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"Cross-Immunity in the Dynamics of Homogeneous and Heterogeneous Populations"

Carlos Castillo-Chavez
Biometrics Unit
Cornell University
Ithaca, NY 14853-7801
U.S.A.

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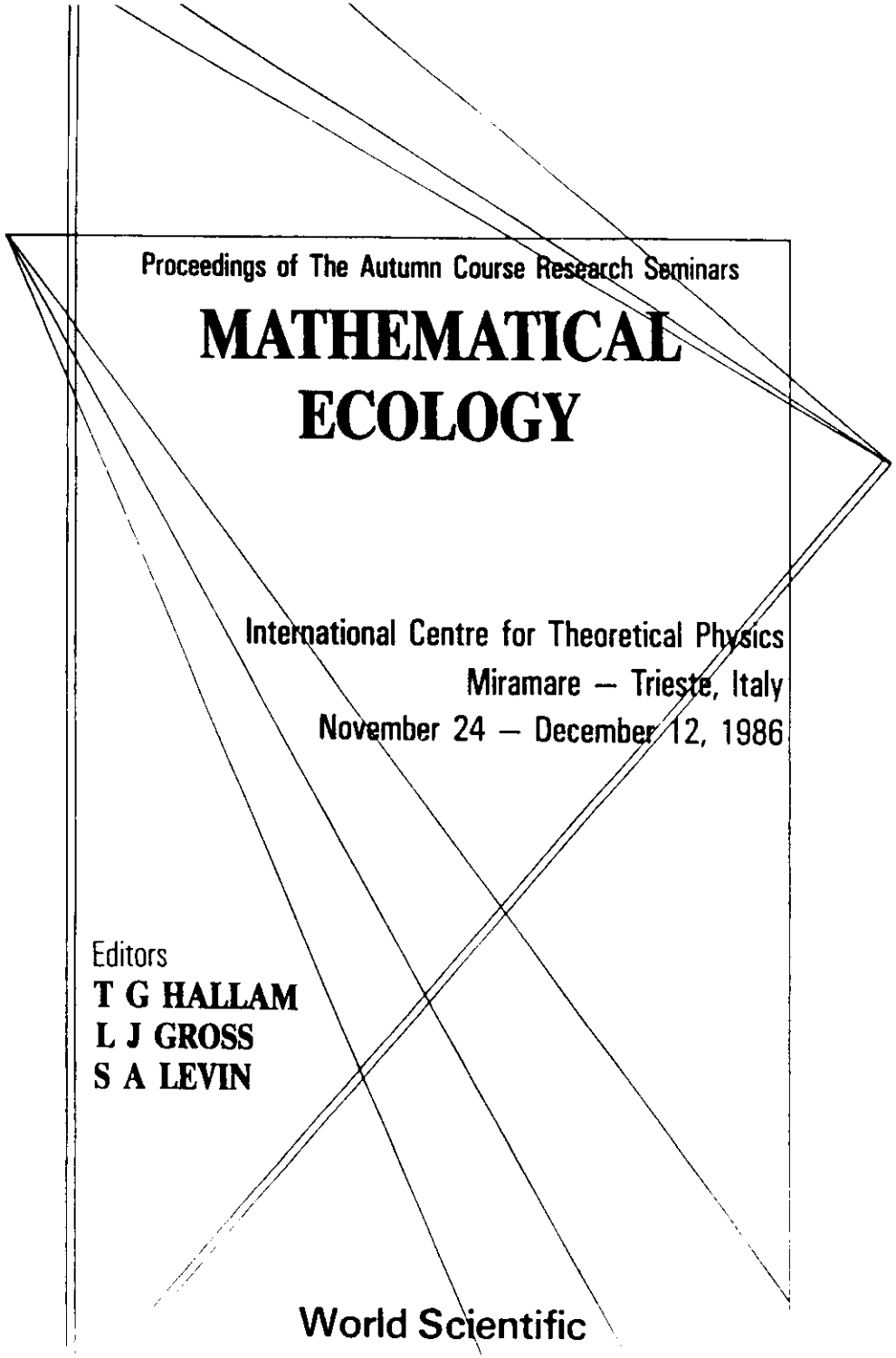

CROSS-IMMUNITY IN THE DYNAMICS OF HOMOGENEOUS AND HETEROGENEOUS POPULATIONS

by

Carlos Castillo-Chavez,[1,2] Herbert W. Hethcote,[3] Viggo Andreasen,[1,2]
Simon A. Levin,[1,2,4,5] and Wei-min Liu[1,2]

1. INTRODUCTION

The epidemiological interactions among co-circulating strains of related viruses have received little attention in the theoretical literature (but see Dietz, 1979; Levin and Pimentel, 1981; Levin, 1983; Castillo-Chavez et al., ms.). Indeed, until recently, little information was available with regard to the level and duration of cross-immunity; but recent studies show a considerable degree of long lasting cross-immunity between related strains (i.e., variants of the same subtype) in human influenza (see the excellent review paper of Couch and Kasel, 1983). Through cross-immunity, the presence of one strain of the virus can reduce the pool of susceptible individuals for co-circulating strains and thereby influence the potential for survival of those strains; this is, in effect, exploitation competition among closely related species. In this paper, we formulate models that incorporate such cross-immunity, and discuss threshold conditions for coexistence.

The co-circulation of viral strains plays a significant role in the dynamics of influenza in humans and myxomatosis in European rabbits in Australia. In both instances, the interactions among different viral strains have produced very complicated

[1]Ecology and Systematics, Corson Hall, Cornell University, Ithaca, NY 14853
[2]Center for Applied Mathematics, Cornell University, Ithaca, NY 14853
[3]Department of Mathematics, University of Iowa, Iowa City, IA 52242
[4]Ecosystems Research Center, Cornell University, Ithaca, NY 14853
[5]To whom reprint requests should be sent.

dynamics, whose analysis poses challenging scientific puzzles (see Fenner and Ratcliffe, 1965; Fox and Kilbourne, 1973; Dowdle et al., 1974; Stuart-Harris and Schild, 1976; Selby, 1976; Beveridge, 1977; Levin and Pimentel, 1981; Fine, 1982; Palese and Young, 1982; Levin, 1983; Dwyer, Levin, and Buttel, ms.). In this paper, our attention is focused upon the dynamics of influenza. For a discussion of myxomatosis, the reader is referred to Dwyer, Levin, and Buttel (ms.). For influenza, we extend the classical epidemiological approaches to allow for immunological interactions between strains (cross-immunity), and find that periodic recurrence cannot be sustained without loss of amplitude. In section 3, we introduce consideration of the age-structure of the population, and discuss how this may contribute to the maintenance of temporally varying incidence rates. The mathematical details will appear elsewhere (Castillo-Chavez et al., 1988.).

2. INFLUENZA

In this section, we discuss briefly the role of cross-immunity in the dynamics of influenza. Three major types of influenza have been identified: A (the most severe), B, and C (see Smith et al., 1933; Francis, 1940; Francis et al., 1950); each type has various subtypes (see Table 1, modified from Couch and Kasel, 1983). In the case of type A, three subtypes have been isolated: H1N1, H2N2, and H3N2; moreover, several strains—comparatively minor variants—are associated with each subtype (for details see Fox and Kilbourne, 1973; Dowdle et al., 1974; Stuart-Harris and Schild, 1976; Selby, 1976; Beveridge, 1977; Palase and Young, 1982; Webster et al., 1982). The maintenance of so many subtypes and strains of the influenza virus is due to its ability to change its antigenic structure (see Webster et al., 1982) rapidly, and to produce variants that have led to recurrent epidemics.

The influenza virus is a microorganism that consists essentially of a conglomerate of seven proteins, five internal and two external. Immunity is believed to be induced by the presence of the surface (i.e., external) glycosylated proteins, the hemagglutinin (HA), and the neuraminidase (NA). The HA molecule has four nonintersecting antigenic regions and the NA has at least three. Evidence suggests that new variants may be produced by the replacement of (at least) one amino acid in each of the four disjoint antigenic regions of the HA molecule (see Couch and Kasel, 1983).

The co-circulation of several strains is a recently documented phenomenon (see Figure 2 in Thacker, 1986); therefore not enough experimental data are available to determine the duration of immunity and cross-immunity to variants. It appears, however (see Section 5), that a high level of immunity to reinfection with H1N1 variants can persist for over twenty years. On the other hand, studies with different subtypes (H1N1, H2N2, H3N2) support the hypothesis of an almost total lack of cross-immunity among them (see Section 5).

The experimental results found in the literature (see Couch and Kasel, 1983) show that cross-immunity:

(a) exhibits subtype specificity,

(b) exhibits cross-reactivity to variants within a subtype, but with reduced cross-reactivity for variants that are antigenically distant from the initial variant, and

(c) exhibits a duration of at least five to eight years.

In this paper, we incorporate such observations into mathematical models that allow investigation of the role of cross-immunity in disease dynamics.

3. CROSS-IMMUNITY IN A HOMOGENEOUS POPULATION

In this section, following Castillo-Chavez et al. (1988.), we formulate a two-strain epidemiological model for a homogeneous population. This population is divided into eight classes: X (fraction susceptible), Y_i (fraction infected by strain i), Z_i (fraction recovered from the other strain), V_i (fraction infected by strain i after recovery from the other strain), and W (recovered from both strains). The interactions among classes are represented in the transfer diagram shown in Fig. 1.

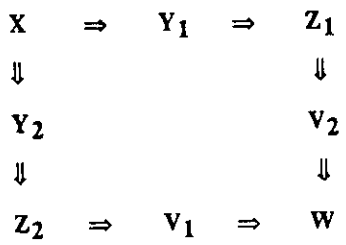

Figure 1

We let β_i denote the transmission coefficient of strain i, and define the susceptibility factor σ_j (where j = 3-i) to be the relative susceptibility of types Z_i and X in terms of their acquisition of strain j. We assume that σ is between 0 and 1. Furthermore, γ_i denotes the recovery rate from strain i, and μ denotes the constant natural mortality rate. The use of the above transfer diagram in conjunction with the "mass-action" law and homogeneous mixing leads to the following system of ordinary differential equations (Castillo-Chavez et al., 1988.):

$$X'(t) = -[\beta_1 (Y_1 + V_1) + \beta_2 (Y_2 + V_2) - \mu]\, X + \mu \quad , \tag{1.1}$$

$$Y_i'(t) = \beta_i (Y_i + V_i)\, X - (\gamma_i + \mu)\, Y_i \quad , \text{ for } i = 1, 2, \tag{1.2}$$

$$Z_i'(t) = \gamma_i Y_i - [\sigma_j \beta_j (Y_j + V_j) + \mu]\, Z_i \quad , \text{ for } i = 1, 2, \tag{1.3}$$

$$V_i'(t) = \sigma_i \beta_i (Y_i + V_i)\, Z_j - (\gamma_i + \mu)\, V_i \quad , \text{ for } i = 1, 2, \tag{1.4}$$

$$W'(t) = \gamma_1 V_1 + \gamma_2 V_2 - \mu W \quad , \tag{1.5}$$

$$X(0) = X_0,\ Y_i(0) = Y_{i0},\ Z_i(0) = Z_{i0},\ V_i(0) = V_{i0},\ W(0) = W_0 \quad , \text{ for } i = 1, 2 \tag{1.6}$$

Recall that j = 3 - i; that is, i = 1, j = 2, or i = 2, j = 1.

This model extends the Dietz-Elveback model (see Dietz, 1979), which is obtained as a special case of the above set of equations when $\sigma_1 = \sigma_2 = 1$. This corresponds to no cross-immunity between strains, while $\sigma_1 = \sigma_2 = 0$ indicates total cross-immunity. Thus, the model is flexible enough to cover the possibilities ranging from closely related strains to distinct subtypes.

Stability analysis and numerical simulations of this model strongly suggest that periodic solutions do not arise by Hopf bifurcation (Castillo-Chavez et al., 1988.). For the symmetric case ($\sigma_1 = \sigma_2$, $\beta_1 = \beta_2$, $\gamma_1 = \gamma_2$), a complete local stability analysis is possible that corroborates the numerical results. For the general case, we have carried out such analysis for boundary equilibria, and have supplemented it by simulations near the unique interior equilibrium. All of these results suggest that the co-circulation of strains is itself not sufficient to drive sustained oscillations. Since a locally stable endemic equilibrium with both strains present is possible, oscillations conceivably could be driven by stochastic fluctuations in the environment. An alternative hypothesis, which we examine next, is that oscillations result from an interaction with the age structure of the host population.

Building age-structure into the reproductive dynamics of a population certainly can drive periodicities if fecundities depend on age in a way that births are pulsed, or that nonlinearity enters. Without these features, however, age-structured models have seemed unable to support sustained oscillations, even if the contact rates are age-specific. This conclusion has been advanced by several authors (see, for example, Dietz and Schenzle, 1985; Anderson and May, 1984; Castillo-Chavez et al.,1988.). However, such models can exhibit very weakly damped oscillations (Anderson and May, 1984). Hence the question naturally arises: can the presence of multiple strains as they co-circulate in a heterogeneous population interact with age-specificity to drive periodic behavior (i.e., be responsible for the observed recurrent epidemics)? We will examine this in the next section. In practice, we also must be aware that weakly damped oscillations will be difficult to distinguish from sustained ones under natural conditions, and that what is called periodic behavior actually may be weakly damped.

4. CROSS-IMMUNITY IN AN AGE-STRUCTURED POPULATION

We let $x(a,t)$, $y_i(a,t)$, $z_i(a,t)$, $v_i(a,t)$, and $w(a,t)$, denote the densities of the individuals in each class defined in the previous section. Here a is an independent variable that denotes the age of an individual. b(a) represents the age-specific contact rate, $\lambda(t)$ denotes the instantaneous force of infection, β_i denotes the transmission scaling factor, $\mu(a)$ is the age-specific mortality rate, and γ_i denotes the (constant) recovery rate. The susceptibility coefficients σ_1 and σ_2 denote different degrees of cross-immunity associated with the interaction of two strains or two subtypes.

In the development of our age-structured model, we make use of the proportionate mixing assumption (see Barbour, 1978; Nold, 1980; Hethcote and Yorke,

1984; Dietz and Schenzle, 1985). Hence the contact rate between susceptible persons of age a and infected ones of age a' is assumed to be proportional to b(a)b(a'). If we now follow our previous transfer diagram while making use of the "mass-action" law, we arrive at the following initial boundary value problem:

$$\frac{\partial x(a,t)}{\partial a} + \frac{\partial x(a,t)}{\partial t} = -(\lambda_1(t)\, b(a) + \lambda_2(t)\, b(a) + \mu(a))\, x(a,t), \tag{2.1}$$

$$\frac{\partial y_i(a,t)}{\partial a} + \frac{\partial y_i(a,t)}{\partial t} = \lambda_i(t)\, b(a)\, x(a,t) - (\gamma_i + \mu(a))\, y_i(a,t), \qquad i = 1, 2 \tag{2.2}$$

$$\frac{\partial z_i(a,t)}{\partial a} + \frac{\partial z_i(a,t)}{\partial t} = \gamma_i y_i\,(a,t) - \sigma_j \lambda_j(t)\, b(a)\, z_i(a,t) - \mu(a)\, z_i(a,t), \qquad i = 1, 2 \tag{2.3}$$

$$\frac{\partial v_i(a,t)}{\partial a} + \frac{\partial v_i(a,t)}{\partial t} = \sigma_i \lambda_i(t)\, b(a)\, z_j(a,t) - (\gamma_i + \mu(a))\, v_i(a,t), \qquad i = 1, 2 \tag{2.4}$$

$$\frac{\partial w(a,t)}{\partial a} + \frac{\partial w(a,t)}{\partial t} = (\gamma_1 + \gamma_2 - \mu(a))\, w(a,t), \tag{2.5}$$

$$\lambda_i(t) = \beta_i \int_0^{\infty} b(a')\, [y_i(a',t) + v_i(a',t)]\, da', \tag{2.6}$$

$$x(0,t) = \rho,\ y_i(0,t) = 0,\ z_i(0,t) = 0,\ v_i(0,t) = 0,\ w(0,t) = 0, \tag{2.7}$$

$$x(a,0) = x_0(a),\ y_i(a,0) = y_{0i}(a),\ z_i(a,0) = z_{0i}(a),\ v_i(a,0) = v_{0i}(a),\ w(0,t) = w_0(a), \tag{2.8}$$

$$\rho = \left[\int_0^{\infty} e^{-M(a)}\, da \right]^{-1} \quad \text{where} \quad M(a) = \int_0^{a} \mu(\alpha)\, d\alpha \,. \tag{2.9}$$

Despite the complexity of this model, some analysis is possible. The initial boundary value problem is well posed. A partial local stability analysis is possible for the case of total cross-immunity ($\sigma_1 = \sigma_2 = 0$). In this situation, there are four types of equilibria: both strains absent, type 1 absent, type 2 absent, or both present. Necessary conditions have been found that guarantee the local stability of the steady-state age distributions associated with the first three equilibria (Castillo-Chavez et al.,1988.). However, the nature of the fourth (interior) equilibrium has not yielded to our mathematical analysis except in very particular circumstances. Therefore, even in this case, we cannot rule out the possibility of periodic solutions arising by Hopf bifurcation. Development of analytical techniques to deal with the transcendental equations involved in the stability analysis of this type of model, and more generally the development of methods to deal with asymptotic behavior, represent challenging mathematical problem of substantial biological importance.

Unable to analyze the model completely, we turned to simulation of a related compartmental model based on our previous transfer diagram, the "mass-action" law, and the proportionate mixing assumption. Simulations with this two-strain model yielded a strong coupling between both strains, and sustained periodic behavior was observed for a wide range of values of the cross-immunity coefficient when realistic parameters for influenza were used. For example, for the symmetric case ($\sigma_1 = \sigma_2 = \sigma$, $\beta_1 = \beta_2$, $\gamma_1 = \gamma_2$), cycles were observed for values of σ between 0.3 and 0.6 when other parameters were given values compatible with the transmission of influenza. Further numerical experiments showed that the interaction between cross-immunity and age-dependent mortality (without age-dependent contact rates) was responsible for the

observed periodic behavior. Experiments with a constant death rate and age-dependent contact rates did not produce sustained periodic behavior. Of course, this does not mean that age-dependent contact rates cannot play a crucial role under other circumstances.

5. EMPIRICAL EVIDENCE FOR CROSS-IMMUNITY

From these simulation results, some questions of practical importance arise: can we determine the relevant values of σ from the epidemiological literature? If so, do these values lie roughly in the range capable of driving periodic behavior? If we cannot estimate σ, can experiments be designed for this purpose? A quick review of some examples shows a promising path.

A 1979 study (see Couch and Kasel, 1983) revealed that less than 3% of those with a prior A/Hong Kong/68 (H3N2) or a prior A/England/72 (H3N2) infection were found to have experienced an infection with A/Port Chalmers/ 73 (H3N2), while 23% with no previous infection not only were infected but had a higher incidence of severe cases of this strain of influenza. That is, a relative frequency of $\sigma = 0.13$ cases was observed. A 1976 study, also mentioned in the above reference, was prompted by the appearance of the strain A/Victoria/75 (H3N2). It showed that the relative frequency of infection by this strain, for those previously infected by a H3N2 virus compared with those who were not, was $\sigma = 0.407$. Furthermore, individuals born before 1952, and hence having a very high probability of a previous infection with an H1N1 variant, rarely have been infected with the (reappearing) H1N1 variants that have been co-circulating since 1977. In addition, the frequency of detection of antibody-positive sera between 1977 and 1978, the year of the reappearence of the H1N1 subtype, changed from 0% to 38% for young people. In contrast, the frequency of detection for antibody-positive sera for older people remained at 9%. Recent studies on the co-circulation of the subtypes H1N1 and H3N2 in the Houston area (see Glezen et al., 1982) have

shown that there is no cross-reactive immunity between these two subtypes. From this type of experiment, the hypothesis has emerged that there is no cross-immunity when both surface antigens are distinctive. Other documented cases of cross-immunity or the lack of it can be found in the papers of (Mulder et al.,1958; Schoenbaum et al., 1976; Monto et al., 1973; Fazekas, 1975).

Can we use this information to estimate reliable values for σ? We suggest the use of the relative frequencies of infection, or the relative frequencies of the levels of antibody-positive sera present in a population once a new subtype or strain has been established, as crude estimates for the values of σ when strains or subtypes are already established and act in a symmetric manner. This procedure may give us a rough estimate for σ. For non-symmetric strains, a more general procedure will probably be needed.

6. DISCUSSION

In this paper we discuss the concept of cross-immunity as it pertains to the dynamics of the infections produced by influenza viruses within a heterogeneous (age-structured) population. Our conclusion is that cross-immunity, in the presence of age-dependent survivorship, provides us with a sufficient mechanism to explain the observed recurrence of several strains. Moreover, it seems possible to estimate all the parameters involved in these models, which would allow us to test them against real data.

One of the messages of this paper is that simpler models will not suffice in the study of the periodic recurrence of co-circulating strains. At present, very few models incorporate factors such as viral heterogeneity and consider interference, cross-immunity, and host heterogeneity. Moreover, those models that do include such factors have been investigated primarily through simulations, thus providing a limited (but

useful) picture of the dynamics (e.g. Dietz, 1979; Levin and Pimentel, 1981; Levin, 1983; Castillo-Chavez et al.,1988.). The near absence of analytical results has left untouched many important questions. One question of particular importance deals with the determination of possible mechanisms responsible for the inter-epidemic persistence of co-circulating virus types, as well as their possible role in fostering the recurrence of such epidemics. This question has received theoretical attention only recently (see Castillo-Chavez et al.,1988.). Related to the last issues is the need to develop mathematical techniques and numerical schemes that give us precise information about the asymptotic behavior of the solutions of these initial boundary value problems.

In conclusion, such models generate a wealth of problems for the mathematician interested in interdisciplinary research. Their study could produce new mathematical results, new mathematical techniques, and most importantly, useful biological insights.

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TABLE 1*

Antigenic classification of hemagglutinin and neuraminidase subtypes of human influenza viruses

Type	Subtype[a]	Period of prevalence	Reference strain variants[b] (H subtype)
A	H1N1	1918 - 1956	A/Puerto Rico/8/34 A/Weiss/1/43 A/FMI/1/47 A/England/1/51 A/Denver/1/57
A	H2N2	1957 - 1967	A/Japan/305/57 A/Taiwan/1/64
A	H3N2	1968 -	A/Hong Kong/8/68 A/England/42/72 A/Port Chalmers/1/73 A/Victoria/1/75 A/Texas/1/77 A/Bangkok/1/79
A	H1N1	1977 -	A/USSR/90/77 A/Brazil/11/78
B	--	1940 -	A/Great Lakes/1739/54 B/Maryland/1/59 B/Singapore/222/79
C	--	1949 -	C/Taylor/1233/49

*modified from Couch and Kasel (1983).

[a]Subtypes refer to type A viruses with antigenically distinctive hemagglutinin and neuraminidase virion surface antigens.

[b]Variants are designated by type, place of initial isolation, strain number, and year of isolation.

LITERATURE CITED

Anderson, R. M., and May, R. M. 1984. Spatial, temporal and genetic heterogeneity in host populations and the design of immunization programmes. IMA J. of Mathematics Applied in Med. and Bio. 1, 233-266.

Barbour, A. D. 1978. Macdonald's model and the transmission of bilharzia. Trans. Royal Soc. Trop. Med. Hyg. 72, 6-15.

Beveridge, W. I. B. 1977. Influenza: The Last Great Plague (London: Heinemann).

Castillo-Chavez, C., Hethcote, H. W., Andreasen, V., Levin, S. A., and Liu, W. 1988. Epidemiological models with age structure and proportionate mixing. J.Math Biology (in press).

Couch, R. B., and Kasel, J. A. 1983. Immunity to influenza in man. Ann. Rev. Microbiol. 37, 529-549.

Dietz, K. 1979. Epidemiologic interference of virus populations. J. Math. Biology 8, 291-300.

Dietz, K. and Schenzle, D. 1985. Proportionate mixing models for age-dependent infection transmission. J. Math. Biology 22, 117-120.

Dowdle, W. R., Coleman, M. T., and Gregg, M. B. 1974. Natural history of influenza type A in the United States, 1957-1972. Progr. Med. Virol. 17, 91-135.

Dwyer, G., Levin, S. A., Buttel, L. 1987. A model of the evolution of virulence in the myxoma virus. (manuscript)

Fazekas de St. Groth, S. 1975. Influenza: antigenic evolution and epidemiology. Bull. Int. Stat. Inst. 66, 476-477.

Fenner, F. and Ratcliffe, F. N. 1965. Myxomatosis (Cambridge: Cambridge University Press).

Fine, P. 1982. Applications of mathematical models to the epidemiology of influenza: a critique. In: Influenza Models, Philip Selby, ed. (Lancaster, Boston and the Hague: MTP Press), pp. 15-85.

Fox, J. P., Kilbourne, E. D., and rapporteurs. 1973. From the National Institutes of Health: epidemiology of influenza - summary of influenza workshop IV. J. Inf. Dis. 128, 361-86.

Francis, T., Jr. 1940. New type of virus for epidemic influenza. Science 92, 405-407.

Francis, T., Jr., Quilligan, J. J. Jr., Minuse, E. 1950. Identification of another respiratory disease. Science 112, 495-497.

Glezen, W. P., Couch, R. B., and Six, H. R. 1982. Am. J. Epidemiology 116, 589-598.

Hethcote, H. W. and Yorke, J. A. 1984. Gonorrhea Transmission Dynamics and Control. Lecture Notes in Biomathematics 56. (Berlin, Heidelberg, New York, Tokyo: Springer-Verlag).

Levin, S. A. 1983. Some approaches to the modelling of coevolutionary interactions. In: Coevolution, M. Nitecki, ed. University of Chicago Press, pp. 21-65.

Levin, S. and Pimentel, D. 1981. Selection of intermediate rates of increase in parasite-host systems. The American Naturalist. 117, 3:308-315.

Mulder, J., Masurel, N. 1958. Pre-epidemic antibody against 1957 strain of the Asiatic influenza in older people living in the Netherlands. Lancet 1, 810-814.

Nold, A. 1980. Heterogeneity in disease-transmission modeling. Math Biosci. 52, 227-240.

Palese, P., and F. J. Young. 1982. Variation of influenza A, B, and C viruses. Science 215, 1468-1474.

Schoenbaum, S. C., Coleman, M. T., Dowdle, W. R., et al. 1976. Epidemiology of influenza in the elderly: evidence of virus recycling. Am. J. Epidemiology 1, 623-625.

Selby, P., ed. 1976. Influenza: Virus, Vaccines, and Strategy. Proceedings of a working group on pandemic influenza, Rougemont, January 26-28 (London and New York: Academic Press).

Smith, W., Andrewes, C. H., and Laidlaw, P. P. 1933. A virus obtained from influenza patients. Lancet 2, 66-68.

Stuart-Harris, C. H. 1982. The epidemiology of influenza - key facts and remaining problems. In: Influenza Models, ed. Philip Selby (Lancaster, Boston and The Hague: MTP Press), pp. 87-123.

Stuart-Harris, C. H., and Schild, G. C. 1976. Influenza: the viruses and the disease, (London: Edward Arnold Ltd.).

Thacker, S. B. 1986. The persistence of influenza in human populations. Epidemiological Reviews 8, 129-142.

Webster, R. G., Laver, W. G., Air, G. M., and Schild, G. C. 1982. Molecular mechanisms of variation in influenza viruses. Nature 296, 115-121 (1982).