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A Generalized Stochastic Model for the Analysis of Infectious Disease Final Size Data

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SUMMARY

A stochastic infectious disease model was developed by Ball (1986, *Advances in Applied Probability* **18**, 289–310) in which the distribution of the length of the infectious period is allowed to have any distribution that can be described by its Laplace transform. We extend this model such that the infection can be transmitted within the population or from an unspecified source outside the population. Also, discrete heterogeneity in the population can be modeled to incorporate variable susceptibility, variable infectivity, and/or mixing behaviors. The model is fitted to serologic data from two influenza epidemics in Tecumseh, Michigan, using maximum likelihood estimation procedures. The estimates show a clustering pattern by age groups.

1. Introduction

Epidemic models can be used as mathematical tools for the analysis of the transmission of infectious diseases. An epidemic model offers a convenient summary to infectious disease data, but a more important use is to provide understanding of the biological and sociological mechanisms of disease transmission (Becker, 1979). The identification of an epidemic model as being either adequate or inadequate for a particular disease can elucidate important characteristics of transmission of that disease. An epidemic model combines biologic characteristics such as susceptibility, infectiousness, and length of infectious period with behavioral characteristics such as hygienic practices and social mixing patterns.

Current epidemic models make various assumptions about the disease transmission process. All of these assumptions are to some extent approximations for the actual process. Dietz and Schenzle (1985) offer a survey of the historical development of many of these models for homogeneous populations. A common assumption is that the infectious period has a constant length. This assumption might lead to the Greenwood model or to the Reed–Frost model (see, for example, Bailey, 1975; Abbey, 1952; and Maia, 1952). These simple models have been extended to allow multiple sources of infection by Longini and Koopman (1982), Longini et al. (1982), and Longini, Monto, and Koopman (1984), and to allow variable susceptibility (Longini et al., 1988; Haber, Longini, and Cotsonis, 1988).

If the length of the infectious period is not considered to be fixed, it is most often assumed to have an exponential distribution. The epidemic model with an exponentially distributed length of infectious period is called the general epidemic model. The exponential distribution is useful because of its constant hazard rate and its lack of memory, but lacks biologic plausibility. No

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other nondegenerate distribution for the length of the infectious period has been used so extensively in epidemic modeling. Ball (1985) has extended this general epidemic to include several types of susceptibles.

The assumption of an exponentially distributed infectious period is untenable to some researchers. Ball (1986) develops a stochastic epidemic model that allows for any distribution for the length of the infectious period, provided that its Laplace transform can be specified. Other generalizations to the so-called general epidemic include various structures for population mixing behaviors. Further extensions of epidemic modeling include prediction of global spread of infectious agents, discussed in papers by Rvachev and Longini (1985) and Longini, Fine, and Thacker (1986).

In this paper, the stochastic model presented by Ball (1986) is further developed to allow a variable length of infectious period, heterogeneous contact rates reflecting variable susceptibility and infectivity as well as mixing behaviors, and multiple sources of infection (see Addy, unpublished Ph.D. dissertation, Emory University, 1988). The model is applied to the Tecumseh, Michigan, influenza data (Monto, Koopman, and Longini, 1985) to illustrate estimation of the contact parameters based on final sizes of epidemics.

2. Recursive Nature of Final Size Probabilities

Consider a population composed of N_i ($i = 1, \ldots, m$) individuals in each of m groups, where each individual is in exactly one group and is susceptible to the infectious disease of interest at the beginning of the epidemic; let $\mathbf{N} = (N_1, N_2, \ldots, N_m)'$ be a vector containing all the initial susceptible group sizes and $N = \sum_{i=1}^{m} N_i$ be the total size of the susceptible population. Furthermore, suppose that if a given susceptible k ($k = 1, \ldots, N_i$) in group i is infected, the length of that person's infectious period is the random variable T_{ik}, with Laplace transform $\phi_i(t) = \mathrm{E}[\exp(-tT_{ik})]$.

An epidemic can be started by one or more persons in the population who are infected at the beginning of the epidemic or by infectious contact from an unspecified source outside the population; let $\mathbf{a} = (a_1, a_2, \ldots, a_m)'$ denote the numbers of initial infectives in the groups. Given these conditions, the epidemic is governed by two types of parameters. The first type is the extra-population escape probability B_i, which is the probability that a susceptible of type i will escape infection from outside the population during the entire course of the epidemic. Then the vector $\mathbf{B} = (B_1, B_2, \ldots, B_m)'$ contains all the extra-population escape probabilities.

The second type of parameter governs within-population disease transmission. The parameter β_{ik} is the rate at which a susceptible of type i has contact with an infective of type k; these contact parameters are stored in the $m \times m$ matrix $\boldsymbol{\beta}$. The contact parameter matrix can be structured to model certain conditions. For example, a model of variable susceptibility and fixed infectivity would have $\beta_{ik} = \beta_i$, so that the contact parameter depends only on the group of the susceptible and not on the group of the infective. The final notation needed is for the random variables of interest. Let N_k^* be the final size in group k, i.e., the number of initial susceptibles in group k who are ultimately infected by the epidemic; analogous to the susceptible population sizes, let $\mathbf{N}^* = (N_1^*, N_2^*, \ldots, N_m^*)'$ and $N^* = \sum_{k=1}^{m} N_k^*$. Of secondary interest but crucial to the development is the total area under the trajectory of infectives in each group. The total area in group k may be regarded as the total person-time units of exposure to infectives of type k and is denoted $T_{\mathrm{A}}^{(k)}$; these group-specific quantities are summarized by $\mathbf{T}_{\mathrm{A}} = (T_{\mathrm{A}}^{(1)}, T_{\mathrm{A}}^{(2)}, \ldots, T_{\mathrm{A}}^{(m)})'$ and $T_{\mathrm{A}} = \sum_{k=1}^{m} T_{\mathrm{A}}^{(k)}$. These total areas include the exposure contributed by the initial infectives.

To simplify notation, the following conventions will be adopted:

$$\mathbf{B}^{\boldsymbol{\omega}} = \prod_{i=1}^{m} B_i^{\omega_i}, \quad \boldsymbol{\phi}(\mathbf{t})^{\boldsymbol{\omega}} = \prod_{i=1}^{m} \phi_i(t_i)^{\omega_i}, \quad \sum_{\mathbf{j}=\mathbf{0}}^{\boldsymbol{\omega}} = \sum_{j_1=0}^{\omega_1} \cdots \sum_{j_m=0}^{\omega_m},$$

and

$$\binom{\mathbf{N}}{\boldsymbol{\omega}} = \binom{N_1}{\omega_1}\binom{N_2}{\omega_2}\cdots\binom{N_m}{\omega_m}.$$

Also, $\boldsymbol{\omega}_i = \{1, \ldots, \omega_i\}$. To distinguish between $\boldsymbol{\omega} = (\omega_1, \ldots, \omega_m)'$ and $\boldsymbol{\omega}_i = \{1, \ldots, \omega_i\}$, note the use of a subscript for the latter ordered set. The vector $\boldsymbol{\omega}$ will never have a subscript. The distinction is even clearer in context since a set and a vector are not interchangeable in algebraic operations, and the ordered set is used only to identify a function or probability.

Crucial to the development of the recursive relations between the final size probabilities is a Wald's identity.

Theorem 1 For all $\mathbf{t} = (t_1, \ldots, t_m)' \in (\mathbf{R}^+)^m$,

$$\mathrm{E}\left(\exp\left(-\textstyle\sum_{k=1}^{m} t_k T_{\mathrm{A}}^{(k)}\right)/\prod_{k=1}^{m}\phi_k(t_k)^{N_k^*+a_k}\right) = 1. \tag{1}$$

Proof See Addy (unpublished dissertation cited previously).

Notice that the compact notation enables the equality in (1) to be written as

$$1 = \mathrm{E}\left(\exp\left(-\mathbf{t}'\mathbf{T}_{\mathrm{A}}\right)/\boldsymbol{\phi}(\mathbf{t})^{\mathbf{N}^*+\mathbf{a}}\right).$$

Next, notation for the final size probabilities is needed. Let $P_{\boldsymbol{\omega}}^{\mathbf{N}}$ be the probability that $\mathbf{N}^* = \boldsymbol{\omega}$ when the initial susceptible group sizes are $\mathbf{N}$, and let $P_{\omega_1,\ldots,\omega_m}^{\mathbf{N}}$ be the probability that exactly individuals $1, \ldots, \omega_i$ are infected in group i $(i = 1, \ldots, m)$ in the same susceptible population. Because of the symmetry of the epidemic,

$$P_{\boldsymbol{\omega}}^{\mathbf{N}} = \binom{N_1}{\omega_1}\cdots\binom{N_m}{\omega_m}\mathbf{P}_{\omega_1,\ldots,\omega_m}^{\mathbf{N}}$$

or, using the compact notation,

$$P_{\boldsymbol{\omega}}^{\mathbf{N}} = \binom{\mathbf{N}}{\boldsymbol{\omega}}P_{\omega_1,\ldots,\omega_m}^{\mathbf{N}}.$$

The dependence on β, $\mathbf{a}$, and $\mathbf{B}$ will not be shown explicitly. Choose integers $j_1, \ldots, j_m$ such that $0 \leqslant \omega_i \leqslant j_i \leqslant N_i$ $(i = 1, \ldots, m)$. The goal is to express $P_{\boldsymbol{\omega}}^{\mathbf{N}}$ as a function of $P_{\boldsymbol{\omega}}^{\mathbf{j}}$ and the model parameters.

The final size probabilities are calculated by considering the probability that certain infections do not occur. Thus, to relate the epidemic among $\mathbf{N}$ and the subepidemic among $\mathbf{j}$, the probability of susceptibles in $\mathbf{N}_i \setminus \mathbf{j}_i = \{j_i + 1, \ldots, N_i\}$ $(i = 1, \ldots, m)$ avoiding infection both from within the population and from outside the population must be considered. The probability of one susceptible in group i avoiding infection from the initial infectives and the $\omega_1, \ldots, \omega_m$ new infectives is, for given values of $T_{\mathrm{A}}^{(k)}$,

$$\exp\left(-\sum_{k=1}^{m}\beta_{ik}T_{\mathrm{A}}^{(k)}\right),$$

since the susceptible must avoid infection from all m groups. Then the probability of all the susceptibles in $\{\mathbf{N}_1 \setminus \mathbf{j}_1, \ldots, \mathbf{N}_m \setminus \mathbf{j}_m\}$ avoiding infection from all the initial and new infectives, again for given values of $T_{\mathrm{A}}^{(k)}$, is

$$\exp\left(-\sum_{i=1}^{m}(N_i - j_i)\sum_{k=1}^{m}\beta_{ik}T_{\mathrm{A}}^{(k)}\right).$$

To remove the dependence on the random variables, the expectations must be taken with respect to the total areas $\mathbf{T}_A$, conditional on $\mathbf{N} = \mathbf{j}$ and $\mathbf{N}^* = \boldsymbol{\omega}$. Then the within-population escape probability is

$$\mathrm{E}\left(\exp\left\{-\sum_{i=1}^{m}\sum_{k=1}^{m}(N_i - j_i)\beta_{ik}T_A^{(k)}\right\} \mid \mathbf{N} = \mathbf{j}, \mathbf{N}^* = \boldsymbol{\omega}\right).$$

The extra-population escape probability for all the susceptiles in $\{\mathbf{N}_1 \setminus \mathbf{j}_1, \ldots, \mathbf{N}_m \setminus \mathbf{j}_m\}$ is $\Pi_{i=1}^{m} B_i^{N_i - j_i} = \mathbf{B}^{\mathbf{N}-\mathbf{j}}$. Therefore the final size probabilities can be related as

$$P^{\mathbf{N}}_{\omega_1,\ldots,\omega_m} = P^{\mathbf{j}}_{\omega_1,\ldots,\omega_m}\,\mathrm{E}\left(\exp\left\{-\sum_{i=1}^{m}\sum_{k=1}^{m}(N_i - j_i)\beta_{ik}T_A^{(k)}\right\}\right)\mathbf{B}^{\mathbf{N}-\mathbf{j}},\ 0 \leqslant \boldsymbol{\omega} \leqslant \mathbf{j} \leqslant \mathbf{N}, \quad (2)$$

where the expectation is conditional on $\mathbf{N} = \mathbf{j}$ and $\mathbf{N}^* = \boldsymbol{\omega}$.

The law of total probability can now be applied to Theorem 1 to yield the following system of equations:

$$1 = \sum_{\boldsymbol{\omega}=\mathbf{0}}^{\mathbf{j}} P^{\mathbf{j}}_{\boldsymbol{\omega}}\,\mathrm{E}\left(\exp\left\{-\sum_{k=1}^{m} t_k T_A^{(k)}\right\} \mid \mathbf{N} = \mathbf{j}, \mathbf{N}^* = \boldsymbol{\omega}\right)/\phi(\mathbf{t})^{\boldsymbol{\omega}+\mathbf{a}}, \quad \mathbf{j} \geqslant \mathbf{0}. \quad (3)$$

Letting $t_k = \sum_{i=1}^{m}(N_i - j_i)\beta_{ik}$ in (3) and applying the relationship in (2), the system can be written as

$$1 = \sum_{\boldsymbol{\omega}=\mathbf{0}}^{\mathbf{j}} \binom{\mathbf{j}}{\boldsymbol{\omega}} P^{\mathbf{N}}_{\omega_1,\ldots,\omega_m}/\phi\left(\boldsymbol{\beta}'(\mathbf{N} - \mathbf{j})\right)^{\boldsymbol{\omega}+\mathbf{a}}\mathbf{B}^{\mathbf{N}-\mathbf{j}}, \quad \mathbf{j} \geqslant \mathbf{0}. \quad (4)$$

This system of equations fully determines the probabilities $P^{\mathbf{N}}_{\boldsymbol{\omega}}$ for specific initial population sizes $\mathbf{N}$ and $\mathbf{a}$.

The compact notation somewhat obscures the probabilities embedded in the above system of equations. Recall that

$$\phi\left(\boldsymbol{\beta}'(\mathbf{N} - \mathbf{j})\right)^{\boldsymbol{\omega}+\mathbf{a}} = \prod_{k=1}^{m}\phi_k\left(\sum_{i=1}^{m}(N_i - j_i)\beta_{ik}\right)^{\omega_k + a_k}.$$

Each term in this product is the probability that the $N_i - j_i$ susceptibles in each group i ($i = 1, \ldots, m$) avoid infection from the $\omega_k + a_k$ infectives in group k ($k = 1, \ldots, m$). The product is then the probability that all the susceptibles avoid all the infectives for the entire durations of their respective infectious periods.

3. Distribution of the Final Size

The recursive relationship between the probabilities given in (2) can be used to develop the joint moment-generating function for the total areas under the trajectories of infectives and the joint probability-generating function for the numbers of susceptibles in each group surviving the epidemic. Since the total area is of secondary interest for our applications, the development of its moment-generating function is outlined in Appendix A. The latter probability-generating function is discussed below. Once this function is known, it can be used to calculate directly the probabilities and the moments of the final size distribution.

Theorem 2 Let $f_{\mathbf{N}}(\mathbf{s})$ be the joint probability-generating function of the numbers of susceptibles in each group surviving an epidemic among initial susceptible groups of size $\mathbf{N}$. Then

$$f_{\mathbf{N}}(\mathbf{s}) = \sum_{\mathbf{k}=\mathbf{0}}^{\mathbf{N}} \binom{\mathbf{N}}{\mathbf{k}} \alpha_{\mathbf{k}}(\mathbf{s})\phi\left(\boldsymbol{\beta}'\mathbf{k}\right)^{\mathbf{N}-\mathbf{k}+\mathbf{a}}\mathbf{B}^{\mathbf{k}},$$

where the $\alpha_{\mathbf{k}}(\mathbf{s})$, $\mathbf{k} \geqslant \mathbf{0}$, are defined by

$$\sum_{\mathbf{k}=\mathbf{0}}^{\mathbf{n}} \binom{\mathbf{n}}{\mathbf{k}} \alpha_{\mathbf{k}}(\mathbf{s})\phi\left(\boldsymbol{\beta}'\mathbf{k}\right)^{\mathbf{n}-\mathbf{k}} = \mathbf{s}^{\mathbf{n}}, \quad \mathbf{n} \geqslant \mathbf{0}. \quad (5)$$

Proof See Appendix B.

Properties of the joint probability-generating function can be utilized to recover the exact probabilities and to calculate means, variances, and covariances of the final sizes in each of the m groups.

To recover the final size probabilities, notice that the functions $\alpha_{\mathbf{k}}(\mathbf{s})$ are polynomials in $\mathbf{s}$ of degree $\mathbf{k}$. Thus the functions can be written as

$$\alpha_{\mathbf{k}}(\mathbf{s}) = \sum_{\mathbf{j}=\mathbf{0}}^{\mathbf{k}} \alpha_{\mathbf{k},\mathbf{j}}\mathbf{s}^{\mathbf{j}},$$

where $\alpha_{\mathbf{k},\mathbf{j}}$ is the coefficient of $\mathbf{s}^{\mathbf{j}} = \Pi_{i=1}^{m} s_i^{j_i}$ in $\alpha_{\mathbf{k}}(\mathbf{s})$. With this definition, (5) can be written as

$$\begin{aligned}\mathbf{s}^{\mathbf{n}} &= \sum_{\mathbf{k}=\mathbf{0}}^{\mathbf{n}} \sum_{\mathbf{j}=\mathbf{0}}^{\mathbf{k}} \binom{\mathbf{n}}{\mathbf{k}} \alpha_{\mathbf{k},\mathbf{j}}\mathbf{s}^{\mathbf{j}}\phi(\beta'\mathbf{k})^{\mathbf{n}-\mathbf{k}} \\ &= \sum_{\mathbf{j}=\mathbf{0}}^{\mathbf{n}} \sum_{\mathbf{k}=\mathbf{j}}^{\mathbf{n}} \binom{\mathbf{n}}{\mathbf{k}} \alpha_{\mathbf{k},\mathbf{j}}\mathbf{s}^{\mathbf{j}}\phi(\beta'\mathbf{k})^{\mathbf{n}-\mathbf{k}},\end{aligned}$$

for any $\mathbf{n} \geqslant \mathbf{0}$. The coefficients $\alpha_{\mathbf{k},\mathbf{j}}$ can be found by equating the coefficients of $\mathbf{s}^{\mathbf{j}}$ on each side of the equation. For any $\mathbf{j} < \mathbf{n}$,

$$\sum_{\mathbf{k}=\mathbf{j}}^{\mathbf{n}} \binom{\mathbf{n}}{\mathbf{k}} \alpha_{\mathbf{k},\mathbf{j}}\phi(\beta'\mathbf{k})^{\mathbf{n}-\mathbf{k}} = \mathbf{0}. \tag{6}$$

Together with $\alpha_{\mathbf{n},\mathbf{n}} = 1$, this system of equations fully defines the $\alpha_{\mathbf{k},\mathbf{j}}$ coefficients. Therefore the probabilities can be written as

$$P_{\mathbf{N}-\mathbf{j}}^{\mathbf{N}} = \sum_{\mathbf{k}=\mathbf{j}}^{\mathbf{N}} \binom{\mathbf{N}}{\mathbf{k}} \alpha_{\mathbf{k},\mathbf{j}}\phi(\beta'\mathbf{k})^{\mathbf{N}-\mathbf{k}+\mathbf{a}}\mathbf{B}^{\mathbf{k}}. \tag{7}$$

In looking at this expression, recall that the subscript of the probability refers to the numbers of initial susceptibles infected during the epidemic, whereas the probability-generating function is defined for the numbers of initial susceptibles surviving the epidemic. Calculation of the recursive coefficients $\alpha_{\mathbf{k},\mathbf{j}}$ can readily be programmed for calculation of the final size probabilities. A subroutine to be used with nonlinear, derivative-free regression in BMDP (Ralston, 1985) for maximum likelihood estimation of the model parameters is given in Addy (unpublished Ph.D. dissertation, Emory University, 1988). The distribution of the length of the infectious period must be completely specified. This distribution is incorporated into the probability structure through its Laplace transform, $\phi(\cdot)$. For most distributions considered, the Laplace transform with argument βk is a function of $\beta\mu k$, where μ is the mean length of the infectious period; thus the contact parameter β, the mean length μ, or the product $\beta\mu$ can be estimated, but not β and μ separately.

In the special case of a constant infectious period, i.e., $T_{\mathrm{I}} \equiv c$ and thus $\phi(t) = \exp(-tc)$, this final size distribution reduces to that given for the model of Longini et al. (1988) and Haber et al. (1988) with either no risk factors or variable susceptibility. The equivalence of the two models with no risk factors is proved in Addy (unpublished dissertation cited previously).

4. Application to Influenza Data

The stochastic epidemic model for a heterogeneous population developed in the previous sections is used to estimate the transmission parameters for influenza A(H3N2) in Tecumseh, Michigan. A continuous epidemiologic survey was conducted in this community from 1976 to 1981, representing a 10% cross-sectional sample of households that was followed prospectively (Monto et al., 1985). The influenza epidemic was defined each year using virus isolation and illness incidence information; each epidemic period was bracketed by pre- and post-epidemic season bleedings. During the 1977–1978 and 1980–1981 influenza seasons, the primary virus

identified was influenza A(H3N2). The data from these two epidemics are combined for this example. The two epidemics are assumed to be independent; earlier work with these data demonstrates their comparability.

For this application, the population is a household. Every individual in each household is classified as child or adult: A child is any individual 0 to 17 years old, and an adult is any individual at least 18 years old. For the Tecumseh survey, antibody was detected by the hemagglutination inhibition (HI) test; any individual with antibody detected in a dilution of 1 in 128 or less before the influenza season was considered to be immune to the virus and was not counted as an initially susceptible individual.

Due to computational restrictions, a maximum of five initial susceptibles is allowed for the estimation procedure. Typically this number is exactly the household size, but the household could include one or more immune individuals. A complete absence of initial infectives for each household is assumed. With this size restriction, there are 567 valid households with a total of 1,414 susceptible individuals. Twenty-six individuals were removed from analysis because of immunity as defined by preseason HI titer. Table 1 shows the distributions of numbers infected in the households.

In using the estimation procedures, two basic questions need to be answered. First, the continuous distribution of the length of the infectious period for influenza is unknown beyond its mean length of 4.1 days; Elveback et al. (1976) specify a discrete distribution with this mean for use in simulation studies. One goal of this analysis is to determine an appropriate distribution for the length of the infectious period. A second goal of this analysis is to determine which model, if any, provides an adequate fit to the selected Tecumseh influenza data.

As an initial analysis, primarily to identify an appropriate distribution for the length of the infectious period, any heterogeneity by age is ignored. The homogeneous population model is fitted with constant and two-parameter gamma distributions for the length of the infectious period, each with mean 4.1 days. The maximum likelihood estimates of β and B for the two distributions are reported in Table 2. A more interpretable form of β is the secondary attack rate (SAR) as defined by Longini and Koopman (1982), the probability that a single susceptible in the population is infected by a single infective in the population. The convention is to express the SAR as a percentage; thus, for a given length infectious period T_I and constant contact rate β, the SAR is

$$\text{SAR} = 100\left[1 - \exp(-\beta T_I)\right].$$

Thus, when T_I is variable, the SAR is calculated by taking the expectation of the above expression,

$$\text{SAR} = 100\left[1 - \text{E}\{\exp(-\beta T_I)\}\right] = 100\left[1 - \phi(\beta)\right],$$

Table 1
Observed distribution of influenza A(H3N2) *infections in* 1977–1978 *and* 1980–1981 *combined epidemics in Tecumseh, Michigan*

No. infected	No. of susceptibles per household[a]				
	1	2	3	4	5
0	110	149	72	60	13
1	23	27	23	20	9
2		13	6	16	5
3			7	8	2
4				2	1
5					1
Total	133	189	108	106	31

[a]The criterion for classifying individuals as susceptible is a preseason hemagglutination inhibition test detecting no antibody in a dilution of 1 in 128 or less. Households with more than five susceptibles are deleted from all analyses.

where $\phi(\cdot)$ is the Laplace transform of the length of the infectious period. Thus the estimated SAR depends on both the estimated β and the specified distribution for the length of the infectious period, generally through the product $\beta\mu$ of β and the mean length of the infectious period μ. The standard error of the SAR is calculated using the delta method on the Laplace transform. Also, the community probability of infection (CPI) as defined by Longini and Koopman (1982), the probability that one susceptible is infected outside the population, is calculated as CPI = $1 - B$. Longini et al. (1988) analyzed these influenza data with a constant length infectious period; their estimates of the SAR and CPI and respective standard errors are comparable to the transformations reported here.

Next, the age stratification is assumed to reflect unspecified heterogeneity in the population. The general model is fitted, yielding the maximum likelihood estimates given in Table 3. The observed and expected frequencies of influenza infection are given in Table 4. For example, there are eleven households with one child and two adults initially susceptible in which one adult is infected during the epidemic; if the length of the infectious period is assumed to have a gamma (2, 2.05) distribution, the expected number of these households is 8.543. The improvement of

Table 2

Maximum likelihood estimates and standard errors for parameters of model of influenza A(H3N2) *infections in* 1977–1978 *and* 1980–1981 *combined epidemics in Tecumseh, Michigan, with homogeneity*

		Estimate	Transformation
Constant distribution:	$T_I \equiv 4.1$		
		$\beta = .0423 \pm .0061$	SAR = 15.9369 ± 2.0873
		$B = .8677 \pm .0097$	CPI = $.1323 \pm .0097$
	Log likelihood	$= -532.974$	
Gamma distribution:	$T_I \sim$ Gamma(2, 2.05)		
		$\beta = .0446 \pm .0071$	SAR = 16.0641 ± 2.2433
		$B = .8674 \pm .0097$	CPI = $.1326 \pm .0097$
	Log likelihood	$= -532.827$	

Table 3

Maximum likelihood estimates and standard errors for parameters of the model of influenza A(H3N2) *infections in* 1977–1978 *and* 1980–1981 *combined epidemics in Tecumseh, Michigan, with unrestricted contact parameters by age* (0–17 *vs* 18+)

		Estimate	Transformation
Constant distribution:	$T_I \equiv 4.1$		
		[a]$\beta_{11} = .0805 \pm .0208$	$SAR_{11} = 28.1186 \pm 6.1227$
		$\beta_{12} = .0354 \pm .0291$	$SAR_{12} = 13.4996 \pm 10.314$
		$\beta_{21} = .0268 \pm .0135$	$SAR_{21} = 10.4080 \pm 4.9593$
		$\beta_{22} = .0401 \pm .0127$	$SAR_{22} = 15.1662 \pm 4.4096$
Child		$B_1 = .8184 \pm .0254$	$CPI_1 = .1816 \pm .0254$
Adult		$B_2 = .8897 \pm .0128$	$CPI_2 = .1103 \pm .0128$
	Log likelihood	$= -522.333$	
Gamma distribution:	$T_I \sim$ Gamma(2, 2.05)		
		[a]$\beta_{11} = .0910 \pm .0263$	$SAR_{11} = 28.9708 \pm 6.4515$
		$\beta_{12} = .0389 \pm .0330$	$SAR_{12} = 14.2256 \pm 10.739$
		$\beta_{21} = .0273 \pm .0146$	$SAR_{21} = 10.3095 \pm 5.0703$
		$\beta_{22} = .0430 \pm .0140$	$SAR_{22} = 15.5452 \pm 4.4420$
Child		$B_1 = .8183 \pm .0250$	$CPI_1 = .1817 \pm .0250$
Adult		$B_2 = .8887 \pm .0127$	$CPI_2 = .1113 \pm .0127$
	Log likelihood	$= -521.922$	

[a]1 = child, 2 = adult. For transmission, the first subscript of the contact parameters refers to the susceptible, the second to the infective.

Table 4
Observed and expected frequencies of influenza A(H3N2) *infections in* 1977–1978 *and* 1980–1981 *combined epidemics in Tecumseh, Michigan, with unrestricted contact parameters by age* (0–17 vs 18+)

Susceptible population	Infected population	Observed	Expected	
			Constant	Gamma
(0, 1)	(0, 0)	108	111.215	111.092
	(0, 1)	17	13.785	13.907
(0, 2)	(0, 0)	130	129.031	128.746
	(0, 1)	22	27.136	27.226
	(0, 2)	11	6.833	7.029
(0, 3)	(0, 0)	7	7.747	7.722
	all other	4	3.253	3.278
(0, 4)[a]	(0, 0)	2	1.253	1.248
	all other	0	.747	.752
(1, 0)[a]	(0, 0)	2	6.547	6.546
	(1, 0)	6	1.453	1.454
(1, 1)	(0, 0)	17	16.748	16.727
	(0, 1), (1, 1)	4	2.923	2.942
	(1, 0)	2	3.329	3.331
(1, 2)	(0, 0)	51	46.646	46.536
	(0, 1)	11	8.485	8.543
	(0, 2), (1, 2)	2	3.787	3.902
	(1, 0)	6	8.307	8.360
	(1, 1)	2	4.774	4.659
(1, 3)	(0, 0)	6	4.611	4.595
	all other	2	3.389	3.405
(1, 4)[a]	(1, 0)	1	.073	.076
	all other	0	.927	.924
(2, 0)[a]	(0, 0)	2	2.009	2.009
	(1, 0)	0	.641	.634
	(2, 0)	1	.350	.357
(2, 1)	(0, 0)	14	14.898	14.877
	(0, 1), (1, 1) (2, 0), (2, 1)	9	5.844	5.843
	(1, 0)	2	4.258	4.280
(2, 2)	(0, 0)	51	47.719	47.599
	(0, 1)	4	7.509	7.656
	(0, 2), (1, 2)	2	3.549	3.306
	(1, 0)	10	12.217	12.541
	(1, 1)	7	6.073	5.607
	(2, 0)	8	5.350	5.226
	(2, 1)	6	4.947	4.993
	(2, 2)	2	2.635	3.072
(2, 3)[a]	(0, 0)	1	1.415	1.253
	(0, 1)	1	.283	.297
	(1, 0)	1	.325	.341
	all other	0	.977	1.109
(3, 1)	(0, 0)	1	2.926	2.922
	all other	5	3.074	3.078

Table 4—*Continued*

(3, 2)	(0, 0)	10	9.981	9.954
	(0, 1), (0, 2)	4	3.125	3.035
	(1, 1), (1, 2)			
	(1, 0)	3	2.755	3.007
	(2, 0), (2, 1)	5	3.122	2.823
	(2, 2), (3, 0)	1	4.018	4.180
	(3, 1), (3, 2)			
(4, 1)[a]	(0, 0)	2	1.600	1.594
	(1, 0)	1	.472	.542
	(4, 1)	1	.305	.355
	all other	0	1.623	1.509
Goodness-of-fit	(19 df)		24.643	25.688
P-value			.173	.139

[a]Denotes susceptible population sizes not included in goodness-of-fit statistics because of small frequencies.

this general model over the homogeneous population model is seen by the likelihood ratio statistic of $\chi^2 = 21.28$ (4 df, $P = .0003$) when the infectious period is assumed to have constant length 4.1.

For each set of contact parameters, a distinct clustering pattern can be seen. For both distributions for the length of the infectious period, the transmission most likely to occur is between children. The next most likely is between adults. Transmission between a child and an adult is the least likely transmission to occur, according to these contact parameter estimates, with a child slightly more likely to be infected by an adult than an adult by a child. Intuitively, this model is reasonable, since even in a family setting children might interact more closely with other children and adults with other adults. The difference in magnitude in the intragroup contact parameters and the difference between the intergroup contact parameters might be partially explained by adults' more hygienic practices and health awareness. In addition, children may be more infectious because of lower levels of neuraminidase antibody, thought to affect virus shedding, from previous infections. Children may also be more susceptible because of less immunity from previous infections. The expected frequencies show no detectable pattern in deviation from the observed frequencies.

Comparisons of this model with other structured models for a heterogeneous population, not presented here, show some improvement. Of the structured models considered, the model of variable susceptibility, defined by $\beta_{ik} = \beta_i$, is the most satisfactory. The general model does not show statistically significant improvement to this model with likelihood ratio test of $\chi^2 = 2.854$ (2 df, $P = .2400$) for the constant (4.1) distribution. The general model also shows no statistically significant improvement to the model of proportional mixing, defined by $\beta_{ik} = \beta_i\beta_k$ ($\chi^2 = 4.012$, 2 df, $P = .1345$). The general model is significantly better than the model of variable infectivity, defined by $\beta_{ik} = \beta_k$ ($\chi^2 = 6.708$, $P = .0349$). The estimated contact parameters in the unrestricted model seem to reflect features of the models of variable susceptibility and proportional mixing.

5. Discussion

The generalized stochastic epidemic model presented in this paper allows a flexible approach to analyzing final size infection data. Separation and estimation of transmission probabilities within and external to a population are possible with a minimum of intervention in a population. Use of final size data allows more precise determination of infection status than is practically possible with more complete incidence data. Earlier research has indicated that complete incidence data contain little information about transmission parameters beyond final size data (Becker, 1976). Also, any latent period can be ignored when final size data are used.

Traditionally, infectious disease models have focused on variable susceptibility and related risk factors, ignoring any variable infectiousness of individuals. In this generalized model, any structured transmission process is allowed. Variable susceptibility, variable infectiousness, proportional mixing, and clustering can each be modeled by appropriate constraints on the contact parameters. A completely general model, with respect to heterogeneity of contact parameters, can also be used to avoid any assumptions about the transmission process. The statistical improvement of the general model over any of the structured, more restricted models can be evaluated by use of likelihood ratio statistics.

A major contribution of this generalized model is the use of a variable length infectious period. Most previous work on epidemic models has either incorporated a constant length infectious period or has adopted the assumption of an exponential distribution, convenient for its constant hazard rate. The length of the infectious period for this generalized model can be any positive random variable, provided its Laplace transform can be specified. Since the underlying distribution for the length of the infectious period is rarely known, this model can be applied to explore possible distributions, as has been done for influenza in the previous section.

The extension of this generalized model from that of Ball (1986) is to include an external source of infection. Ball (personal communication) has commented that the external source of infection could be equivalently modeled by specifying a group i' for every group i ($i = 1, \ldots, m$). These groups, each with one initial infective and zero initial susceptibles, would mimic the external source of infection. However, the approach of this paper demonstrates the separate modes of transmission more clearly. Also, the calculation of the recursive probabilities and thus the maximum likelihood estimation is simpler with fewer groups.

A conclusive identification of the distribution of the length of the influenza infectious period could not be made with the Tecumseh data. Based on the results presented here and other distributions considered, use of the gamma distribution seems to provide a satisfactory fit to the data most consistently. However, no clear distinctions among the various distributions can be made. A larger data set, either by number of populations or by maximum population size, might clarify this issue. Final size distributions generated by arbitrarily specifying the distribution of the length of the infectious period and appropriate parameters suggest that the final size distribution is more strongly affected by the distribution of the length of the infectious period when the mean length is greater. The constant length distribution seems to be adequate for diseases with short and acute infectious periods, such as influenza, but would not be adequate for a disease such as AIDS that has a long and variable infectious period.

This analysis of influenza transmission is the first time that variable susceptibility and variable infectivity have been simultaneously modeled. In previous work with influenza data, only variable susceptibility has been considered. The effective of variable infectivity, however, can be seen to have a critical impact on the transmission probabilities. The results also demonstrate a clustering tendency by age. When the general model is fitted to the Tecumseh data, the contact parameters suggest that intragroup transmission (child to child or adult to adult) is most likely to occur, while intergroup transmission is less likely. Although the difference is not statistically significant, a child is more likely to be infected by an adult, than an adult by a child. This result, combined with the probabilities of intragroup transmission, suggests that children are more susceptible than adults to any kind of transmission. These relative relationships among the contact parameters, or equivalently among the SARs, are similar to those estimated for rhinovirus transmission (Rampey, unpublished Ph.D. dissertation, Emory University, 1988).

The generalized model presented in this paper offers a flexible statistical tool for modeling infectious diseases. The model is appropriate for any infectious disease for which final size data are available and the researcher is willing to postulate the distribution of the length of the infectious period. Discrete heterogeneity among individuals in the population can be modeled by specifying a pattern of transmission such as variable susceptibility or by an unspecified pattern as

used in the general model for age discussed above. Possible extensions of this model include time-dependent contact parameters and incorporation of continuous variables defining heterogeneity.

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RÉSUMÉ

Un modèle stochastique de maladie infectieuse a été développé par Ball (1986, *Advances in Applied Probability* **18**, 289–310), et dans lequel la durée de la période contagieuse admet toute distribution pouvant être décrite par sa transformée de Laplace. On généralise ce modèle aux infections transmises à l'intérieur de la population ou par une source contaminante quelconque extérieure. Des facteurs discrets d'hétérogénéité peuvent aussi être inclus dans le modèle pour tenir compte de diverses susceptibilités à l'infection, contagiosités et/ou comportements. Le modèle est ajusté à des données sérologiques d'épidémies grippales relevées à Tecumseh, Michigan, par les méthodes d'estimation du maximum de vraisemblance. Les estimations montrent un aspect d'agrégats par groupes d'age.

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Appendix A

Distribution of the Total Area Under the Trajectory of Infectives

Because the groups within the population are not independent, the joint Laplace transform of the total area must be found by considering simultaneously the total areas for the m groups. Thus the function is

$$h_{\mathbf{N}}(\mathbf{t}) = \mathrm{E}\left(\exp\left(-\sum_{k=1}^{m} t_k T_{\mathrm{A}}^{(k)}\right)\right).$$

Notice that this function is identified by a vector $\mathbf{N}$ of integers (the initial susceptible group sizes) and that its argument is a vector $\mathbf{t} = (t_1, \ldots, t_m)'$.

The joint Laplace transform can be expressed as the sum of conditional Laplace transforms:

$$h_{\mathbf{N}}(\mathbf{t}) = \sum_{\omega=\mathbf{0}}^{\mathbf{N}} P_{\omega}^{\mathbf{N}} \psi_{\mathbf{N},\omega}(\mathbf{t}), \tag{A1}$$

where $\psi_{\mathbf{N},\omega}(\mathbf{t}) = \mathrm{E}(\exp(-\sum_{k=1}^{m} t_k T_{\mathrm{A}}^{(k)}) \mid \mathbf{N}^* = \boldsymbol{\omega})$. This conditional Laplace transform can be written as

$$\psi_{\mathbf{N},\omega}(\mathbf{t}) = \psi_{\mathbf{j},\omega}(\mathbf{t} + \boldsymbol{\beta}'(\mathbf{N} - \mathbf{j}))/\psi_{\mathbf{j},\omega}(\boldsymbol{\beta}'(\mathbf{N} - \mathbf{j})), \quad \mathbf{0} \leqslant \boldsymbol{\omega} \leqslant \mathbf{j} \leqslant \mathbf{N}, \tag{A2}$$

where $\boldsymbol{\beta}$ is the $m \times m$ matrix of contact rates β_{ij}, $(i, j) = 1, \ldots, m$.

Define the function $h_{\mathbf{N},\omega}(\mathbf{t}) = P_{\omega}^{\mathbf{N}} \psi_{\mathbf{N},\omega}(t)$. Using the relation in (A2),

$$h_{\mathbf{N},\omega}(\mathbf{t}) = \binom{\mathbf{N}}{\boldsymbol{\omega}} h_{\boldsymbol{\omega},\boldsymbol{\omega}}(\mathbf{t} + \boldsymbol{\beta}'(\mathbf{N} - \boldsymbol{\omega}))\mathbf{B}^{\mathbf{N}-\boldsymbol{\omega}}. \tag{A3}$$

A second useful function is $g_{\mathbf{N},\omega}(\mathbf{t})$, defined by $g_{\mathbf{N},\omega}(\mathbf{t}) = h_{\boldsymbol{\omega},\boldsymbol{\omega}}(\mathbf{t} + \boldsymbol{\beta}'(\mathbf{N} - \boldsymbol{\omega}))$. Using this function, the joint Laplace transform can be written as

$$h_{\mathbf{N}}(\mathbf{t}) = \sum_{\omega=\mathbf{0}}^{\mathbf{N}} \binom{\mathbf{N}}{\boldsymbol{\omega}} g_{\mathbf{N},\omega}(\mathbf{t})\mathbf{B}^{\mathbf{N}-\boldsymbol{\omega}}.$$

Now the functions $\psi_{\mathbf{j},\omega}(\mathbf{t})$, $h_{\mathbf{j},\omega}(\mathbf{t})$, and $g_{\mathbf{N},\omega}(\mathbf{t})$ can be used in the application of Theorem 1, as first seen in (3), to yield the following system:

$$1 = \sum_{\omega=\mathbf{0}}^{\mathbf{j}} \binom{\mathbf{j}}{\boldsymbol{\omega}} h_{\boldsymbol{\omega},\boldsymbol{\omega}}(\mathbf{t} + \boldsymbol{\beta}'(\mathbf{j} - \boldsymbol{\omega}))\mathbf{B}^{\mathbf{j}-\boldsymbol{\omega}}/\boldsymbol{\phi}(\mathbf{t})^{\boldsymbol{\omega}+\mathbf{a}}. \tag{A4}$$

Letting $\mathbf{t} = \mathbf{t} + \boldsymbol{\beta}'(\mathbf{N} - \mathbf{j})$ in (A4) yields

$$1 = \sum_{\omega=\mathbf{0}}^{\mathbf{j}} \binom{\mathbf{j}}{\boldsymbol{\omega}} g_{\mathbf{N},\omega}(\mathbf{t})\mathbf{B}^{\mathbf{j}-\boldsymbol{\omega}}/\boldsymbol{\phi}(\mathbf{t} + \boldsymbol{\beta}'(\mathbf{N} - \mathbf{j}))^{\boldsymbol{\omega}+\mathbf{a}}. \tag{A5}$$

More complete derivations of (A2)–(A5) are given in Addy (unpublished Ph.D. dissertation, Emory University, 1988).

To proceed further, two lemmas, proven in Addy (unpublished dissertation) and also in Ball (1986), are needed:

Lemma A1 Let $(h_{\mathbf{n}})$ and $(g_{\mathbf{n}})$ be two m-dimensional sequences such that

$$h_{\mathbf{n}} = \sum_{\mathbf{j}=\mathbf{0}}^{\mathbf{n}} \binom{\mathbf{n}}{\mathbf{j}} \mathbf{x}^{\mathbf{n}-\mathbf{j}} \mathbf{g}_{\mathbf{j}}, \quad \mathbf{n} \geqslant \mathbf{0},$$

where $\mathbf{x}$ is an m-dimensional vector constant. Then

$$g_{\mathbf{n}} = \sum_{\mathbf{j}=\mathbf{0}}^{\mathbf{n}} \binom{\mathbf{n}}{\mathbf{j}} (-\mathbf{x})^{\mathbf{j}} h_{\mathbf{n}-\mathbf{j}}, \quad \mathbf{n} \geqslant \mathbf{0}.$$

Lemma A2 If $\gamma_{\boldsymbol{\omega}}(\mathbf{t})$, $\boldsymbol{\omega} \geqslant \mathbf{0}$, are defined by

$$\sum_{\omega=\mathbf{0}}^{\mathbf{j}} \binom{\mathbf{j}}{\boldsymbol{\omega}} \gamma_{\boldsymbol{\omega}}(\mathbf{t})\boldsymbol{\phi}(\mathbf{t} + \boldsymbol{\beta}'\boldsymbol{\omega})^{\mathbf{j}-\boldsymbol{\omega}} = 1, \quad \mathbf{j} \geqslant \mathbf{0},$$

then, for $\mathbf{j} \geqslant \mathbf{0}$,

$$\sum_{\omega=0}^{\mathbf{j}} \binom{\mathbf{j}}{\omega} (-1)^{\omega} \gamma_{\omega}(\mathbf{t}) \left[\mathbf{1} - \phi(\mathbf{t} + \beta'\omega)\right]^{\mathbf{j}-\omega} = \delta_{\mathbf{j},\mathbf{0}}.$$

To apply Lemma A1, the functional operators D_k ($k = 1, \ldots, m$) are needed. Define D_k by

$$D_k f(t_1, \ldots, t_m) = f(t_1 + \beta_{k1}, \ldots, t_m + \beta_{km}).$$

Also, for $\mathbf{n} \geqslant \mathbf{0}$, let $\mathbf{D}^{\mathbf{n}} = \Pi_{i=1}^{m} D_i^{n_i}$. Applying this operator product to $g_{\omega,\omega}(\mathbf{t})$ yields

$$\mathbf{D}^{\mathbf{N}-\omega} g_{\omega,\omega}(\mathbf{t}) = g_{\omega,\omega}(\mathbf{t} + \beta'(\mathbf{N} - \omega)).$$

Comparison of the system of equations as written in (A5) and the companion system with $\mathbf{N} = \omega$ and $\mathbf{t} = \mathbf{t} + \beta'(\mathbf{N} - \omega)$ shows that

$$g_{\mathbf{N},\omega}(\mathbf{t}) = g_{\omega,\omega}(\mathbf{t} + \beta'(\mathbf{N} - \omega)) = \mathbf{D}^{\mathbf{N}-\omega} g_{\omega,\omega}(\mathbf{t}).$$

For a simpler notation, let $g_{\omega,\omega}(\mathbf{t}) = g_{\omega}(\mathbf{t})$. Now

$$h_{\mathbf{N}}(\mathbf{t}) = \sum_{\omega=0}^{\mathbf{N}} \binom{\mathbf{N}}{\omega} g_{\mathbf{N},\omega}(\mathbf{t}) \mathbf{B}^{\mathbf{N}-\omega} = \sum_{\omega=0}^{\mathbf{N}} \binom{\mathbf{N}}{\omega} \mathbf{B}^{\mathbf{N}-\omega} \mathbf{D}^{\mathbf{N}-\omega} g_{\omega}(\mathbf{t}).$$

Lemma A1 holds equally well when $\mathbf{x}$ is replaced by the product functional operator $\mathbf{D}$, so that

$$g_{\mathbf{N}}(\mathbf{t}) = \sum_{\omega=0}^{\mathbf{N}} \binom{\mathbf{N}}{\omega} (-\mathbf{B})^{\omega} \mathbf{D}^{\omega} h_{\mathbf{N}-\omega}(\mathbf{t}). \tag{A6}$$

Now let $\mathbf{j} = \mathbf{N}$ in (A5) to get

$$\phi(\mathbf{t})^{\mathbf{N}+\mathbf{a}} = \sum_{\omega=0}^{\mathbf{N}} \binom{\mathbf{N}}{\omega} \mathbf{D}^{\mathbf{N}-\omega} g_{\omega}(\mathbf{t}) \mathbf{B}^{\mathbf{N}-\omega} \phi(\mathbf{t})^{\mathbf{N}-\omega}. \tag{A7}$$

When the expression in (A6) is substituted into the system of equations in (A7), the following system can be derived, as is done in Addy (unpublished dissertation cited previously):

$$\phi(\mathbf{t})^{\mathbf{N}+\mathbf{a}} = \sum_{\omega=0}^{\mathbf{N}} \binom{\mathbf{N}}{\omega} \mathbf{B}^{\mathbf{N}-\omega} \mathbf{D}^{\mathbf{N}-\omega} h_{\omega}(\mathbf{t}) \left[\phi(\mathbf{t}) - \mathbf{1}\right]^{\mathbf{N}-\omega}. \tag{A8}$$

This last system of equations enables the following theorem defining the unconditional Laplace transform to be proved.

Theorem A1 If $\gamma_{\omega}(\mathbf{t})$, $\omega \geqslant \mathbf{0}$, are defined as in Lemma A2, then

$$h_{\mathbf{N}}(\mathbf{t}) = \sum_{\omega=0}^{\mathbf{N}} \binom{\mathbf{N}}{\omega} \gamma_{\omega}(\mathbf{t}) \mathbf{B}^{\omega} \phi(\mathbf{t} + \beta'\omega)^{\mathbf{N}-\omega+\mathbf{a}}, \quad \mathbf{N} \geqslant \mathbf{0}.$$

Proof See Addy (unpublished dissertation).

Calculation of the recursive functions $\gamma_{\omega}(\mathbf{t})$ enables easy calculation of the joint Laplace transform of the total area. Since there is no simple way to write the function for a general $\mathbf{t}$, the most common use of the Laplace transform is to recover the moments of the total areas. The recursive functions enable this calculation to be done simultaneously for any susceptible population size $\mathbf{N}$.

Appendix B

Proof of Theorem 2

The probabilities $P_{\mathbf{N}-\mathbf{k}}^{\mathbf{N}}$ and $P_{\mathbf{N}-\mathbf{k}}^{\mathbf{N}-\mathbf{k}}$ are related by

$$P_{\mathbf{N}-\mathbf{k}}^{\mathbf{N}} = \binom{\mathbf{N}}{\mathbf{k}} P_{\mathbf{N}-\mathbf{k}}^{\mathbf{N}-\mathbf{k}} \, \mathrm{E}\left(\exp\left(-\sum_{i=1}^{m} \sum_{j=1}^{m} k_i \beta_{ij} T_{\mathrm{A}}^{(j)}\right)\right) \mathbf{B}^{\mathbf{k}},$$

where the expectation is conditional on $\mathbf{N} = \mathbf{N} - \mathbf{k}$ and $\mathbf{N}^* = \mathbf{N} - \mathbf{k}$. Recalling the functions defined in Appendix A, the relation can be written as

$$\begin{aligned} P^{\mathbf{N}}_{\mathbf{N}-\mathbf{k}} &= \binom{\mathbf{N}}{\mathbf{k}} P^{\mathbf{N}-\mathbf{k}}_{\mathbf{N}-\mathbf{k}} \psi_{\mathbf{N}-\mathbf{k},\mathbf{N}-\mathbf{k}}(\boldsymbol{\beta}'\mathbf{k})\mathbf{B}^{\mathbf{k}} \\ &= \binom{\mathbf{N}}{\mathbf{k}} h_{\mathbf{N}-\mathbf{k},\mathbf{N}-\mathbf{k}}(\boldsymbol{\beta}'\mathbf{k})\mathbf{B}^{\mathbf{k}} \\ &= \binom{\mathbf{N}}{\mathbf{k}} g_{\mathbf{N}-\mathbf{k}}(\boldsymbol{\beta}'\mathbf{k})\mathbf{B}^{\mathbf{k}}. \end{aligned}$$

Therefore, the joint probability-generating function can be written as

$$f_{\mathbf{N}}(\mathbf{s}) = \sum_{\mathbf{k}=\mathbf{0}}^{\mathbf{N}} \binom{\mathbf{N}}{\mathbf{k}} g_{\mathbf{N}-\mathbf{k}}(\boldsymbol{\beta}'\mathbf{k})\mathbf{B}^{\mathbf{k}}\mathbf{s}^{\mathbf{k}}. \tag{B1}$$

Now the theorem can be proved by showing that the above summation is equal to the hypothesized summation:

$$\begin{aligned} f_{\mathbf{N}}(\mathbf{s}) &= \sum_{\mathbf{k}=\mathbf{0}}^{\mathbf{N}} \binom{\mathbf{N}}{\mathbf{k}} \alpha_{\mathbf{k}}(\mathbf{s})\boldsymbol{\phi}(\boldsymbol{\beta}'\mathbf{k})^{\mathbf{N}-\mathbf{k}+\mathbf{a}}\mathbf{B}^{\mathbf{k}} \\ &= \sum_{\mathbf{k}=\mathbf{0}}^{\mathbf{N}} \binom{\mathbf{N}}{\mathbf{k}} \alpha_{\mathbf{k}}(\mathbf{s})\mathbf{B}^{\mathbf{k}} \sum_{\boldsymbol{\omega}=\mathbf{0}}^{\mathbf{N}-\mathbf{k}} \binom{\mathbf{N}-\mathbf{k}}{\boldsymbol{\omega}} \mathbf{B}^{\mathbf{N}-\mathbf{k}-\boldsymbol{\omega}}\mathbf{D}^{\mathbf{N}-\mathbf{k}-\boldsymbol{\omega}} g_{\boldsymbol{\omega}}(\boldsymbol{\beta}'\mathbf{k})\boldsymbol{\phi}(\boldsymbol{\beta}'\mathbf{k})^{\mathbf{N}-\mathbf{k}-\boldsymbol{\omega}} \\ &= \sum_{\mathbf{k}=\mathbf{0}}^{\mathbf{N}} \sum_{\boldsymbol{\omega}=\mathbf{0}}^{\mathbf{N}-\mathbf{k}} \binom{\mathbf{N}}{\mathbf{k}} \binom{\mathbf{N}-\mathbf{k}}{\boldsymbol{\omega}} \alpha_{\mathbf{k}}(\mathbf{s})\mathbf{B}^{\mathbf{N}-\boldsymbol{\omega}}\boldsymbol{\phi}(\boldsymbol{\beta}'\mathbf{k})^{\mathbf{N}-\mathbf{k}-\boldsymbol{\omega}}\mathbf{D}^{\mathbf{N}-\mathbf{k}-\boldsymbol{\omega}} g_{\boldsymbol{\omega}}(\boldsymbol{\beta}'\mathbf{k}) \\ &= \sum_{\mathbf{k}=\mathbf{0}}^{\mathbf{N}} \sum_{\boldsymbol{\omega}=\mathbf{0}}^{\mathbf{N}-\mathbf{k}} \binom{\mathbf{N}}{\mathbf{k}} \binom{\mathbf{N}-\mathbf{k}}{\boldsymbol{\omega}} \alpha_{\mathbf{k}}(\mathbf{s})\mathbf{B}^{\mathbf{N}-\boldsymbol{\omega}}\boldsymbol{\phi}(\boldsymbol{\beta}'\mathbf{k})^{\mathbf{N}-\mathbf{k}-\boldsymbol{\omega}} g_{\boldsymbol{\omega}}(\boldsymbol{\beta}'(\mathbf{N}-\boldsymbol{\omega})) \\ &= \sum_{\boldsymbol{\omega}=\mathbf{0}}^{\mathbf{N}} \sum_{\mathbf{k}=\mathbf{0}}^{\mathbf{N}-\boldsymbol{\omega}} \binom{\mathbf{N}}{\boldsymbol{\omega}} \binom{\mathbf{N}-\boldsymbol{\omega}}{\mathbf{k}} \alpha_{k}(\mathbf{s})\mathbf{B}^{\mathbf{N}-\boldsymbol{\omega}}\boldsymbol{\phi}(\boldsymbol{\beta}'\mathbf{k})^{\mathbf{N}-\boldsymbol{\omega}-\mathbf{k}} g_{\boldsymbol{\omega}}(\boldsymbol{\beta}'(\mathbf{N}-\boldsymbol{\omega})) \\ &= \sum_{\boldsymbol{\omega}=\mathbf{0}}^{\mathbf{N}} \binom{\mathbf{N}}{\boldsymbol{\omega}} \mathbf{B}^{\mathbf{N}-\boldsymbol{\omega}} g_{\boldsymbol{\omega}}(\boldsymbol{\beta}'(\mathbf{N}-\boldsymbol{\omega}))\mathbf{s}^{\mathbf{N}-\boldsymbol{\omega}} \\ &= \sum_{\boldsymbol{\omega}=\mathbf{0}}^{\mathbf{N}} \binom{\mathbf{N}}{\boldsymbol{\omega}} \mathbf{B}^{\boldsymbol{\omega}} g_{\mathbf{N}-\boldsymbol{\omega}}(\boldsymbol{\beta}'\boldsymbol{\omega})\mathbf{s}^{\boldsymbol{\omega}}. \end{aligned}$$

This summation is exactly (B1), defining the joint probability-generating function $f_{\mathbf{N}}(\mathbf{s})$ of the multivariate final size.