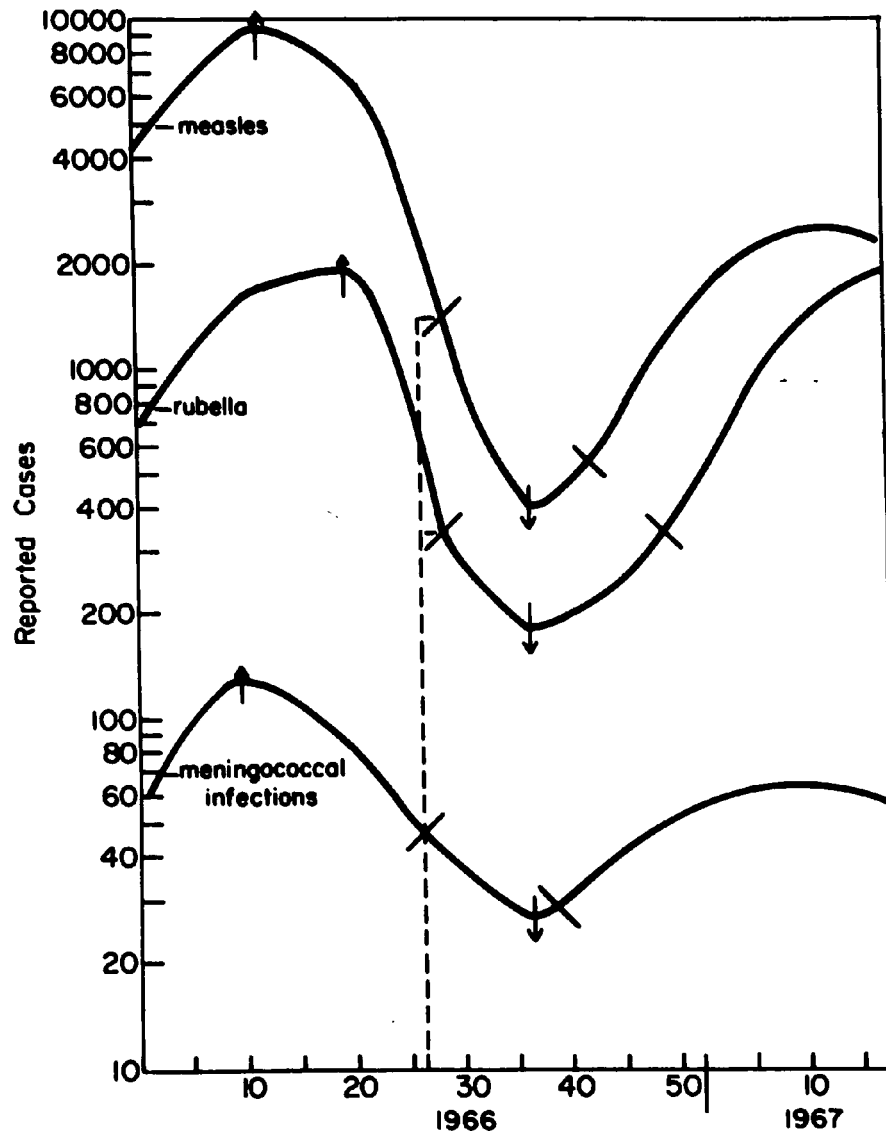


FIGURE 4
RESPIRATORY TRANSMITTED DISEASE, U.S.A., 1966
APPROXIMATION OF THE CRITICAL POINTS ON THE INCIDENCE CURVE

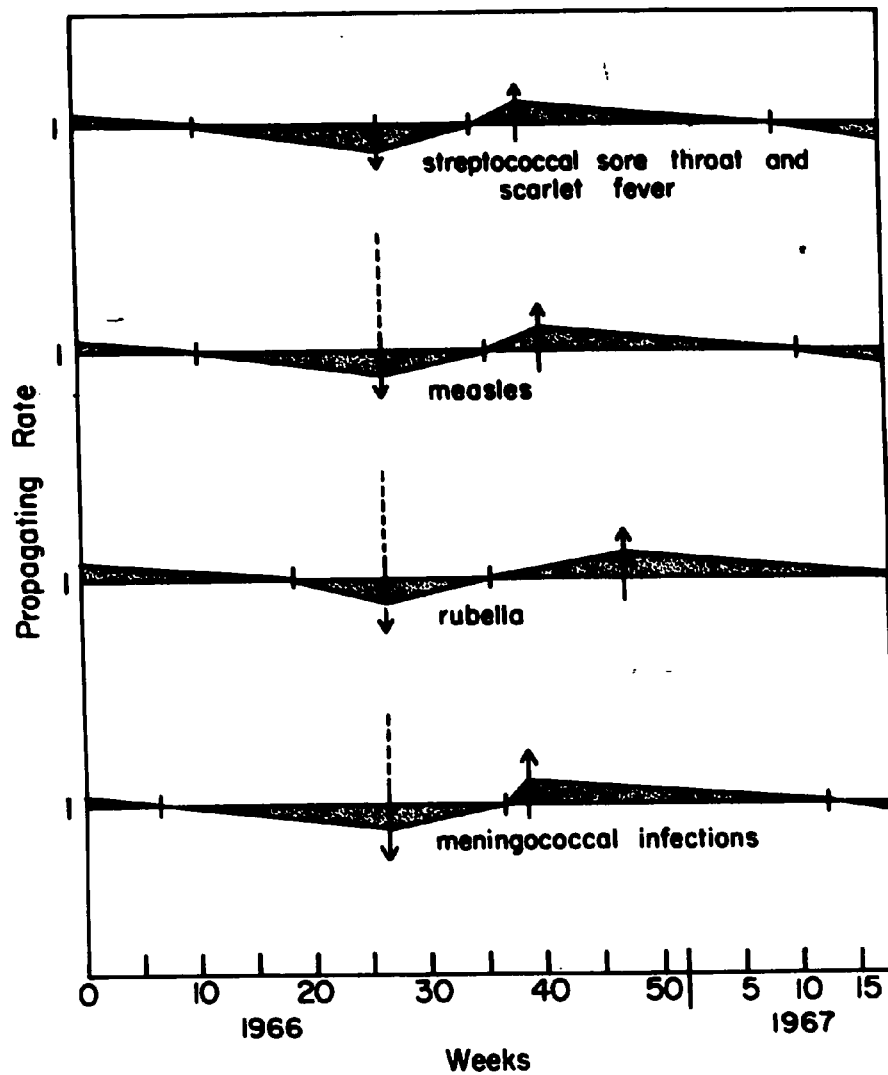


FIGURE 5
RESPIRATORY TRANSMITTED DISEASES, U.S.A., 1966
OUTLINE OF THE SEASONAL PATTERN OF PROPAGATION, BASED ON THE TIME OF
OCCURRENCE OF CRITICAL POINTS ON THE INCIDENCE CURVE (11)

2. The time of changeover from a propagating rate below 1 to a propagating rate above 1 has some tendency to coincide for the diseases under comparison. This tendency, however, appears less marked than does that for minimum propagation. This changeover usually occurs about the beginning of September.

3. The time of occurrence of maximum propagation varies considerably for the different diseases but this variation seems to follow a more or less predictable pattern. It appears that the longer the incubation period is, the later will be the occurrence of maximum propagation. In addition to the length of the incubation period, other factors may account for the speed of attaining maximum propagation; these will be discussed below.

4. The time of occurrence of the changeover from a propagating rate above 1 to a propagating rate below 1 also varies considerably. As with maximum propagation, the longer the incubation period the later seems to be the occurrence of this changeover.

To explain the propagation patterns noted above, it is necessary to examine two major influences involved in disease propagation: availability of susceptibles and favorability of environmental conditions. Availability of a large proportion of susceptibles in a given population is not in itself sufficient assurance that a given person-to-person disease will be propagated from infective individuals. Of importance is whether the susceptibles are distributed mainly among social aggregates or clusters with high or low risk of transmission. Some clusters may favor propagation by one mode of spread more than by another. For example, a cluster experiencing considerable crowding has a high risk for propagation of respiratory spread disease. This same cluster may otherwise practice excellent hygiene and be at low risk for propagation of fecal-oral spread disease.

Assume the presence of infectives within clusters containing available susceptibles. The rate of exhaustion of available susceptibles within a cluster will tend to vary inversely with the length of the incubation period, since the shorter the incubation period the more generations of passage can occur within a given time. A more rapid

decrease in the proportion of available susceptibles, however, tends to cause a more rapid fall in the propagating rate. This may explain the earlier occurrence of maximum propagation (which is the same as saying the earlier onset of a fall in the propagation level), as well as the earlier changeover from a propagating rate level above 1 to that below 1, for diseases with a shorter incubation period.

If there is the presence in the community of large numbers of high risk clusters containing a high proportion of susceptibles, as it appears to be with streptococcal sore throat, there would be the tendency for a delay in the attainment of maximum propagation assuming continued favorable environmental factors.

To summarize the above reasoning, two factors are suggested as favoring the earlier occurrence of a maximum propagation level: first, a shorter incubation period and second, a smaller number of available susceptibles or high risk clusters.

The tendency for the minimum propagation levels of respiratory spread disease to coincide in time of occurrence is explained in the following manner. With the recurrence of environmental conditions unfavorable to propagation, low propagating rates result for all respiratory transmitted diseases with a resulting fall in incidence. A lowered incidence could be expected to result in a decreased concentration of infectives and a greater remaining proportion of available susceptibles within affected clusters. When environmental conditions favoring respiratory spread begin to increase, a simultaneous increase in the propagation level of all diseases in the group could result since the infectives for each of the diseases would tend to be distributed among adequate numbers of susceptibles to whom propagation may take place.

To repeat, it is suggested that for the minimum propagation levels to coincide in time of occurrence it is essential that the infectives for each disease be distributed within clusters containing relatively high proportions of susceptibles; this may result in a rise in the propagation level in response to the increase in environmental factors favoring spread. It is further suggested that this redistribution of

infectives may exist when a period of relatively low incidence has preceded the onset of rise in environmental factors favoring spread. Should this re-distribution not yet have occurred and should the infectives be present mainly within clusters containing a small proportion of susceptibles, then a continued fall in the propagating rate within affected clusters would tend to overshadow any rise in propagation stimulated by an improvement in environmental factors. For the respiratory diseases used in this comparative study, the conditions essential for the minimum propagation levels to coincide in time are apparently satisfied.

B. Enteric Transmitted Diseases

Most enteric spread diseases in the United States have declined markedly in incidence and have been more or less confined to certain high risk groups among the population. It has been less difficult to control fecal-oral transmission than respiratory droplet transmission. Contributing to the reduction in enteric spread disease have been the installation of municipal water and sewerage systems, improved wells and septic tanks, safer food processing and storage, cleaner households, vector control, and improvement in personal hygienic practices. Also of importance have been such specific measures as immunization against poliomyelitis and drug therapy for diseases of bacterial origin.

As an enteric spread disease is reduced to only a small number of reported cases, there is a concomitant loss of its characteristic seasonal periodicity. As a result it has been difficult to outline a distinct seasonal pattern of propagation for enteric spread diseases using recently reported data for the United States, with few exceptions.

Unlike respiratory spread diseases that are transmitted mainly by respiratory droplets, enteric spread diseases may be transmitted by a number of routes. Depending upon the dominant routes of spread, varying seasonal propagation patterns could be expected to result.

In the United States viral hepatitis* is presently the most commonly reported enteric spread disease. The smoothed-out incidence and propagating rate curves for viral hepatitis in the United States in 1952 are drawn in Figure 6. A four week interval between succeeding generations is used in computing the propagating rates. The resulting pattern of the propagating rate may be considered typical of the patterns developed for other years. In Figure 6 the propagating rate curve lies below the base level 1 from the 4th week of the year to almost midyear. It then rises above the value 1 and continues to an ill-defined maximum that occurs about early fall. It then declines to a minimum level just above 1 by late fall and finally rises to a second and greater maximum at the end of the year. Within a few weeks after the second maximum the curve declines to a level below 1. Both periods of the year at which the propagating rate curve is highest correspond to the periods during which social mixing and person-to-person contact seem most intense, that is during the warmer months and particularly at the year-end holiday season. This suggests the need for further study of this relationship.

The Israeli experience with viral hepatitis is illustrated in Figure 7, based on data obtained from the Israel Central Bureau of Statistics.⁵ Because of the relatively small numbers of reported cases, cases for a given month are totalled for the 13 year period 1953-1965 and the monthly totals adjusted to give equal length to each month (Table 1). Using a one month interval between generations, the monthly propagating rates are computed. Figure 6 and Figure 7 are compared. It is interesting to note that the composite propagating rate pattern for viral hepatitis in Israel is essentially unimodal, with the rates above 1 occurring during the warmer months, June to November. The highest levels are reached during the main holiday period, which occurs in Israel in September and October. The absence of a marked year-end rise in the propagating rate in Israel may reflect less intense person-to-person contact than experienced in the United States for the same period.

* Most of the cases reported as viral hepatitis are thought to be cases of infectious hepatitis.

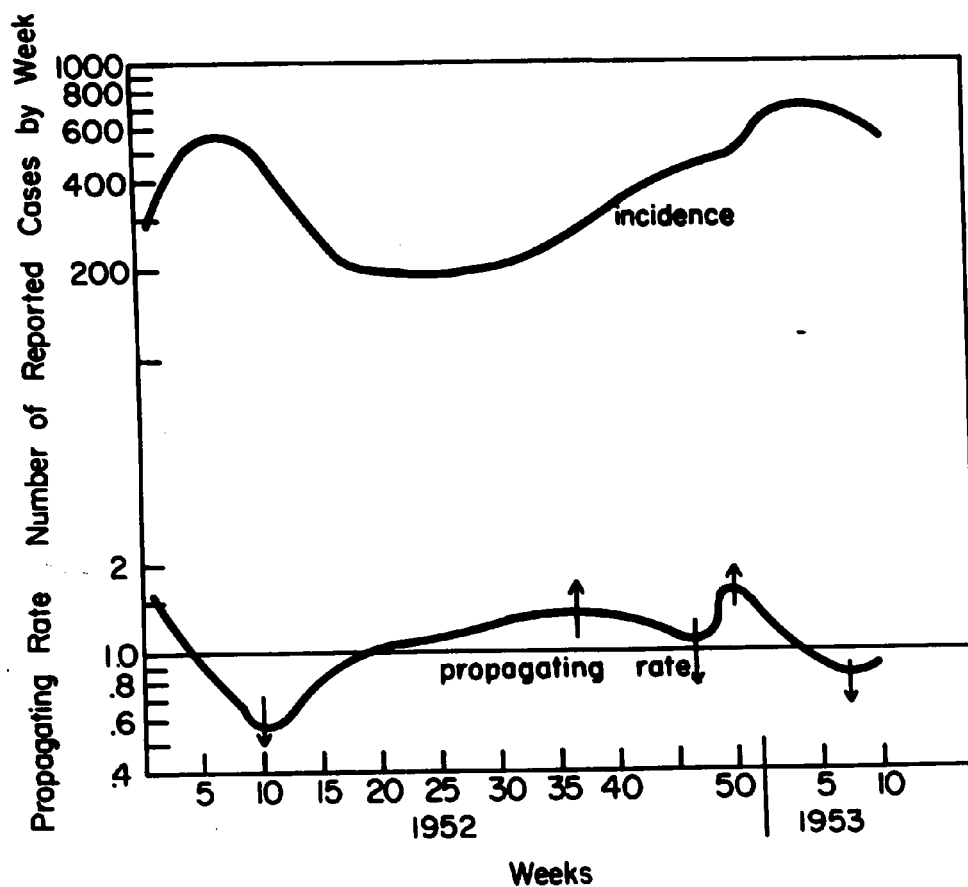


FIGURE 6
VIRAL HEPATITIS, U.S.A., 1952
THE SEASONAL INCIDENCE AND PROPAGATING RATE CURVES

Table 1

Viral Hepatitis
Reported Cases and Propagating Rate by Month, Israel, 1953-1965

Year	Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.	Jan.
1953 Cases	168*	144	108	71	41	40	35	43	50	72	129	150	119
Rate	.95**	.68	.68	.55	1.03	.83	1.24	1.22	1.38	1.87	1.12	.79	
1954 Cases	119	75	50	40	35	52	72	130	182	185	248	270	175
Rate	.69	.60	.83	.83	1.58	1.33	1.81	1.46	.98	1.39	1.05	.65	
1955 Cases	175	130	99	59	80	55	55	52	74	96	140	174	176
Rate	.82	.68	.62	1.31	.71	.96	.94	1.48	1.24	1.52	1.20	1.01	
1956 Cases	176	83	71	68	32	39	56	56	87	162	173	246	245
Rate	.52	.77	1.00	.44	1.30	1.38	1.00	1.61	1.79	1.11	1.38	1.00	
1957 Cases	245	121	113	81	45	49	44	37	39	65	54	113	140
Rate	.54	.85	.74	.53	1.14	.86	.83	1.11	1.59	.87	2.02	1.24	
1958 Cases	140	92	117	73	76	92	143	151	113	188	206	194	180
Rate	.73	1.53	.65	1.00	1.26	1.50	1.06	.77	1.60	1.14	.91	.93	
1959 Cases	180	142	144	120	149	76	77	82	94	78	109	196	150
Rate	.87	.91	.86	1.20	.53	.97	1.07	1.19	.80	1.45	1.73	.77	
1960 Cases	150	158	195	168	159	208	195	264	301	289	352	288	305
Rate	1.17	1.11	.89	.91	1.36	.90	1.36	1.18	.93	1.26	.79	1.06	
1961 Cases	305	237	184	118	76	57	59	44	46	47	46	51	66
Rate	.87	.70	.66	.62	.78	1.00	.74	1.10	.98	1.02	1.07	1.29	
1962 Cases	66	49	52	32	42	72	126	200	267	430	486	457	521
Rate	.83	.96	.64	1.25	1.80	1.68	1.60	1.38	1.56	1.17	.91	1.14	
1963 Cases	521	299	205	117	121	101	81	79	68	82	70	100	167
Rate	.64	.62	.59	1.00	.86	.77	.97	.90	1.16	.89	1.37	1.68	
1964 Cases	167	129	108	96	100	64	115	110	121	199	225	286	284
Rate	.86	.75	.92	1.00	.67	1.73	.96	1.14	1.59	1.17	1.23	.99	
1965 Cases	284	287	234	134	119	127	130	121	128	160	203	237	223
Rate	1.12	.74	.59	.86	1.10	.98	.94	1.09	1.20	1.34	1.11	.94	
Composite*** Propagating Rate	.80	.78	.72	.88	.99	1.15	1.15	1.19	1.27	1.23	1.10	1.00	

*Reported cases by month

**Propagating rate by month, adjusted by weighting length of each month to 30 days

***See text for method of computation

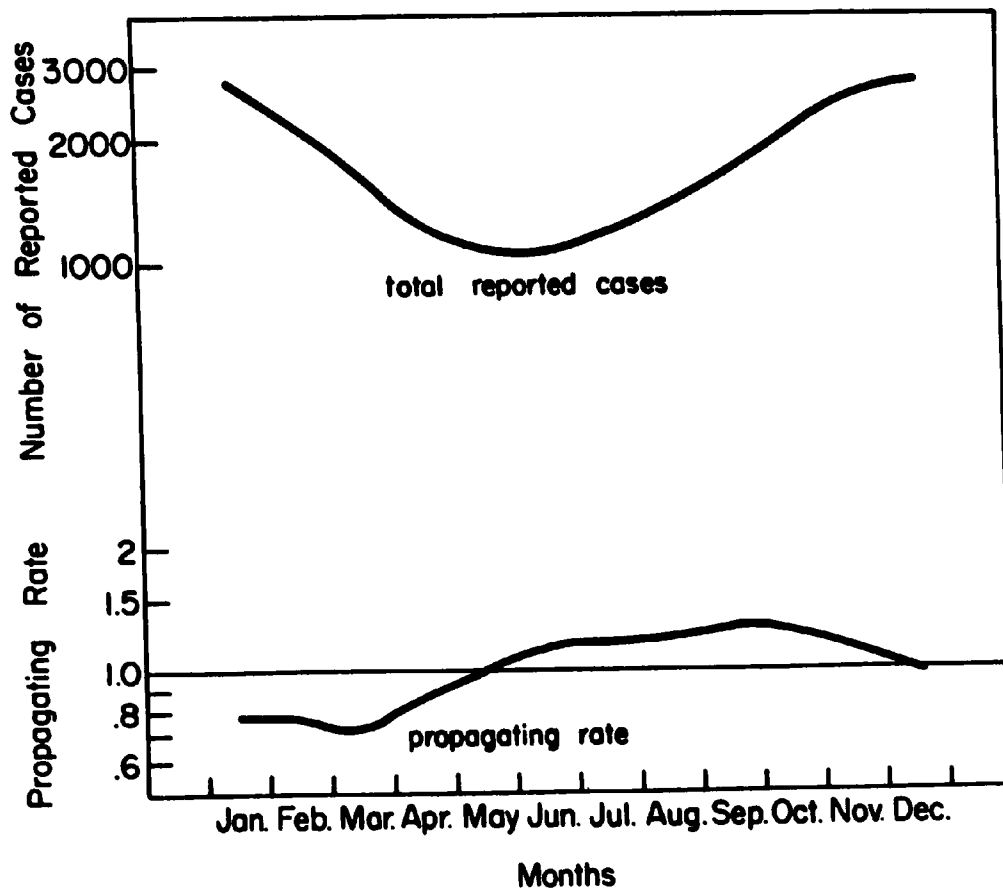


FIGURE 7

VIRAL HEPATITIS, ISRAEL, 1953-1965

THE TOTAL CASES REPORTED (ADJUSTED) DURING A 13 YEAR PERIOD BY MONTH
& THE PROPAGATING RATE BY MONTH BASED ON THESE MONTHLY CASE TOTALS

The incidence and propagating rate curves for poliomyelitis in the United States for the year 1952 are shown in Figure 8. The seasonal pattern is similar to those of other years before effective control of the disease through immunization was introduced. A comparison of the propagating rate pattern of poliomyelitis with that of viral hepatitis in Figure 6 reveals considerable differences. While these differences might be explained on the basis of dissimilar routes of transmission, another approach to reconcile these differences is contained in the following reasoning.

Infectious hepatitis, because of its long incubation period, tends only to slow build-ups or declines in incidence whenever factors favoring transmission alter in intensity with the changing seasons of the year. In contrast, poliomyelitis, with a much shorter incubation period of about 10 days, may develop more rapid rises or falls in incidence level with a consequent tendency to greater variability in the remaining proportion of susceptibles within affected clusters at different seasons of the year -- a tendency to relatively high proportions of susceptibles following low incidence levels but relatively low proportions following high incidence levels.

Assuming that infectious hepatitis and poliomyelitis have identical routes of spread, their different propagating rate patterns could then be explained on the basis of availability of susceptibles. The earlier attainment of the maximum propagating rate for poliomyelitis could be the result of the more rapid using up of susceptibles within affected clusters. At the end of the year an increase in environmental factors favoring disease propagation may be reflected less strongly for poliomyelitis because of a lesser proportion of available susceptibles within the affected clusters than exists for infectious hepatitis. It should be noted that shortly before this period poliomyelitis had been at a relatively high incidence level. Therefore the proportion of susceptibles in clusters possessing infectives was probably reduced.

The above is not intended to imply that the propagating rate curve of poliomyelitis is unaltered by an increase of environmental

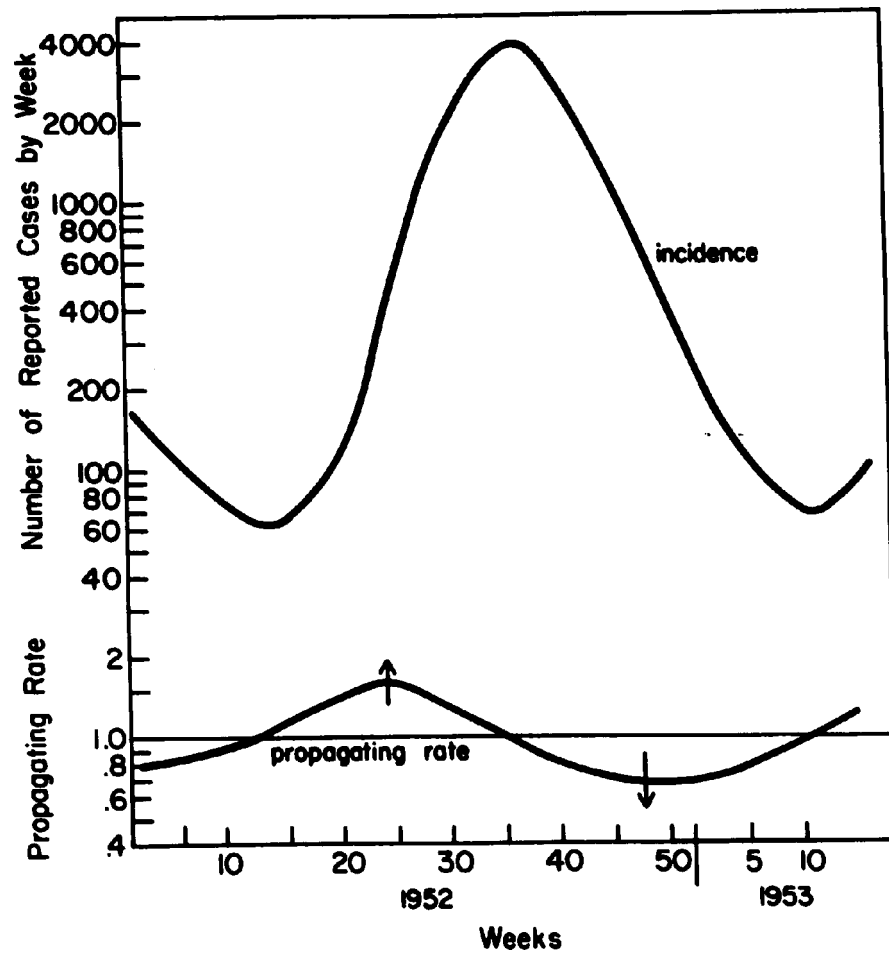


FIGURE 8
POLIOMYELITIS, U.S.A., 1952
THE SEASONAL INCIDENCE AND PROPAGATING RATE CURVES

conditions favoring spread at the end of the year. Rather it is suggested that the influence of environmental conditions is partially masked by the reduction of available susceptibles within affected clusters.

C. Diseases Transmitted by Other Modes of Spread

With some modifications, the same basic approach used in measuring and plotting the propagating rates for respiratory and enteric spread diseases might be applied to diseases having other modes of transmission, e.g., by insect-vector spread, provided that the human host is, as assumed for respiratory and enteric spread diseases, the reservoir for most infections. The various modifications in method will not be pursued except to illustrate briefly how they might be instituted for vivax malaria.

The first step, as previously described, is drawing the smoothed-out incidence curve on semi-logarithmic paper. For malaria, the interval between source and secondary case cannot be estimated to equal the average length of the incubation period. Instead, the interval will be estimated to equal the total of the following three component intervals.

1. Following the onset of clinical symptoms there is a delay of three to fourteen days before gametocytes appear in the blood. Consider also that the quality of the gametocytes seems to deteriorate progressively with time, inhibiting their effectiveness to cause infection in the mosquito vector. Therefore, a degree of limitation exists as to time of transmission. The most likely time of transmission from human host to mosquito might be estimated to occur, on the average, 10 days following the onset of clinical symptoms.⁶

2. The incubation period in the Anopheles mosquito, from infection to excretion of sporozoites, is ten days. For transmission from infective mosquito to a human host the process must take place within several days following onset of excretion of sporozoites since the usual life span of the mosquito under natural conditions is surprisingly short, perhaps no more than fifteen days in length.

The interval from infection of the mosquito to transmission to a human host will be estimated as averaging 12 days.^{7, 8}

3. The incubation period for Plasmodium vivax in the human host is about 14 days.

The interval from clinical onset of a source case to clinical onset of a secondary case may be estimated as the total of the above component intervals, $10 + 12 + 14 = 36$ days. The propagating rates may now be determined using the difference in heights of the incidence curve plotted on semi-logarithmic paper, with source and secondary heights separated by an interval of 36 days or approximately five weeks.

The computed propagating rate must be assigned to a proper place in time. For enteric and respiratory spread diseases the propagating rates were assigned to the time of onset of the source case since it was presumed that transmission took place at or near this time.

However, for malaria the two steps in transmission from human source case to human secondary case were estimated to occur first at 10 days and then at $10 + 12 = 22$ days following clinical onset of the source case. The propagating rate might then be assigned midway between these points in time, namely at 16 days following the onset of the source case, thereby approximating the period during which combined propagation takes place. Vector-borne diseases will be further considered in a later section.

Chapter III

APPLICATIONS OF THE PROPAGATING RATE METHOD OF INTERPRETING INCIDENCE

Several examples of the possible use of the propagating rate method in public health research and practice will be described briefly.

A. Studying the Relationship of Various Factors to Disease

Propagation

The relationship of temperature to the incidence level of viral hepatitis in Israel has been previously studied. The conclusion drawn was that comparisons of temperature with incidence failed to show any consistent correlation.⁹ The temperature-incidence relationship will now be re-examined using the propagating rate method.

Figure 9 shows the monthly average propagating rate and incidence in Israel for the period 1953 to 1965. For the same period the monthly average minimum and maximum daily temperatures for Tel Aviv, the demographic center of the country, are also plotted. Unlike the relationship of incidence with temperature, a fairly direct relationship of the propagating rate to the rise and fall in mean temperature is shown in Figure 9. Further study is needed to determine the nature of the relationship between temperature and the propagation rate. Similar comparisons may be extended to other geographic areas and other factors studied as well.

B. Predicting Incidence

A commonly used method of predicting disease incidence is by determining the median or mean incidence for the preceding five years for the comparable period. Another approach is by use of the

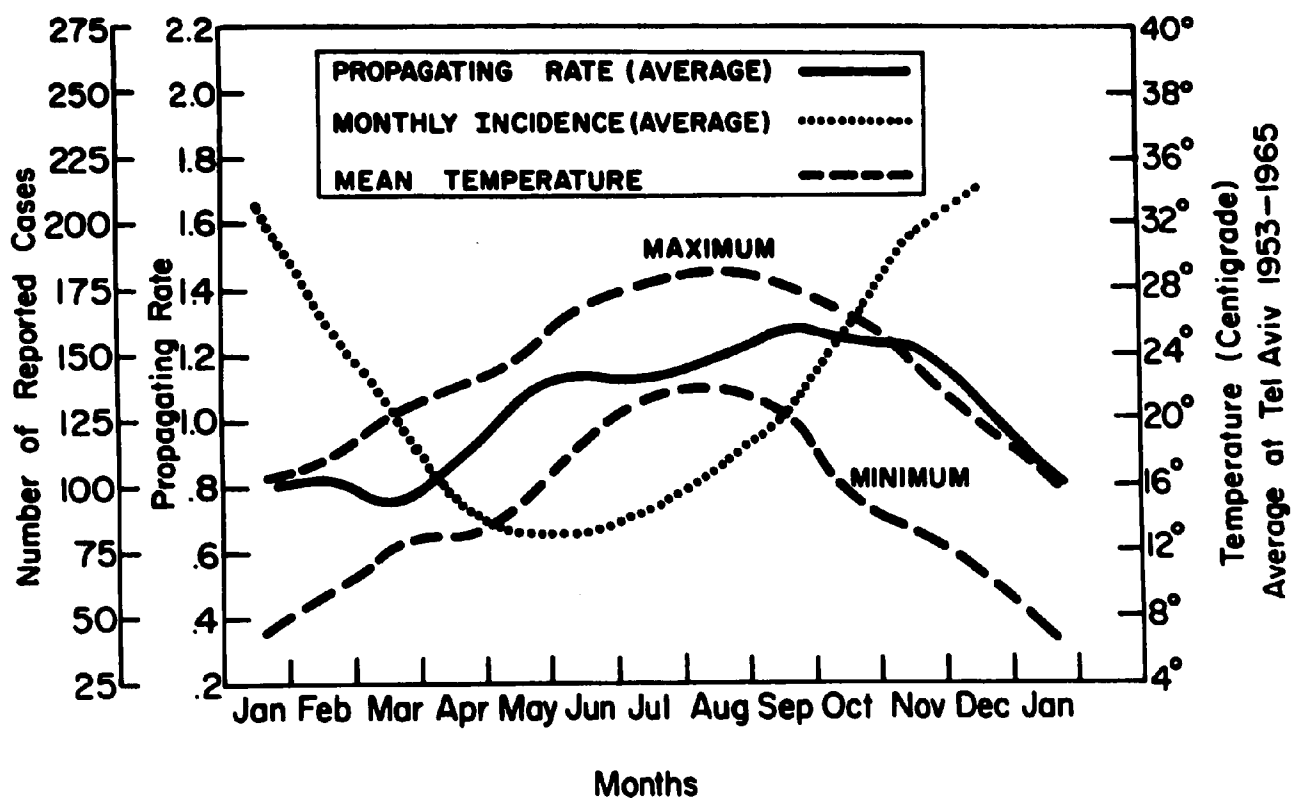


FIGURE 9
RELATIONSHIP OF THE AVERAGE MONTHLY PROPAGATING RATE OF VIRAL
HEPATITIS IN ISRAEL TO MEAN TEMPERATURE, 1953-1965

propagating rate experienced in previous years. This latter method is demonstrated for viral hepatitis in the United States in Table 2 and Figure 10.

The first column of Table 2 lists the years 1965 and 1966 in 4 week intervals. The second column gives the average propagating rate over the preceding five years for the given intervals. In the third column the number of cases listed for the respective interval has been predicted eight weeks (2 intervals) in advance. The prediction of the number of cases for interval 3, for example, is based on the number of cases reported in interval 1 and the average propagating rates listed for intervals 1 and 2. The method is represented symbolically as follows:

$$\text{Cases}(I) * \text{MR}(I) * \text{MR}(I+1) \rightarrow \text{PCases}(I+2)$$

where $\text{Cases}(I)$ is the known number of reported cases for interval I ,
 $\text{MR}(I)$ and $\text{MR}(I+1)$ are the mean propagating rates for the
preceding five years for intervals I and $I+1$ respectively,
and

$\text{PCases}(I+2)$ is the predicted number of reported cases for
interval $I+2$.

The fourth column lists the known number of reported cases for each interval. The last column compares the predicted or expected (E) to the known number of reported or observed cases (O). The use of the antilog of the absolute $\log O/E$ results in a comparison that gives as much weight to underpredicting as it does to overpredicting.

The results in Table 2 are graphically depicted in Figure 10. In the instance shown the propagating rate method gives a much closer prediction of incidence than does the previous five year average incidence experience. The average proportional error of prediction, obtained by averaging the ratios in the last column of Table 2 and deducting the base ratio 1, was approximately .08 or 8%. The above method was tried for a series of consecutive years with similar results. This represents a marked improvement over the usual methods of predicting.

Table 2

Predicting the Number of Reported Cases of Viral Hepatitis
in the U.S.A. 8 weeks in Advance by the Propagating Rate Method

Year, by 4 Week Intervals	Propagating Rate Average for Preceding 5 Years	Predicted Number of Reported Cases 2 Intervals (8 weeks) in Advance (E)	Number of Reported Cases (O)	Antilog (Log O/E)
1965				
1	1.122	--	3102	--
2	.949	--	3123	--
3	.939	3303	3132	1.055
4	.956	2783	2900	1.042
5	.822	2812	2481	1.113
6	.836	2279	2231	1.022
7	1.073	1705	2041	1.197
8	.981	2001	2135	1.067
9	1.166	2148	2192	1.020
10	1.018	2442	2592	1.061
11	.975	2602	2523	1.031
12	1.084	2573	2513	1.024
13	1.194	2667	2515	1.060
1966				
1	1.108	3252	2833	1.148
2	.948	3327	3013	1.104
3	.901	2976	3005	1.010
4	.929	2573	2640	1.026
5	.844	2516	2488	1.011
6	.848	2070	2546	1.230
7	1.060	1781	2056	1.154
8	.973	2289	2348	1.026
9	1.167	2120	2177	1.027
10	.994	2667	2429	1.098
11	.965	2526	2743	1.086
12	1.056	2330	2870	1.232
13	1.127	2796	2791	1.002
Average = 1.08				

Average proportional error of estimate = 8%

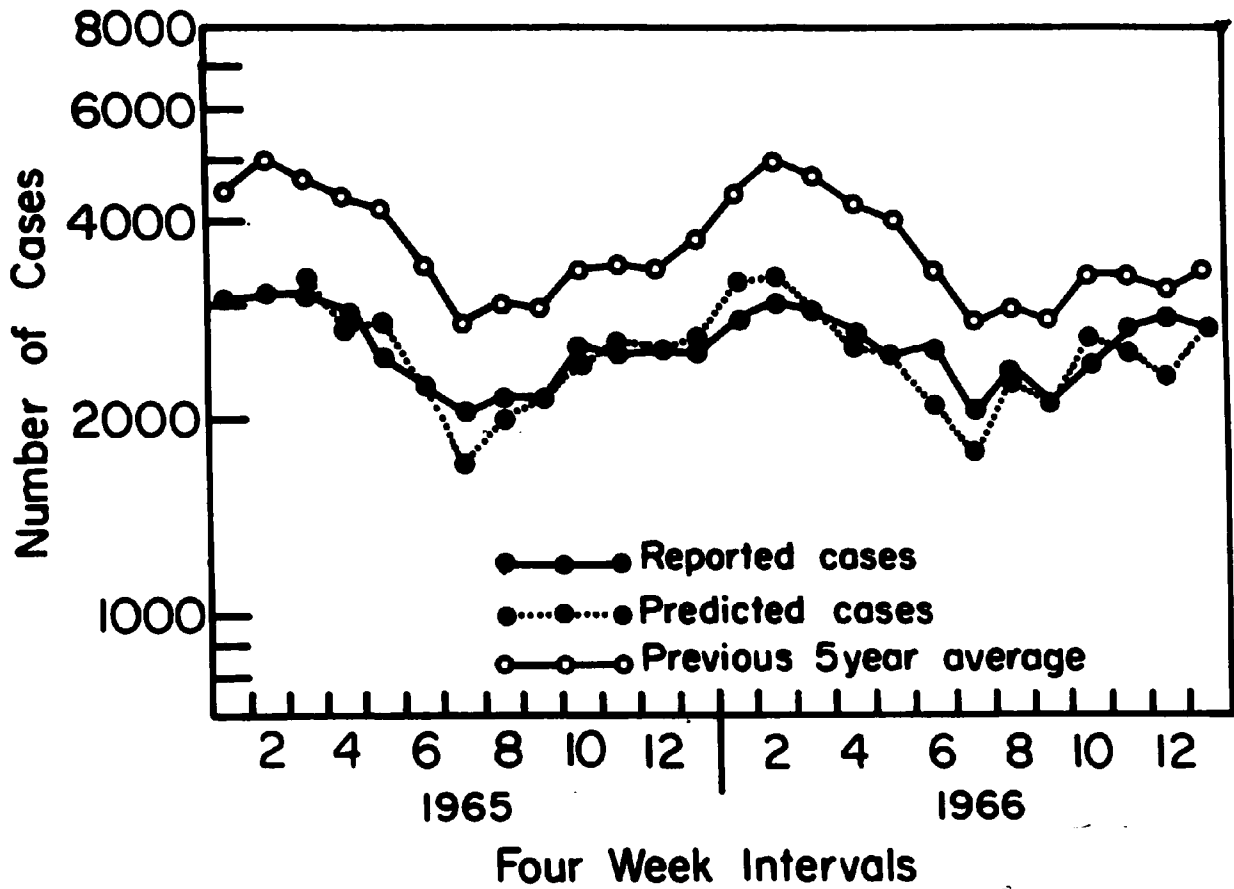


FIGURE 10
PREDICTING THE NUMBER OF REPORTED CASES OF VIRAL HEPATITIS, U.S.A.,
1965-1966 EIGHT WEEKS IN ADVANCE BY THE PROPAGATING RATE METHOD

The further into the future the prediction, the greater was the average proportional error of prediction obtained. Thus for viral hepatitis in the United States for 1965 and 1966, when the prediction was for four weeks (one interval) in advance, the average error was only 6% as opposed to 8% for two intervals in advance. Variations in the above method of predicting may be used, such as developing the average propagating rate from more or fewer years and using the composite propagating rates determined by totalling reported cases for an interval over a number of years. The length of the interval used in the formula for predicting is the interval between generations, which for person-to-person spread disease is estimated to equal the length of the incubation period.

The advantage of the propagating rate method of predicting is that it is a product of the most recent incidence experience (number of cases in the last reported interval) and of past year tendencies (the average propagating rate for the preceding years). Other methods tend to rely on incidence experience of past years alone.

C. Disease Control Planning - Selecting the Most Advantageous Time of Conducting A Limited Control Program

When resources are limited it is desirable to know at which time a given amount of disease control may yield maximum benefit.

Consider the following hypothetical situation: an acute communicable disease has an incidence pattern with a seasonal high and a seasonal low; that treatment can render an infective non-communicable prior to any propagation; that a treatment program is to be applied only during a limited period of time such as the average interval between succeeding generations of cases; and that both before and after the application of the program the usual propagating rate pattern prevails. Assume that for each infective rendered non-communicable one figurative unit of control is required.

To obtain an equivalent reduction of disease incidence subsequent to the operation of the control program, with least expenditure of control units, the program should be conducted during the time period

of lowest incidence. To illustrate, (Figure 11) suppose the program is conducted instead during the highest incidence period over one generation interval of time and further suppose that the number of infectives occurring within this period is 50 times that occurring in a similar period during the lowest incidence season. To reduce the number of infectives, say by one-half, will then require 50 times the number of control units necessary had the lowest incidence season been chosen. Yet, with either choice, assuming resumption of the usual seasonal pattern of propagation, the subsequent reduction in cases would be similar.

The above illustration presumes that following the application of the control program the propagating rate pattern will return to a course that would have been followed had the program not been applied. A reduction in subsequent incidence, however, slows the rate of depletion in the pool of susceptibles and this may favor a rise in the propagating rate above the seasonal level, and thereby progressively lessen the continuing benefit of the original control program.

D. Evaluating the Effectiveness of a Control Program

The initial step in evaluating the effectiveness of a control program is in developing a base line for comparison. This may consist of a propagating rate curve composed of the median propagating rates, for specific time intervals, experienced for the disease for a number of years preceding the commencement of the program. A tendency for propagating rate values to be lower than median values during the application of control measures would be suggestive of efficacy in the controls instituted.

Several pitfalls in interpreting the results should be noted.

- 1) The institution of a control measure may stimulate greater interest in reporting the disease and thus alter the quality of reporting with an effect on the propagating rates. Such changes in quality of reporting, however, can be expected to level off, either to the former level or to a new plateau, and thereby enable truer comparisons.

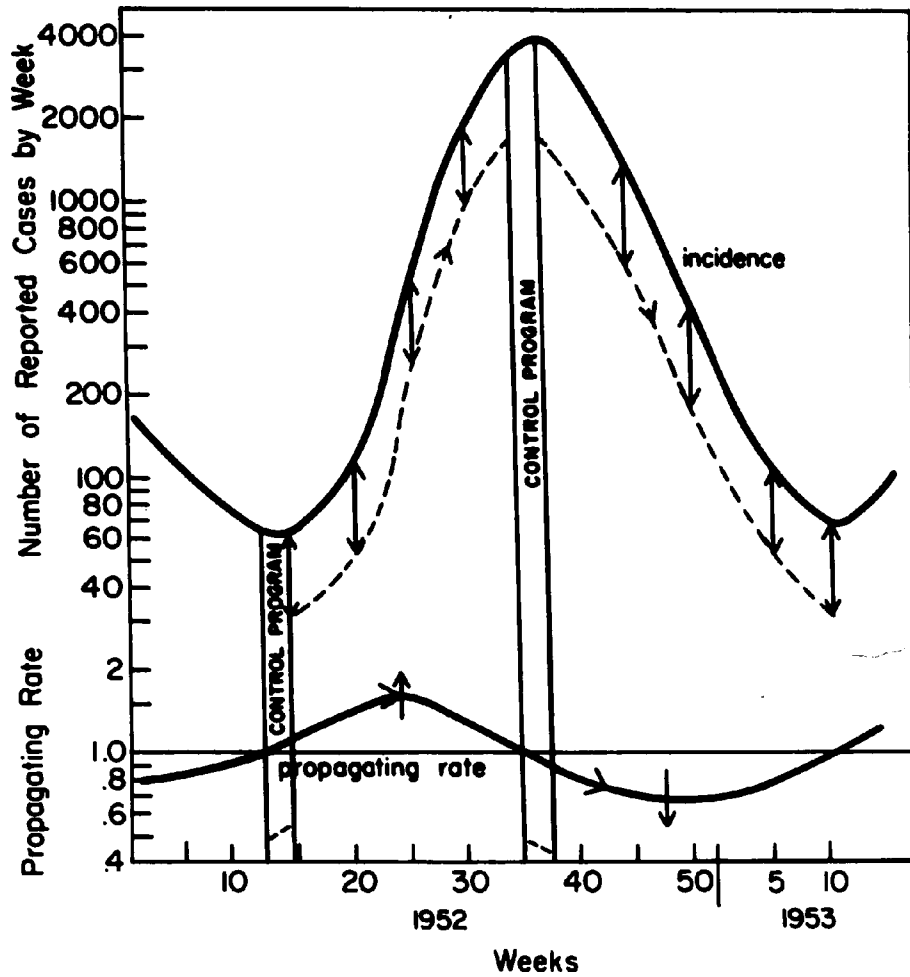


FIGURE 11

Time-selective application of treatment to render infectives non-communicable. Assuming resumption of normal propagating rates following treatment, to yield the same reduction in cases more treatment is required during high incidence than during low incidence, since the proportion of infectives treated is the same.

2) Since some variability in the propagating rates for a given interval occurs from year to year, conclusions based solely on small changes in magnitude for only a limited time span may not be meaningful. 3) If the control program is not being applied relatively uniformly to all parts of the population used in the measurement of the propagating rates, the interpretation of the results may be paradoxical. For example, when treatment is directed mainly against a particular segment of the population, a marked reduction in incidence among the treated will tend to make subsequent incidence more a product of the untreated group. If now, during the period under observation, the untreated normally experience higher propagating rates than the treated, then despite continuance of the treatment program, higher propagating rates may result -- with the possible erroneous conclusion that the control program has become less effective or even detrimental.

Even when control measures are known to be of definite value, an examination of the control effort by the above method may prove useful. Figure 12 shows the incidence and propagating rates of measles in the United States for biweekly periods for the years 1965-67, during which a considerable vaccination effort against measles was in progress. For comparison, the median incidence and propagating rate values for respective intervals based on the experience of 1960-64, is drawn in a recurring cyclic fashion. During the 1960-64 period measles vaccination was minimal and the incidence curves for individual years are closely similar both in magnitude and quality. In computing the propagating rates the interval between generations was estimated at 2 weeks. It is observed in Figure 12 that the propagating rates during the first half of each of the years 1965-1967 tend to be lower than those of the median values for 1960-64 while during the third quarter of each year they tend to be higher. During the fourth quarter no clear tendencies are noted.

What is evident from the above is that a uniform reduction in the level of propagation has not occurred throughout the whole year

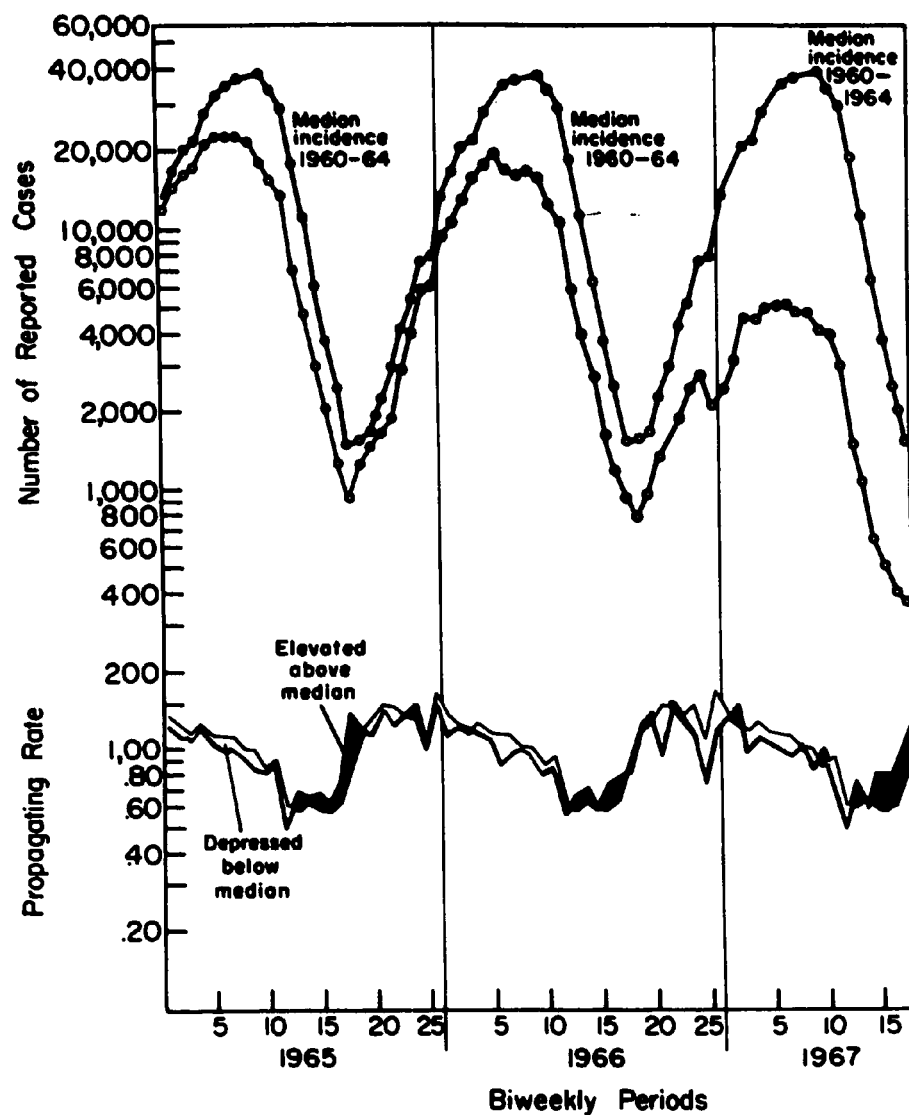


FIGURE 12
INCIDENCE AND PROPAGATING RATES OF MEASLES, U.S.A., 1965-1967
COMPARED WITH MEDIAN VALUES FOR 1960-1964

since massive measles vaccination was begun. The propagating rates tend to be reduced during the first half of each year which is also the period of greatest incidence. The reverse tendency occurs during the third quarter of the year which is the period of lowest incidence.

The comparative increase in the propagating rates during the third quarter was not explainable on the basis of disproportional decreases in incidence among different geographic regions of the country, in order to produce a "paradoxical" rise. A possible explanation for the above increase is as follows: Immunization not only protects the vaccinated but blocks further transmission and may thus contribute to a larger pool of susceptibles within social clusters. The higher the proportion of available susceptibles the greater the likelihood of propagation when an infective is introduced into the cluster. Should the control program be sufficiently relaxed during the third quarter with lower incidence, higher propagating rates could occur as a result of the increased proportion of available susceptibles.

E. Estimating the Incubation Period for a Person-to-Person Spread Disease in a Closed Population

The development of a method for closely estimating the incubation period of a disease by utilizing the characteristics of its incidence curve could prove helpful in the further investigation of the disease as to source and etiology. The method presented here, which makes use of the propagating rate, is developed by first constructing a model outbreak of person-to-person spread disease in a closed population. The attempt throughout will be to maintain simplicity of approach yet provide a rule-of-thumb method of estimating certain parameters. Other models concerning disease transmission¹² usually involve a degree of mathematics beyond the background training of most public health workers whose understanding of the method presented is necessary for practical application and trial.

The considerations upon which the outbreak and, subsequently, the formula for the estimated incubation period are based will be briefly outlined.

1) Reviewing incidence curves of closed population* outbreaks, of relatively short duration and lacking in effective control measures, reveals that the greater the initial propagating rate the greater the incidence curve is skewed to the left. This could be stated in another manner: namely, the greater the initial propagating rate the greater the length of the time axis under the incidence curve to the left of the mode compared with that to the right of the mode. The ratio of the left to right time axis components could be termed the time-axis ratio for the incidence curve (Table 3). Note that greater initial propagating rates tend to result in more infectives at the mode but with fewer susceptibles available at that time. This combination of factors forces a more abrupt fall in incidence.

2) When the duration of an outbreak is short there is less likelihood for changes in the propagating rates caused by seasonal environmental changes. Therefore changes in the propagating rates could be considered mainly a function of the availability of susceptibles. Under these conditions, there is a tendency for the propagating rates to decrease progressively as the outbreak proceeds. The greater the initial propagating rate the faster the decline in the propagating rate from generation to generation. In turn, this is attributed to the more rapid depletion of available susceptibles.

3) When a population is homogeneous, the proportion of decrease in the propagating rate from generation to generation might be expected to be the proportion of susceptibles that have been rendered non-susceptible as the outbreak has progressed. This could be expressed as follows:

$$R(I) = R(o) * (1 - \text{SumA}(I) / \text{Pop}), \quad (1)$$

where $R(I)$ is the propagating rate at generation I ,

$R(o)$ is the propagating rate at onset,

$\text{SumA}(I)$ is the total number of cases rendered non-susceptible up to and including generation I and

Pop is the population of susceptibles at onset.

Communities, however, rarely possess a homogeneity of population. Even within institutional populations there tends to be a heterogeneous

* The term "closed population" implies little or rare contact with people outside the population group.

Table 3
Model of a Person-to-Person Spread Outbreak in a Closed Population.
Number of Susceptibles at Onset Equals 100.

Propagating Rate at Onset	I Number of Cases by Generation of Cases (Number of Susceptibles Remaining)											Time-axis ² Ratio	GPRATE ³ Value
	1	2	3	4	5	6	7	8	9	10	11		
2.0	1 (99)	2 (97)	4 (93)	6 (87)	10 (77)	12 (65)	10 (55)	6 (49)	3 (46)	1 (45)	1 (44)	5:4.3 = 1.2	1.6
3.0	1 (99)	3 (96)	8 (88)	19 (69)	27 (42)	14 (28)	3 (25)	1 (24)				4:2.7 = 1.5	2.3
4.0	1 (99)	4 (95)	14 (81)	37 (44)	29 (15)	3 (12)						3.5:1.9 = 1.8	2.8
5.0	1 (99)	5 (94)	22 (72)	57 (15)	7 (8)							3:1.4 = 2.1	3.8

¹The values were computed in real numbers and rounded-off to integers.

²The right limb of the time-axis is measured up to the projected point of intersection of the incidence curve and the base line, set at the level of the number of cases in the first generation.

³Geometric mean propagating rate for passages from first to modal generation.

Table 4

Model of a Person-to-Person Spread Outbreak in a Closed Population.
Number of Susceptibles at Onset Equals 200.

Propagating Rate at Onset	Number of Cases by Generation of Cases (Number of Susceptibles Remaining)													Time-axis Ratio	GPRATE Value
	1	2	3	4	5	6	7	8	9	10	11	12	13		
2.0	1 (199)	2 (197)	4 (193)	7 (186)	12 (174)	19 (155)	22 (133)	20 (113)	13 (100)	6 (94)	3 (91)	1 (90)	1 (89)	6:5.2 = 1.2	1.7
3.0	1 (199)	3 (196)	9 (187)	23 (164)	46 (118)	49 (69)	18 (51)	4 (47)	1 (46)					4.5:3.2 = 1.4	2.4
4.0	1 (199)	4 (195)	15 (180)	49 (131)	84 (47)	19 (28)	2 (26)							4:2.1 = 1.9	3.0
5.0	1 (199)	5 (194)	23 (171)	85 (86)	78 (8)	1 (7)								3.5:1.4 = 2.5	3.6

clustering of contacts. The clustering results from such divisions as sleeping, dining and work units as well as other social groupings. It seems logical to expect that under conditions where contacts are clustered the occurrence of cases would also be clustered. Thus the proportion of susceptibles would tend to become smaller in the populations in greatest proximity to infective cases. The effective reduction of susceptibles should therefore be considered greater for clustered populations than for the general population since the reduction occurs where its influence is greatest, that is in proximity to the infectives. The above formula would, therefore, not tend to reflect the degree of reduction in the propagating rate due to the loss of susceptibles. Formula (1) may then be modified by carrying the remaining proportion of susceptibles to an exponent which will be chosen as 2.

$$R(I) = R(o) * (1 - \text{Sum}A(I) / \text{Pop})^2 \quad (2)$$

The choice of the exponent 2 in formula (2) was made on the assumption that the intensity of contact -- the likelihood of becoming infected and therefore of reducing the proportion of susceptibles -- is proportional to the inverse square of the proximity of susceptibles to infectives. If this phenomenon does exist, the exponent 2 enables an approximation of the true decrease in the propagating rate that results for a given reduction in susceptibles among the total population.

4) When a person-to-person spread disease is introduced to one member of a susceptible population of size $\text{Pop}(K)$ with the initial propagating rate $R(J)$, then the formula for the number of cases by generation, represented by the array A , is as follows:

$$A(1, J, K) = 1 \quad (3)$$

$$A(I+1, J, K) = A(I, J, K) * R(J) * (1 - \text{Sum}A(I, J, K) / \text{Pop}(K))^2 \quad (4)$$

where $A(I, J, K)$ is the number of cases in the I th generation for the J th initial propagating rate and the K th population of susceptibles.

Tables 3 and 4 are examples of a series of tables that have been constructed based on Formulas (3) and (4) using a range in susceptible population size at onset of 100-1000 and initial propagating rates from 2.0 to 5.0.

5) If $A(M,J,K)$ represents the number of cases in the modal generation and $A(1,J,K)$ the number of cases in the first generation then $A(M,J,K)$ may be derived from $A(1,J,K)$ by multiplying the latter either serially by the propagating rate for each generation preceding the modal generation or by the geometric mean propagating rate (antilog arithmetic mean log propagating rate) carried to the exponent of the number of intervening passages. If $A(M,J,K)$ and $A(1,J,K)$ are both known and the number of generations of passages between them is $M-1$, the geometric mean propagating rate, GPRATE, may be determined from the following formula:

$$A(M,J,K) = A(1,J,K) * \text{GPRATE}(J,K)^{(M-1)} \quad (5)$$

$$\text{or } \log \text{GPRATE}(J,K) = \frac{\log A(M,J,K) - \log A(1,J,K)}{M - 1} \quad (6)$$

Employing formula (6), the GPRATE values have been computed for different initial propagating rates as shown in Tables 3-5. Since both the GPRATE and the time-axis ratio values are functions of the initial propagating rate, knowing the time-axis ratio value permits the estimate of the corresponding GPRATE value through use of tables giving the interrelationships. The method for estimating the incubation period, herein outlined, employs the variable GPRATE in the formula and estimates this value by first computing the time-axis ratio, a relatively easy procedure.

6) The number of generations of passage between the first generation and the modal generation may be represented by the following equation:

$$(M-1) = \frac{\log A(M,J,K) - \log A(1,J,K)}{\log \text{GPRATE}(J,K)} \quad (7)$$

If T , the time span between onset of the first generation and that of the modal generation, is known, the average interval between generations can be calculated.

$$\begin{aligned} \text{Average Interval Between Generations} &= \frac{T}{(M-1)} \\ &= \frac{T * \log \text{GPRATE}(J,K)}{\log A(M,J,K) - \log A(1,J,K)} \quad (8) \end{aligned}$$

It was previously assumed that the average incubation period and the average interval between generations were of approximately the same length. Maintaining this assumption, the estimated incubation

Table 5
Model of Person-to-Person Spread Outbreak,
Closed Populations of 100-1000 Susceptibles

Propagating Rate at Onset	Time-Axis Ratio					Geometric Mean Propagating Rate				
	100	200	300	1000	Average	100	200	300	1000	Average
2.0	1.2	1.2	1.2	1.2	1.2	1.6	1.7	1.7	1.7	1.7
3.0	1.5	1.4	1.5	1.5	1.5	2.3	2.4	2.4	2.5	2.4
4.0	1.8	1.9	1.8	1.7	1.8	2.8	3.0	3.3	3.3	3.1
5.0	2.1	2.5	2.9	3.0	2.6	3.8	3.6	3.6	3.8	3.7

period for a person-to-person spread disease in a closed population may be set to equal the right side of the equation in formula (8).

7) Application of the model to natural outbreaks requires additional modifications of formula (8). Examination of a curve of incidence does not usually reveal the number of cases by generation of cases. In lieu of the number of cases by generation, the array A may represent the number of cases for a given time interval. In order to select the proper length for the time interval, the model outbreak is re-examined. The ratio $A(M,J,K)/A(1,J,K)$ is always the highest ratio obtainable between generations of cases that occur from the first generation to the modal generation. Thus the interval selected should be such that $A(M)/A(1)$ also gives this highest ratio obtainable, where $A(1)$ is the number of cases in the first interval and $A(M)$ is the number of cases in the modal interval and the intervals are of equal length. Widely scattered cases on either side of the main body of the incidence curve may be ignored.

8) To estimate the geometric mean propagating rate, GPRATE, the time-axis ratio is first measured and, from Table 5, the corresponding GPRATE value is obtained. Table 5 was constructed by determining the average time-axis ratio and the average GPRATE value that corresponds to a given initial propagating rate, for model outbreaks with susceptible populations ranging in size from 100 to 1000. For the range of population considered, the two sets of values differed only slightly for different population sizes. Many of the naturally occurring closed population outbreaks are within the above population range.

9) The formula may now be written in its final form:

$$\text{Estimated Incubation Period} = \frac{T \cdot \log \text{GPRATE}}{\log A(M) - \log A(1)} \quad (9)$$

where T is the time span measured from the midpoint of onset of cases in the first interval to the midpoint of onset of cases in the modal interval.

GPRATE is the geometric mean propagating rate and is estimated from Table 5 by first determining the corresponding time-axis ratio.

To compute the time-axis ratio the time axis under the incidence curve is sectioned by the selected time interval; the modal interval is located and the number of intervals to the left of the latter is divided by the number of intervals to the right. This method conforms with that used in the model.

A(1) is the number of cases in the first interval.

A(M) is the number of cases in the modal interval.

10) The goodness of fit for the formula has been tested for a number of closed population outbreaks of person-to-person spread disease. Close agreement with what is considered the usual incubation period was generally obtained. Two computational examples follow:

a) A measles outbreak occurred on St. Georges Island, Alaska in 1963.¹¹ The histogram in Figure 13 plots the occurrence of cases by 2 day intervals. The time interval giving the greatest A(M)/A(1) ratio is 12 days.

Thus A(1) = 1 and A(M) = 40

T = 41 days

The time-axis ratio is $3:1.83 = 1.64$. (3 intervals to the left and 1.83 intervals to the right of the modal interval.) From Table 5, by interpolation, the corresponding value of GPRATE = 2.7.

Estimated incubation period = $\frac{(41)*\log 2.7}{\log 40 - \log 1} = 11.0$ days.

b) An outbreak of an acute respiratory disease occurred aboard the ship "Golden Bear" while at sea on a training cruise in 1965.¹² Most of the 267 aboard were sea cadets.

The histogram in Figure 14 plots the occurrence of cases by 1 day intervals.

The time interval giving the greatest A(M)/A(1) ratio is 1 day.

Thus A(1) = 1 and A(M) = 17.

T = 10 days

The time-axis ratio is $10:9 = 1.11$ (10 intervals to the left and 9 intervals to the right of the modal interval). The corresponding GPRATE value according to Table 5 by extrapolation is 1.5.

Estimated incubation period = $\frac{(10)*\log 1.5}{\log 17 - \log 1} = 1.4$ days.

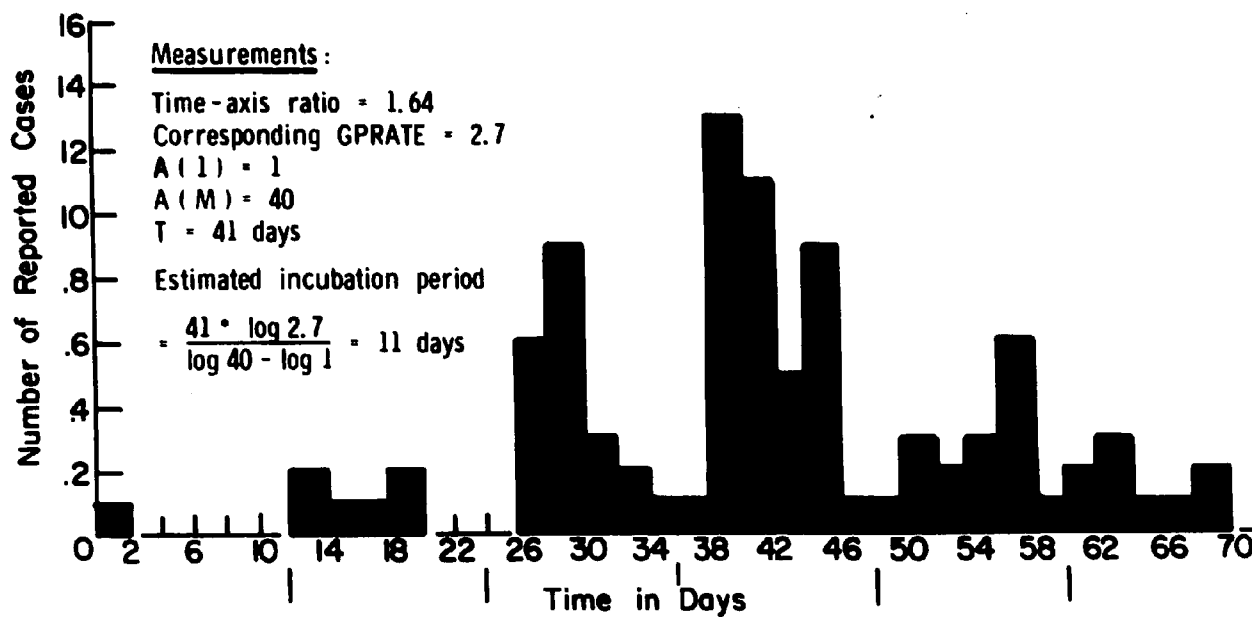
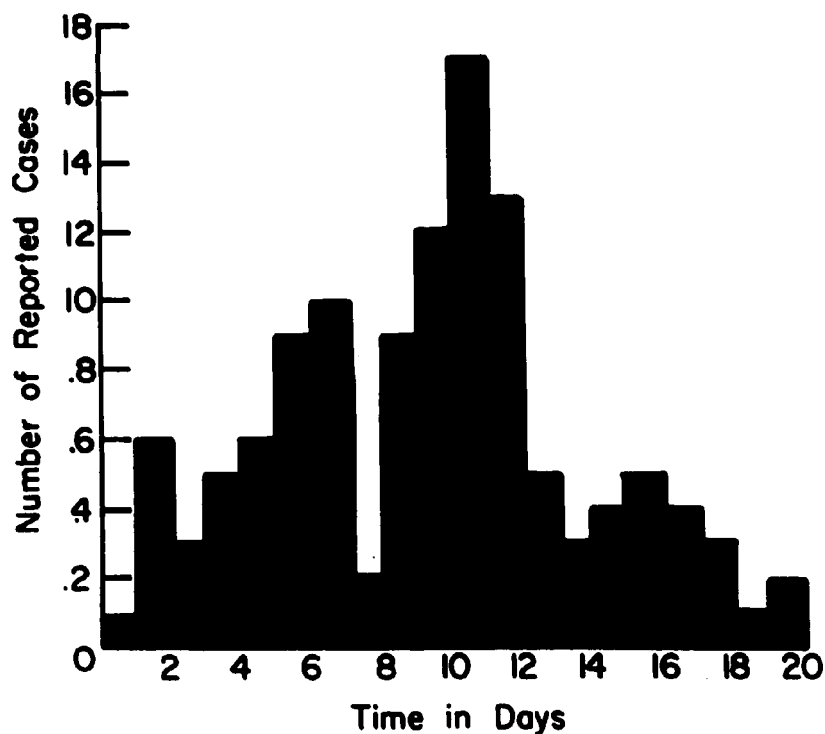


FIGURE 13
ESTIMATING THE INCUBATION PERIOD FOR A PERSON-TO-PERSON SPREAD
DISEASE IN A CLOSED POPULATION
Measles, St Georges Island, Alaska, 1963



Measurements

Time-axis ratio = $10/9 = 1.1$

Corresponding GPRATE = 1.5

$A(1) = 1$

$A(M) = 17$

$T = 10$ days

Estimated incubation period

$$= \frac{(10) * (\log 1.5)}{(\log 17) - (\log 1)} = 1.4 \text{ days}$$

Proportion unaffected:

Observed = .45

Expected according to model = .45

FIGURE 14

ESTIMATING THE INCUBATION PERIOD FOR A PERSON-TO-PERSON SPREAD
DISEASE IN A CLOSED POPULATION

An Acute Respiratory Disease, Aboard Cruise Ship "Golden Bear", 1965

In addition to the use of the model for estimating the incubation period, other uses have been considered such as estimating the proportion of inapparent infections during the course of an outbreak. In the respiratory disease outbreak illustrated above the proportion of unaffected was observed as .45 of the total population aboard ship. According to the model the expected number of unaffected that agrees with the measured time-axis ratio is also .45. This suggests the possibility that despite possible total susceptibility of the population at onset of the outbreak the escape from apparent infection could be largely due to the chance escape from any form of infection whatsoever, including the inapparent variety.

11) The possible use of Formula (9) in estimating the generation interval of vector-borne disease is illustrated by the following examples:

a) An outbreak of yellow fever occurred in Dakar, Senegal in 1927.¹³ Dakar at that time was considered a more or less closed population. The temperatures in the region are sufficiently high to permit the survival of Aedes aegypti throughout the year.

Assuming uniform environmental conditions during the outbreak and a closed population, Formula (9) is employed in estimating the interval between generations.

The monthly report of cases is as follows:

Jun	Jul	Aug	Sep	Oct	Nov	Dec
3	13	28	55	28	19	11

The time-axis ratio from the above is 1:1 = 1. The lowest time-axis ratio given in Table 5 is 1.2 and the corresponding GPRATE value is 1.7. Arbitrarily these values will be employed since for a non-common source outbreak with uniform environmental conditions the time-axis ratio would be expected to be greater than 1.

Then, T = 90 days, GPRATE = 1.7, A(1) = 3 and A(M) = 55.

Estimated interval between generations of cases

$$= \frac{(90) \cdot \log 1.7}{\log 55 - \log 3} = \frac{(90) \cdot (.23045)}{1.74036 - .47712} = 16.3 \text{ days.}$$

According to "Control of Communicable Diseases in Man"³ for yellow fever the intrinsic incubation period is 3-6 days and the extrinsic

incubation period is 9-12 days. The combined intrinsic-extrinsic incubation period is therefore 12-18 days.

Thus the estimate derived from the formula approximates the combined intrinsic-extrinsic incubation period.

b) An outbreak of a dengue-like disease occurred in the small semi-rural community of Guaynabo, Puerto Rico from August 1 to November 16, 1963.¹⁴ Seasonal variation in temperature and rainfall at Guaynabo is slight.

Assuming uniform environmental conditions and a closed population, Formula (9) is employed to estimate the interval between generations for the above outbreak.

The weekly report of cases is as follows:

4, 1, 2, 8, 11, 29, 31, 59, 32, 30, 25, 27, 14, 7, 18

The greatest $A(M)/A(1)$ ratio is obtained by dividing the time axis into 2 week intervals. The resulting time-axis ratio is $3.5:3 = 1.2$ and the corresponding $GPRATE = 1.7$. $T = 49$ days, $A(1) = 5$ and $A(M) = 91$.

Estimated interval between generations of cases

$$= \frac{49 \cdot \log 1.7}{\log 91 - \log 5} = \frac{(49) \cdot (.23045)}{1.95904 - .69897} = 9.3 \text{ days.}$$

According to "Control of Communicable Disease in Man"³ dengue has an intrinsic incubation period of 3-15 days and an extrinsic incubation period of 8-11 days. The combined intrinsic-extrinsic incubation period is then 11-26 days.

The interval between generations estimated by the above formula is less than the minimum combined intrinsic-extrinsic incubation period normally observed for dengue. This difference might be reconciled as follows:

1) Transmission from a human host to a vector host and visa versa may occur close to the onset of infectiousness for either host and produce a short generation interval. This could have occurred due to the vector frequency observed throughout the region involved.

2) The intrinsic and/or extrinsic incubation periods of the disease might have been shorter than that usually observed for

dengue. The disease, although clinically similar, was serologically different from any type of dengue previously identified in the Carribean.

3) A prolonged infective state of either the human or vector host could result in a decrease in the formula estimate. An underlying assumption in the use of the formula is that transmission occurs at or near the onset of infectivity. While the infective state of dengue in the human host is considered relatively short,³ for the vector host this is not definitely known and would probably be dependent on the survival time of the Aedes mosquito. The survival time in nature of Aedes aegypti, however, may be much shorter than the 6 to 8 weeks usually stated.¹⁵

Chapter IV

SUMMARY AND CONCLUSIONS

The examination of the incidence curve may yield valuable information concerning the dynamics of a disease process but interpretation by conventional methods alone may sometimes be misleading. To improve the quality and yield of information obtainable from the incidence curve the "propagating rate" is proposed. It is defined as the ratio of secondary cases to source cases for person-to-person spread disease.

Two methods of measuring the propagating rate from an incidence curve are described. In both methods it is assumed that for an acute person-to-person spread disease propagation usually occurs at or near the time of onset of illness. Therefore the interval between source and secondary cases is approximated by the incubation period of the disease. In the first method of measurement, the time axis is divided into intervals each equal to the incubation period. Cases reported in a given interval are then considered secondary to those occurring in the preceding interval. The resulting propagating rate is then assigned to the interval in which propagation took place, namely the interval of the source cases. The second method, though similar to the first, enables the plotting of a continuous propagating rate curve. This is accomplished by first constructing the incidence curve as a continuous smoothed-out curve on semi-logarithmic paper. The heights of the curve are measured at two points on the time scale separated by the length of the incubation period. The difference in height gives a measure of the level of propagation and is ascribed to the same point in time as the first of the two incidence heights.

The interrelationships between critical points on the log incidence curve and those on the propagating rate curve are described.

When the two curves are smoothed-out the point of inflection of the descending limb of the log incidence curve tends to occur one incubation period following the minimum level of the propagating rate curve. The point of inflection of the ascending limb of the log incidence curve tends to occur one incubation period following the maximum level of the propagating rate curve.

The propagating rate curves for several acute respiratory spread diseases in the United States were compared. The minimum level of the propagating rate curve of each disease tended to occur at the same time for any year under study. The maximum level, however, tended to occur later for diseases with longer incubation periods. These findings are explained on the basis of 1) availability of susceptibles within affected clusters at the time of seasonal environmental changes and 2) the influence of the length of the incubation period on the rate of attrition of susceptible populations.

Because of a low prevailing incidence for most reported enteric spread diseases in the United States, their consideration was limited to viral hepatitis (infectious hepatitis) and poliomyelitis. The seasonal propagating rate pattern for viral hepatitis in the United States appears bimodal with higher levels during the warmer months and again, but more pronouncedly, during the year-end holiday season. It is during these periods that the degree of person-to-person contact in the United States seems more intense than at other times of the year; thus the suggested importance of close person-to-person contact in the transmission of viral hepatitis. For comparison the seasonal propagating rates for viral hepatitis in Israel were plotted with a resulting unimodal curve, with levels elevated during the warmer months and rising to a maximum in early fall, which for Israel corresponds to the main holiday season. Differences in the propagating rate patterns between poliomyelitis and viral hepatitis in the United States are explained primarily on the basis of incubation period length and availability of susceptibles, rather than on the existence of major differences in mode of spread.

A suggested modified form of the propagating rate to measure the relative levels of propagation of a vector spread disease such as malaria is described. The method combines the intervals between infection and transmission for both the human and vector hosts.

A number of possible uses of the propagating rate method are illustrated, with some interesting findings.

a) Studying the relationship of various factors to disease propagation

The propagating rate curve of viral hepatitis in Israel when compared with the mean seasonal temperature curve showed a fairly close direct relationship between the two.

b) Predicting incidence

A simple method for predicting incidence by means of the propagating rate was described. For viral hepatitis in the United States the method enabled predictions of incidence eight weeks in advance with an average proportional error of estimate of 8%. The method appears to offer an improvement over other techniques of predicting incidence.

c) Disease Control Planning

The most advantageous time of conducting a limited control program is considered to be during the period of minimum incidence for the hypothetical situation examined.

d) Evaluating the effectiveness of a control program

The recent trend of measles in the United States was studied by means of the propagating rate. It was noted that following the widespread adoption of measles vaccination the propagating rate levels have tended to be lower during the high incidence season, but during the lower incidence season these rates have tended to reach higher levels than previously. This latter increase is speculated as being due to a possible lessening of the immunization program during the lower incidence season coupled with the existence of an increased pool of susceptibles due to the blocking action to transmission by the immunized.

e) Estimating the incubation period for a person-to-person spread disease in a closed population

A method of estimating the length of the incubation period of a person-to-person spread disease is developed by constructing a model of closed population outbreaks through use of the propagating rate. The goodness of fit of the model is illustrated by two closed population outbreaks. For a measles outbreak in an Alaskan Eskimo village the estimated incubation period obtained was 11 days. For an outbreak of an acute respiratory disease of unknown etiology aboard a cruise ship at sea, the estimated incubation period was 1.4 days.

The propagating rate method appears to offer a useful approach toward an understanding of disease incidence.

BIBLIOGRAPHY

1. Tarter, Holcomb and Kronmal. After the histogram what? A description of new computer methods for estimating the population density. Proceedings - A.C.M. National Meeting, 1967.
2. Sartwell, P.E. The incubation period and the dynamics of the infectious disease. American Journal of Epidemiology, 83:204-215, 1966.
3. Gordon, J.E. and others. Control of communicable diseases in man. 10th edition. New York, American Public Health Association, 1965.
4. Public Health Service. Morbidity and Mortality. Weekly reports.
5. Israel Central Bureau of Statistics. Statistical Bulletin of Israel. Yearly edition.
6. Porter, R.J. Personal communication. Jan. 19, 1968.
7. Pampana, E. A Textbook of Malaria Eradication. London, Oxford University Press, 1963. Page 37.
8. Porter, R.J. Laird, R.L. and Dusseau, E.M. Studies on malarial sporozoites. II. Effect of age and dosage of sporozoites on their infectiousness. Experimental Parasitology, 1954, 3:267-274.
9. U.S. Department of Health, Education and Welfare, Communicable Disease Center, Hepatitis Surveillance, Report No. 25, March 31, 1966, 27 pages.
10. Bailey, N.T.J. The Mathematical Theory of Epidemics. New York, Hafner Publishing Co., 1957.
11. Brody, J.A. The infectiousness of rubella and the possibility of reinfection. American Journal of Public Health, 1966, 56:1082-1087.
12. Dodge, H.J. An epidemic of acute respiratory disease during a training cruise. Unpublished epidemiology exercise.

13. Ramsey, George H. Yellow Fever in Senegal with special reference to the 1927 epidemics. American Journal of Hygiene, 13:150, 1931.
14. Neff, John M. Dengue fever in a Puerto Rican Community. American Journal of Epidemiology, 86:162-184, 1967.
15. Christophers. Aedes Aegypti, Cambridge, At the University Press, 1960. p. 548-550.

APPENDIX

The Incidence and Propagating Rate Curves: Interrelations of Critical Points

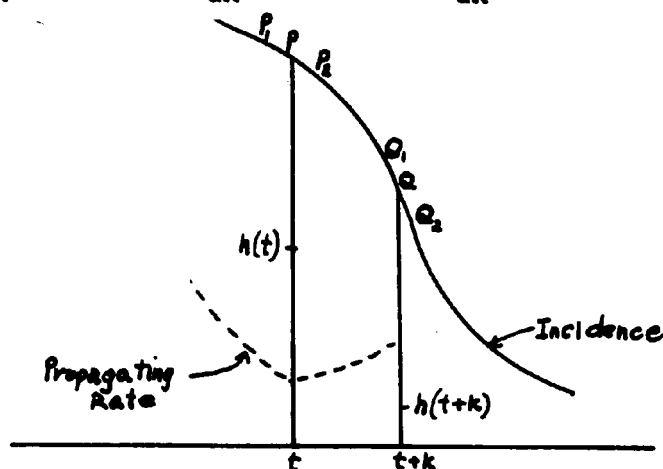
When the incidence curve is plotted on semi-logarithmic paper, the point of inflection on the descending limb of the smoothed-out incidence curve tends to occur one incubation period following the minimum of the propagating rate:

The propagating rate at time x is $R(x) = h(x+k)/h(x)$. (k is length of incubation period)

$$\log R(x) = \log h(x+k) - \log h(x)$$

Let the minimum of the propagating rate occur at t

$$\text{Then } \frac{d \log R(t)}{dx} = \frac{d \log h(t+k)}{dx} - \frac{d \log h(t)}{dx} = 0$$



Now consider the descending limb of the continuous log incidence curve shown in the figure. Let a approach the value zero and let points P_1 , P , and P_2 on the log incidence curve occur at times $t-a$, t and $t+a$ respectively; let points Q_1 , Q and Q_2 occur at times $t-a+k$, $t+k$ and $t+a+k$ respectively.

Since $\frac{d \log R(t-a)}{dx}$ is negative, the slope of the log incidence curve at Q_1 is less than the slope at P_1 .

Since $\frac{d \log R(t+a)}{dx}$ is positive, the slope at Q_2 is greater than the slope at P_2 .

If the slope of $R(x)$ has been negative (the propagating rate has been decreasing) for at least k period of time preceding $t-a$, then the continuous log incidence curve has been decreasing its

slope continuously between P1 and Q1; therefore the increase in slope between P2 and Q2 must have occurred between Q1 and Q2. Since a approaches zero, Q1 and Q2 approach Q and the transition from a decreasing slope to an increasing slope occurs at Q, that is a point of inflection of the log incidence curve.

A similar argument may be applied to show that if $R(t)$ is at a maximum, $h(t+k)$ will tend to occur at the time of inflection of the ascending limb of the smoothed-out log incidence curve.

Consider again the smoothed-out continuous incidence curve. If $R(x)$ is greater than 1.0, the height of the incidence curve between time x and $x+k$ rises; conversely, if $R(x)$ is less than 1.0, the height of the incidence curve between x and $x+k$ falls. It then follows that if $R(x) = 1.0$, the extremum on the continuous incidence curve will occur between time x and time $x+k$, that is, the extremum will tend to occur at approximately time $x+k/2$. If $R(x) = 1.0$ occurs on the rising limb of the propagating rate curve, the extremum that follows is a minimum but if $R(x) = 1.0$ occurs on the descending limb, the extremum that follows is a maximum.