OBSERVATIONS RELATED TO PATHOGENESIS OF DENGUE HEMORRHAGIC FEVER.
V. EXAMINATION OF AGE SPECIFIC SEQUENTIAL INFECTION RATES USING A MATHEMATICAL MODEL†

Experimental studies of dengue infections in humans suggest that immunity to homologous virus challenge is probably of lifelong duration. Individuals infected with one type of dengue virus and then exposed to a second serotype within 3-6 months may develop modified disease or no disease at all. Studies of dengue infection in Bangkok have suggested that infection with one type of dengue virus sensitizes an individual so that subsequent infection with another type elicits a hypersensitivity reaction producing the dengue hemorrhagic fever (DHF) syndrome. Since at least four types of dengue viruses are simultaneously endemic in Bangkok, it is theoretically possible that hypersensitivity reactions could occur during the second, third or fourth heterologous infection. The limits of the interval between sensitizing and eliciting infections are unknown, but the evidence of short duration heterologous protection cited above plus the seasonal periodicity of dengue transmission in the tropics suggests that most DHF may result from heterologous infections occurring at an interval of one year or more.

It is the purpose of this paper to utilize the above observations in a study of mathematical models which permit prediction of age specific secondary or tertiary infection rates in populations exposed to three or four different dengue viruses. Results from models have been compared with available epidemiologic data, particularly age specific hemorrhagic fever hospitalization rates, to evaluate hypotheses concerning the number of infections and the interval between infections required to produce DHF.

METHODS. MATHEMATICAL MODELS

Two models of dengue infection patterns are examined: 1) the double sequential model and 2) the triple sequential model.

The first model is based on the assumption that DHF is caused by infection with a second dengue serotype; any sequence of infection with two dengue types presumably...
causes the disease. Sequential infections occurring within the same year eliminated an individual from the DHF risk group.

It was assumed in setting up the triple sequential model that infection with a third dengue virus in a population previously infected with two other dengue types causes DHF. In this instance, if two different infections occurred within the same year this individual was regarded as DHF susceptible providing the third dengue infection occurred during a subsequent year.

The period of time within which first homologous infection and infection with the second or third virus type must occur in order for an individual to be included in the "risk" group will be called 'T.' There is no evidence that a "sensitizing" dengue infection must occur within a fixed time before heterologous infection. However, the effect of this factor on the expected distributions was studied to find if such a restriction must be imposed in order to obtain a "good fit."

The effects of two variables on the "expected" DHF distributions were studied:
1. Total dengue transmission rate (average annual dengue transmission rate).
2. Transmission rates for individual dengue serotypes.

Both models were studied under the following conditions:
1. Dengue transmission rates constant from year to year.
2. Dengue transmission rates varying from year to year.

A scale factor, F, has been introduced for purposes of illustration which ensures that the rates calculated from the model agree with those observed at the age at which the latter reaches a maximum. Under the secondary infection hypothesis the quantity 1/F would be an estimate of the proportion of persons exposed to multiple dengue infection who subsequently get DHF with secondary antibody response. The restriction will be made that it is the same for all age groups.

In all models it has been assumed that:
1. A fixed proportion of the population will be attacked by dengue viruses each year; the possibility of chance fluctuation in this proportion will not be considered.
2. At most, one attack from a single virus type can occur in one year. Where there are three dengue viruses, eight possible events can therefore be defined for each person for one year (X₁, X₂, . . . , X₈) according to the number of attacks and the viruses involved. The events are represented in Figure 1.
3. Dengue transmission rates are identical for all age groups.
4. Death rates due to other causes, or drop-out rates, are the same for individuals included in DHF "risk" groups as for others.

Sequences of infection experience at different ages, 1 to age 16, were calculated by a deterministic model. DHF attack rates were calculated from the proportion of susceptibles, using simple laws of combining probabilities and sequential calculations. Calculations were carried out on an IBM 7094 digital computer.

Definitions and calculations common to both models.*

F = Maximum expected rate/Maximum observed rate.
p₁(t) = Dengue 1 transmission rate for age t, where t = 1, 2 . . . , 16. Similarly for dengue 2 and dengue 3.

q₁(t) = 1 - p₁(t). Similarly for q₂(t) and q₃(t).

Q₁₉(t) = Proportion not attacked by dengue by end of age t.

* Definitions and calculations for four viruses are similar.
FIG. 1. Assuming, at most, one attack from a single virus type in one year, persons exposed to dengue 1, dengue 2 and dengue 3 must experience one of the above events each year.

\[ Q_{1m}(t) = \frac{3}{i=1} q_i(t) \]

**Double sequential model**

Dengue transmission rates constant. The proportion of the population "susceptible" to infection with heterologous virus is calculated from the following triangular arrays:

\[ p_{i.m}(s,t) = \text{Proportion of subjects who reach age } t \text{ and who were infected for the first time with } D1 \text{ at age } s \text{ and never infected by } D2 \text{ or } D3. \]

Similarly for \( p_{2,13}(s,t) \) and \( p_{3,12}(s,t) \).

\[ p_{1.m}(s,t) = p_{1.m}(1) \cdot q_2(1) \cdot q_3(1) \]

Where \( s < t \)

\[ p_{1.m}(s, t) = p_{1.m}(s, t-1) \cdot q_2(t) \cdot q_3(t) \]

\[ p_{1.m}(t, t) = p_1(t) \cdot q_2(t) \cdot q_3(t) \cdot Q_{1m}(t-1) \]
Fig. 2. The shaded area represents the proportion susceptible to heterologous infection at end of age \( t \), under the double sequential model \( (T = 3) \). The population represented by the lined area has already been at least doubly infected and hence is excluded from the risk group.

Figure 2 shows possible categories into which individuals can fall at end of age \( t \). \( p_{1.23}(t) \), as an example, is subdivided according to year of first infection with D1. The shaded areas, \([p_{1.23}(t)], [p_{2.13}(t)], \text{and} [p_{3.12}(t)]\), represent the proportion susceptible at end of age \( t \), when \( T = 3 \).

\[
p_{1.23}(t) = \sum_{s=t-T+2}^{t} p_{1.23}(s,t)
\]

Similarly for \( p_{2.13}(t) \) and \( p_{3.12}(t) \)

(Note: \( T \geq 2 \))

Fig. 3. The shaded area represents the proportion of the population infected with heterologous virus (dengue 2 and/or dengue 3) during the year \( t+1 \) under the double sequential model.
\[ p_{2,3.1(t+1)} = \text{Proportion attacked by at least dengue 2 or dengue 3 during year of age (t+1). Similarly for } p_{1,2.3(t+1)} \text{ and } p_{1,2.2(t+1)}. \]

\[ p_{2,3.1(t+1)} = 1 - q_0(t+1) \cdot q_6(t+1) \]

As an example, \( p_{2,3.1(t+1)} \) is represented by the shaded area in Figure 3.

The proportion acquiring DHF at age \((t+1)\) would then be equal to: \( P(t+1)/F \), where:

\[ P(t+1) = p_{*,*,m(t)} \cdot p_{2,3.1(t+1)} \]

\[ + p_{*,*,m(t)} \cdot p_{1,2.3(t+1)} \]

\[ + p_{*,*,m(t)} \cdot p_{1,2.2(t+1)} \]

**Dengue rates varying.** Calculations with dengue transmission rates varying from year to year are essentially the same as those outlined above. However, the calculations must be carried out a number of times to obtain an expected age specific DHF distribution for a given year.

As an example, the expected DHF age specific distribution for the year 1964 was calculated using estimates of dengue transmission rates for the years 1958 to 1964.

Using terminology similar to that used in previous calculations:

\[ P(t) = \text{Proportion acquiring DHF at age (t).} \]

\[ p_i(t) = \text{Dengue transmission rates for types 1, 2, and 3.} \]

\[ i = 1, 2, 3 \]

\[ t = \text{year of age} \]

\[ y = \text{year} \]

Let \( y = 1 = 1958 \)

### Table 1. Computation of Expected Age Specific DHF Rates with Dengue Transmission Rates Varying from Year to Year

| Year | 1958 | 1959 | 1960 | 1961 | 1962 | 1963 | 1964 |
|------|------|------|------|------|------|------|------|
| Dengue transmission rates | \( p_1(1) \) | \( p_1(2) \) | \( p_1(3) \) | \( p_1(4) \) | \( p_1(5) \) | \( p_1(6) \) | \( p_1(7) \) |
| Expected DHF rates | \( P(1) \) | \( P(2) \) | \( P(3) \) | \( P(4) \) | \( P(5) \) | \( P(6) \) | \( P^*(7) \) |
| Dengue transmission rates | \( p_1(1) \) | \( p_1(2) \) | \( p_1(3) \) | \( p_1(4) \) | \( p_1(5) \) | \( p_1(6) \) | \( p_1(7) \) |
| Expected DHF rates | \( P(1) \) | \( P(2) \) | \( P(3) \) | \( P(4) \) | \( P(5) \) | \( P^*(6) \) |
| \( . \) | \( . \) | \( . \) | \( . \) | \( . \) | \( . \) | \( . \) |
| \( . \) | \( . \) | \( . \) | \( . \) | \( . \) | \( . \) | \( . \) |
| \( . \) | \( . \) | \( . \) | \( . \) | \( . \) | \( . \) | \( . \) |
| \( . \) | \( . \) | \( . \) | \( . \) | \( . \) | \( . \) | \( . \) |
| Dengue transmission rates | \( p_1(1) \) |
| Expected DHF rates | \( P^*(1) \) |
Calculations were carried out as described in Table 1. The expected age specific dengue hemorrhagic fever (DHF) distribution for the year 1964 would then be equal to (reading column under 1964):

| Age | Rate |
|-----|------|
| 1   | P*(1) |
| 2   | P*(2) |
| 3   | P*(3) |
| 4   | P*(4) |
| 5   | P*(5) |
| 6   | P*(6) |
| 7   | P*(7) |

**Triple sequential model**

The proportion of the population "susceptible" to triple infection at end of age (t) is shown in Figure 4. The calculations for this model are presented below. It will be noted that in the case of this model the expected DHF distribution was computed only for T = 16. Because of the large number of sequential combinations possible, fixed intervals between first and second and second and third dengue infections were postulated.

\[
p_{12.3}(t) = P_{13.2}(t) \cdot P_{12.3}(t) \frac{P_{13.2}(t) 
\]

**FIG. 4.** The shaded area represents the proportion susceptible to heterologous infection at the end of age t under the triple sequential model (T = 16).
The proportion acquiring DHF at age \((t+1)\) would then be equal to:

\[
P(t+1)/F \text{ where:}
\]

\[
P(t+1) = p_{23.1}(t) \cdot p_1(t+1) + p_{13.2}(t) \cdot p_2(t+1) + p_{12.3}(t) \cdot p_1(t+1)
\]

Computations for the triple sequential model with varying dengue transmission rates were carried out using the same procedure as for the double sequential model.

**Data**

Data used in this analysis were obtained from three sources:

1. A study of Bangkok area hospital admission records.
2. Clinical and virological studies on a large sample of hospitalized DHF cases.
3. A randomized serological survey of the Bangkok area.

Two age-specific distributions of DHF were derived from the data and used for comparison with the distributions predicted by the models. The first was based on the total DHF hospitalizations for 1958-1964, and the age specific DHF rates for 1962-1964. The second was calculated only from the age specific DHF rates for 1964. These data have been published together with reasons for accepting them as fairly representative of true disease incidence.

Corrections were made on the age-specific distributions to account for differences between the age classification of the observed and expected curves. Since hospitalized cases are classified by age at time of admission, end of year rates for comparison with the expected values were estimated by extrapolation.

The observed distributions were also corrected to include only cases with a secondary antibody response. Figure 5 shows the distribution by age of the ratio, secondary responses/total cases.

**Figure 5.** The distribution by age of the ratio, secondary responses to dengue viruses/total cases.
Dengue transmission rates were estimated in 1962 from antibody conversion rates, the proportion of individuals converting from HI negative to HI positive over the DHF epidemic season.

It was found that the prevalence ratios of different dengue virus types in Bangkok was of the order of 1/1/1 or, possibly, 1/2/1 (D1/D2/D3). This was determined from virus isolation studies of DHF and dengue fever patients and of suspensions of Aedes aegypti mosquitoes collected from various areas of the city.

RESULTS

Age specific distributions of DHF rates predicted by the double sequential and the triple sequential models were calculated.

"Expected" distributions were derived using different values for total dengue transmission rates, transmission rates for individual dengue serotypes and T, the number of years within which heterologous infection must occur.

For dengue transmission rates constant from year to year a wide range of dengue rates was examined. The expected distributions were compared with an average observed distribution based on epidemiological data for 1958-1964. Expected rates were calculated only for the first 16 years of age since few cases have been observed in individuals over that age in Bangkok.

For transmission rates that varied from year to year estimates of dengue transmission rates for 1958-1964 were used (Table 2) to calculate expected age specific DHF rates for the children up to seven years. These were compared with observed rates for 1964.

The observed and expected distributions are superimposed on graphs for comparison. It may be noted that only distributions calculated with individual dengue rates in the ratio 1/2/1 (D1/D2/D3), are presented for illustration. Within the range studied, the ratio of the individual dengue transmission rates had little effect on the expected DHF distributions.

| Year | Estimated dengue transmission rate (%) |
|------|----------------------------------------|
| 1958 | 44.6                                   |
| 1959 | 2.8                                    |
| 1960 | 11.0                                   |
| 1961 | 3.9                                    |
| 1962 | 41.0                                   |
| 1963 | 25.8                                   |
| 1964 | 52.3                                   |
Several characteristics of the expected and the observed DHF distributions were compared: year of age at maximum, expected rate at age 16, and the ratio, width of the expected curve/width of the observed curve, at half height. The criteria for a “good fit” were chosen arbitrarily. It was required that: (1) the age at maximum correspond exactly to that value for the observed distribution; (2) the expected rate of age 16 be less than 0.5/1000 and; (3) the ratio of widths lie between 0.8 and 1.2.

Comparisons of observed and expected distributions for each model will be discussed below.

Double sequential model

*Dengue transmission rates constant.* The double sequential model was studied with total dengue rates varying from 6 to 60%, T varying from 2 to 16, and with the relative proportions of D1/D2/D3 at: 1/1/1, 1/2/1, 2/2/1 and 6/3/1.

![Effect of Total Dengue Transmission Rates on Age at Maximum](image)

**Fig. 6.** Age at which maximum expected DHF rate occurs for different dengue transmission rates and different T values. Double sequential model.
The effects of total dengue rates and $T$ on the age at maximum are shown in Figure 6. For low total dengue transmission rates, the age at maximum varies considerably with $T$. As an example, for total dengue, $0.15$, the age at maximum for $T = 5$ and $T = 16$ are 5 and 9 respectively. These distributions are shown in Figures 7 and 8. With a high total dengue rate of $0.40$, the age at maximum is the same for all values of $T > 4$. The age at maximum was the same for all proportions of $D_1/D_2/D_3$ studied.

The effect of total dengue transmission rates on the rate expected at age 16 for $T = 5$ and $T = 16$ is shown in Figure 9. The ratio of $D_1/D_2/D_3$ had no effect on this parameter. The rate at age 16 is dependent upon the total dengue transmission rate; higher dengue rates resulting in lower expected DHF rates. This dependence is greater with higher values of $T$. As previously mentioned, distributions in which the expected DHF rate at 16 were higher than 0.5/1000 were considered "poor fits" to the observed distributions. For high total dengue transmission rates, this value was low. As an example, for total dengue rate of $0.45$, with $T = 5$ the rate at age 16 is 0.01/1000 as shown in Figure 10. In contrast, for total dengue rates of

![Double Sequential Model](image)

**Fig. 7.** Observed DHF hospitalization rates and rates predicted by the double sequential model for ages 1-16. A constant dengue transmission rate of 15% is assumed ($T = 5$). SF = scale factor. $2^o$ = secondary.
**Fig. 8.** A constant dengue transmission rate of 15% is assumed ($T = 16$).

**Effect of Average Dengue Transmission Rates on Rate at Age 16**

Double Sequential Model

**Fig. 9.** Predicted DHF rates at age 16 for different average annual dengue transmission rates, different ratios of $D1/D2/D3$ and for $T = 5$ and $T = 16$ (double sequential model).
FIG. 10. Observed DHF rates and rates predicted by the double sequential model for ages 1 to 16. Constant dengue transmission rate of 45% is assumed (T = 5). SF = scale factor.

0.15, and 0.21, Figures 7 and 8 show that the expected rates for age 16 are over 0.51/1000 and 0.25/1000, respectively. For total dengue rates in the midrange, the choice of T is important in obtaining a “good fit” to the data. Results obtained with different proportions of the serotypes, were quite similar, in the range studied.

Reasonably low values for the expected DHF rate at age 16 can be obtained with total dengue transmission rates greater than .15 with T ≥ 5.

The effect of total dengue transmission rates on the width of the expected age specific DHF distribution is shown in Figure 11. Values of the ratio, width expected/width observed distributions at half height are plotted for T = 5 and for the different proportions of D1/D2/D3. For T = 5, width ratios between 0.8 and 1.2 can be attained only with total dengue rates lower than 0.21. This effect is exemplified changing total dengue transmission rate from .30 to .15 at T = 5 which accounts for an increase in the width of the expected distribution from 0.71 to 0.89.

Larger values of T also have the effect of broadening the expected distribution. For example, for a constant dengue rate of .30 a change in T from 5 to 16 results in a change in the ratio, width observed, from .71 to
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Effect of Average Dengue Transmission Rates on Width Exp/Width Obs
Double Sequential Model

Values for all Ratios
DI/D2/D3 are same

"good fit"

As was previously mentioned, these are the arbitrarily chosen limits within which a "good fit" can be obtained with respect to its variable. Both of these expected distributions would be considered reasonable on this basis.

Scale factors obtained with different dengue transmission rates are shown in Figure 12 for this model. For total dengue rates in the range .15-.26, F is between 13 and 25.

By inspection, "good fits" of expected distributions to the observed distribution, are obtained with the double sequential model, dengue rates constant from year to year, with dengue transmission rates in the range 0.15 to 0.21. Within this range, expected distributions with maxima at 4-5 years of age, reasonable low rates at age 16 and widths within the accepted range can be obtained with T values of 4-5 years. Good fits were also obtained for T = 16 with annual dengue transmission rates between .30 and .36. However, epidemiological studies in Bangkok suggest that average dengue transmission rates do not exceed .25.
Since four dengue serotypes have been isolated from hemorrhagic fever patients in Bangkok, the double sequential model was examined using four different viruses. For these computations a ratio D1/D2/D3/D4 of 9/18/9/4 was used. Expected DHF rates were computed with total dengue transmission rates from .06 to .60 and with T = 3 through 16. Expected DHF rates were almost identical to those calculated for the three virus model.

**Dengue transmission rates varying from year to year.** Estimates of dengue transmission rates for the years 1958-1964 were used to calculate the expected distribution for 1964.

DHF rates for the first seven years of age are presented for comparison with the observed distribution.

The relative proportions of the individual dengue rates had little effect on the appearance of the expected distributions with both models.

Figures 13 and 14 show the expected distributions of DHF for 1964 obtained with the double sequential model, T = 5, and 16 respectively. The distribution calculated with T = 5 corresponded to the observed distribu-
**Mathematical model**

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**Fig. 13.** Observed DHF rates and rates predicted by the double sequential model for ages 1 to 16. Estimated dengue transmission rates for years 1958-1964 (Table 2), which varied considerably from year to year, were used to compute predicted distribution (T = 5).

The relationship between total dengue transmission rates and age at maximum for the expected distributions is shown in Figure 15. Increasing the total dengue rate has the effect of decreasing the age at the maximum rate.

As noted before, this same relationship was observed with the double sequential model at T = 16; however, the maxima obtained with the triple sequential model occur at higher ages. From Figure 15 it appears that a maximum at age 4-5 can be obtained only with total dengue transmission rates greater than .60.
The expected rates at age 16 were considerably higher with the triple sequential model than with the double sequential model. The effect of dengue transmission rates on the rate at age 16 is shown in Figure 16. A rate as low as .5/1000 can be obtained with this model only with total dengue rates over .60 with $T = 16$. Although a reasonable rate at age 16 can probably be obtained with smaller $T$, it is expected that total dengue transmission rates greater than .26-.36 would be required. Deviations from a 1/1/1 ratio for the dengue serotypes had the effect of increasing the rate at age 16. This effect was more marked at higher dengue rates.

All expected distributions derived using the triple sequential model were considerably more broad than the observed distribution.

Dengue transmission rates varying. The expected DHF distribution obtained with the triple sequential model with varying dengue rates ($T = 16$) is shown in Figure 17. As with annual dengue transmission rates constant, age at maximum was shifted to the right. The predicted curve was a "poor fit" to the observed age specific DHF hospitalization rates.
**DISCUSSION**

Of all the models examined, only the double sequential model (secondary dengue age specific infection rates) produced a curve which was a "good fit" with observed age specific DHF hospitalizations in Bangkok. As with all models, results were highly dependent upon the average annual dengue transmission rate. As might be expected, the population of "susceptibles" was depleted rapidly if high yearly dengue transmission rates were assumed. When dengue infection rates were in the range of those predicted for Bangkok during the 10-15 years before 1962 (i.e., 12-18%) "good fits" were obtained when T = 5 or slightly greater. In the 3 virus system, at any average yearly transmission rate, variation in the proportion between dengue 1, 2 or 3 between 1/1/1 to 6/3/1 had little effect on expected age specific distributions. A "good fit" was also obtained when the double infection model, T = 5, was used to estimate DHF age specific hospitaliza-
Effect of Average Dengue Transmission Rates on DHF Rate at Age 16 Triple Sequential Model

Fig. 16. Predicted DHF rates at age 16 for different total dengue transmission rates and different ratios of D1/D2/D3. Triple sequential model (T = 16).

Data obtained with the double sequential model in a 4 virus system (not shown) were very similar to the three virus system.

The triple sequential model was examined only at T = 16. This model was not a "good fit" for several reasons: a) If it is assumed that sensitizing and eliciting intervals between dengue infections must be one year or more, the expected DHF rates at ages 1 and 2 would be 0 in the triple sequential model. b) The DHF rate at age 16 predicted by the triple sequential model was considerably higher than predicted by the double sequential model. On the basis of the finding that the expected rate at age 16 is inversely related to the dengue transmission rate, it was concluded that "good fits" will probably be obtained with the triple sequential model only with average annual dengue transmission rates higher than .30 (30%). This exceeds the average dengue infection rates estimated for Bangkok in recent years. c) Age at maximum in triple sequential models was higher than in observed DHF hospitalizations.
Using realistic epidemiological data with the double sequential model, the scale factor was 17.6. The probability, therefore, of acquiring DHF, given that infection with a second heterologous dengue virus within five years of primary infection causes disease, is roughly 1/18 for persons in this "risk" group. Since approximately 40\% of DHF patients have the dengue shock syndrome (DSS) the probability of those "at risk" of acquiring DSS would be approximately 1/45. This is close to the ratio between DSS and estimated secondary dengue infections of 1/30 measured by Russell, et al. during the 1966 outbreak of DHF on Koh Samui, an island off the coast of Thailand.

A dengue infection sequence not dealt with above is the possibility that two or more infections within a single dengue transmission season (approximately 6 months) result in DHF. This would include simultaneous infections or infections occurring at a short interval. If such infection occurrences are governed by chance, they would constitute a proportion of the population less than observed DHF hospitalizations in any age group. Further, it is obvious that the rate of simultaneous or near simultaneous double or triple dengue infections would be proportional to the total dengue
infection rate and to the number of susceptibles in each age group. The number of susceptibles at progressively increasing ages is a monotonically decreasing curve. Such a curve would be a poor fit with observed DHF hospitalization rates.

The concept of a finite period of sensitization (T) has come out of this model. There are no data from humans to support a T of approximately five years. However, many persons were infected with type 3 dengue viruses during the 1963 Puerto Rican outbreak who had serologic evidence of a dengue infection that had to have occurred 20 or more years previously.7 No cases of DHF were observed in this outbreak.7 Waning of sensitization in the absence of repeated antigenic stimuli occurs in a variety of allergic disorders.

It will be recognized that the mathematical model is necessarily limited by some basic assumptions. Are Aedes aegypti bites and thus, dengue transmission rates constant for all age groups? Is the hemorrhagic fever response to dengue infection constant for all ages? Such information would be valuable.

The model predicts relationships between total dengue infection rates and expected age distribution of DHF. For example, at an average annual infection rate of 15%, approximately 50% of DHF cases would be expected to occur in children aged 6 years or less. At a 6% total dengue infection rate annually, a larger percentage of cases would be expected in older children and young adults; 50% of cases would include children through age 9. Recent data from both Manila and Singapore show just such a shift in age distribution of clinically diagnosed hemorrhagic fever cases.8,9 Virological studies of random samples of clinical hemorrhagic fever are needed so that the age distribution of patients with secondary dengue antibody responses may be known. It is of interest that the modal ages of hemorrhagic fever hospitalizations in Manila and Singapore are higher (5-9 years) than in Bangkok (3-4 years). This may reflect in the former cities a pattern of intermittent virus transmission.

Finally, it may be possible to make further measurements of F, the ratio between observed DHF and secondary dengue infections occurring within a period of five years. This technique could be used to study the "virulence" of various sequences of primary and secondary dengue infections and the susceptibility to DHF of persons of various ages, ethnic or other population sub-groups.

SUMMARY

A mathematical evaluation was made of the hypothesis that dengue hemorrhagic fever (DHF) occurs in persons who have had previous dengue
immunologic experience. Age specific double and triple sequential infection rates with 3 or 4 dengue virus types endemic were calculated for 1) a wide variation of average annual dengue transmission rates, 2) varying proportions of each virus type, and 3) various values of T, the limiting interval between first and second dengue infection required to produce DHF. These data were compared with average annual age specific DHF hospitalization rates for Bangkok, 1958-1964. The “goodness of fit” between predicted and observed curves was determined by comparing the age at maximum, the width of curves, and the DHF rate at age 16. Using realistic average annual dengue virus transmission rates, the double sequential infection model gave a “good fit” with observed data when it was assumed that primary and secondary infections must occur within a period of five years. The model allows for prediction of age at maximum, DHF rates at various ages and the proportion of persons acquiring secondary dengue infections within five years who are hospitalized for DHF at various annual dengue virus infection rates. These predictions might be tested in field studies.

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