COMPUTERIZED EPIDEMIOLOGICAL MODEL OF TYPHOID FEVER WITH AGE STRUCTURE AND ITS USE IN THE PLANNING AND EVALUATION OF ANTITYPHOID IMMUNIZATION AND SANITATION PROGRAMMES†‡

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Abstract—An epidemiological model of typhoid fever[1] was further developed. Age structure was added to the population dynamics, but nonessential epidemiological classes were eliminated. Thus the dynamics of the disease in specific age groups can be studied, and the effect of public health interventions in these groups simulated. The model is based on the natural history of the disease and represents the multistate epidemiological structure which is fully computerised. It enables simulation of endemic processes in the various age groups of the population and the effects of control measures such as immunization and/or sanitation on the natural course of infection in various age strata of the population. In view that typhoid fever is a public health problem primarily in endemic areas of developing countries, the examples of model applications are related to such situations. The simulation of the effectiveness of immunization and sanitation programmes are confined to the endemic conditions in such countries. The construction and the structure of the model are fully described. The computer program system is given in the Appendix, and the article provides all relevant information necessary for the use of the model for public health purposes.

1. INTRODUCTION

A computerised model simulating typhoid fever dynamics has already been constructed[1, 2] with a view to its possible use for forecasting trends in the natural course of infection and the effect of preventive measures like sanitation and vaccination on such trends[1, 2]. In this model the possible relationship between the typhoid morbidity rate and age has been ignored for simplicity’s sake. Consequently, the model could only be used to evaluate the impact of mass vaccination but not immunization schemes on the disease transmission and incidence.

In developing countries where typhoid fever is still a public health problem, young age-groups are usually the most affected, and health service intervention programmes would need to be age-specifically oriented to protect the population highly exposed to risk.

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Examples of such programmes are vaccination and revaccination at given ages, health education of certain population targets, food sanitation at school level, etc.

To assist the public health administrator in planning and evaluating antityphoid control programmes, a new age-structured epidemiological model of typhoid fever was constructed and is presented in this study.

The system approach followed has great analogy with the method already developed for the construction of models simulating childhood infections like diphtheria[2], whooping cough[2], poliomyelitis[3] and measles[3].

2. NATURAL HISTORY AND DYNAMICS OF THE DISEASE

Data on the natural history of typhoid fever used in the construction of the model, i.e. incubation period, duration of illness, morbidity, fatality, carrier rate and other rates, were compiled from numerous studies on typhoid in various countries.

In deciding on numerical values to be given to each parameter, attention was paid to prevailing opinions, as well as to their critical appraisal. There were considerable variations in many of the parameters, and it was therefore necessary to come to some arbitrary compromises in order to arrive at definite numerical values to be used in the construction of the model.

During the natural course of typhoid fever, the population passes through various epidemiological classes[1, 2]. Susceptibles become infected and are incubating the infection during latent period before the clinical symptoms develop in some individuals, while the others pass through mild or symptomless infection. The illness ends either by recovery or death. Those who recover return either to susceptibility or become resistant for a shorter or longer period of time, or become short or life long carriers, but finally all except permanent carriers return to the state of susceptibility.

In the previous model[1, 2] all these classes were included, and the duration of the stay of the population in these classes and of the epidemiological processes were expressed in days, the day being the time unit in the computerized iterative calculation. In the present model only the epidemiological classes which are important in disease dynamics, namely those playing a significant role in disease dynamics, in particular in its transmission, were retained, and 1 month was taken as the unit of time for computer iteration. There was a need to simplify the model which became complex because of the introduction of the age structure of the population.*

Bailey and Duppenthaler in their sensitivity analysis of the previous model[4] have demonstrated that certain epidemiological classes identified in the model[1, 2] did not contribute significantly to the quantitative behavior of the model. It was therefore possible to exclude in the new model the incubating class (a very small fraction only of it being infectious) and the small class of noninfectious sick[1, 2]. The model being highly insensitive to these epidemiological categories, its validity was not affected by this structure simplification needed in order to avoid requirements for large computer memory and the excessive, unnecessary computation.

3. STRUCTURE OF THE MODEL

The model covers the individuals up to 80 years of age. The population was divided into epidemiological classes identifiable in the natural course of the disease. The dynamics of the disease are reflected in the time-related flow of individuals of various age groups.

* Preliminary comparative test runs carried out with the previous model showed that the change in time step used did not affect substantially the simulations and had consequently no significant impact on their interpretation.
through these classes. The structure of the model and the symbols adopted are presented in the flow chart of Fig. 1 on the disease dynamics.

The annual entry into the system is from the newborn, and the annual exit is made of a small fraction of each epidemiological class corresponding to deaths from all causes including typhoid fever (class $x_8$) for individuals dying during the sickness period (class $x_2$). As the model includes only the population up to 80 years of age, individuals reaching this age also leave the system.

Figure 1 shows that the newborn are all susceptible (class $x_1$) as there is no passive immunity. The susceptibles who are infected go for 1 month to class $x_2$, which contains both symptomatic and asymptomatic cases in the same ratio as in the previous model [1], that is 2 to 8. The fatality rate applied to the symptomatic cases determines the number of deaths from typhoid fever transferred in class $x_8$. Some of the surviving infected go back to the class of susceptibles, while the others move either into class $x_3$ (infectious temporary carrier for 3 months) or directly into class $x_5$ (noninfectious resistant for 1
year). Some of the temporary carriers become infectious permanent carriers (class $x_4$) and others become noninfectious resistant for 1 year (class $x_5$). The majority of the latter will subsequently remain resistant for 10 years (class $x_6$) before recovering their initial susceptibility status. A fraction of the temporary carriers and resists for 1 year goes directly to class $x_1$ (susceptible).

Susceptibles of any age can go to class $x_7$ when they are successfully vaccinated; they stay in this class for the mean duration of protection conferred by the vaccine, and then go back to class $x_1$ (susceptible).

4. PARAMETRIC VALUES

The dynamics of the disease depend on the length of stay of individuals in the various epidemiological classes and on the distribution of those leaving one epidemiological class by transfer to the other classes. The corresponding coefficients of transfer $R_{u,v}$, where $u$ is the class of origin and $v$ the class of destination, are determined by the force of infection (see next section), the natural evolution of the disease and the characteristics of intervention procedures[1, 2].

The parameters controlling the structure of the population and the force of infection were fixed at levels that would permit the simulation of situations actually observed in areas where typhoid fever still prevails.

*Force of infection*

Special consideration is needed concerning the coefficient $R_{1,2}$ which quantifies the transfer of susceptible individuals to the infectious class per unit of time. The number of individuals infected per unit of time is the result of an interaction between the number of susceptibles, the number of infectious persons and a factor called force of infection, which is a consolidated expression of all the variables that affect the transmission of infection, like frequency of contact, effective challenge dose, health practices and habits, etc. Thus the coefficient $R_{1,2}$ is equal to the product of the proportion of infectious individuals in the population by the force of infection, and the number of new infected persons per unit of time will be equal to the product of the number of susceptibles by the coefficient $R_{1,2}[2]$.

The force of infection controls the rate and amount of infection circulating in the population. In the present typhoid fever model the risk of transmission is age-dependent. The numerical values of the force of infection used to validate the model and shown in Table 1 were derived from reliable age-specific case incidences reported by health authorities.

<table>
<thead>
<tr>
<th>Age (in years)</th>
<th>Force of infection$^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>0.0100</td>
</tr>
<tr>
<td>5</td>
<td>0.0200</td>
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<tr>
<td>10</td>
<td>0.0700</td>
</tr>
<tr>
<td>21</td>
<td>0.0700</td>
</tr>
<tr>
<td>35</td>
<td>0.0245</td>
</tr>
<tr>
<td>50</td>
<td>0.0110</td>
</tr>
<tr>
<td>79</td>
<td>0.0035</td>
</tr>
</tbody>
</table>

$^*$ The force of infection is automatically generated for each year of age by linear interpolation between the successive values shown in this column.
Typhoid morbidity

As in the previous model, it was assumed that 20% of the individuals passing through the illness period are detected as typical acute clinical cases (symptomatic), and incidence rates refer to these clinical cases only.

Typhoid mortality

Provision exists in the model for use of age-dependent fatality rates. However, in the absence of strong evidence for such need, a constant fatality rate of 2% was applied to the clinical cases in the simulations so far carried out. As 20% only of the infected individuals develop clinical disease, the coefficient $R_{2,6}$ is equal to 0.004.

Carriers

Except for a small fraction which returns to the susceptible class ($R_{2,1} = 0.10$), the surviving infected (clinical and subclinical cases) become either temporary carrier ($R_{2,3} = 0.20$) or in most cases directly temporary resistant ($R_{2,5} = 0.70$). Only 10% of the temporary carrier go back to the susceptible class ($R_{3,1} = 0.10$), while 30% of them become permanent carrier ($R_{3,4} = 0.30$), and the rest goes to the temporary resistant class ($R_{3,5} = 0.60$).

Resistants

After 1 year, 10% of the temporary resistants return to susceptibility ($R_{5,1} = 0.10$), while the great majority remains resistant for a further 10 years ($R_{5,6} = 0.90$) before going back to the susceptible class $x_1$.

Immunization

It was assumed that by immunization a certain proportion of susceptible individuals become immune for the period of protection conferred by the vaccine. This proportion is measured by the efficacy of the immunization, which is itself the product of the immunization coverage and the effectiveness of the vaccine used. The coefficient $R_{1,7}$ controls the transfer of individuals of eligible age to the vaccinated class $x_7$, and the coefficient $R_{2,1}$ controls their move back to susceptibility at the end of the protection period. The parametric values used are specified in the presentation and discussion of the simulations actually carried out.

Improvements in sanitation

Any relevant improvement in sanitation would result in a decrease in the risk of infection. Safer excreta disposal would reduce the transmission of infection from carriers to susceptibles; health education in personal and environmental hygiene would diminish the force of infection pressure on people adopting healthier behaviour; similar beneficial effects may result from food sanitation at school level. Simulations with appropriate parametric values will be described in the section on applications of the model.

Population

The model was constructed for individuals up to the age of 80 years. The age profile of the population concerned is controlled by the birth rate and by the age-specific death
rates applied to the successive classes of age. Many complex demographic situations could be envisaged; however, to avoid difficulties in the interpretation of the findings, the actual simulations presented here were programmed for a stationary population as close as possible to the life table survivals calculated for a country representative of regions where typhoid fever is still a public health problem. Annual cohort of 100,000 live births were therefore admitted at successive years of age to specific death rate values adapted from the life table of Chile, 1969–1970. As shown in Table 2, the simulated population was very close to the 1969–1970 life table survivals published for Chile by the Statistical Office of the United Nations UN Demographic Yearbook, 1974. This similarity strengthens the validity of the model in epidemiological situations common to populations with comparable demographic characteristics.

Seasonality

By appropriate changes of the force of infection related to the seasonality of the disease incidence, the seasonal patterns of morbidity and mortality can be simulated as was done with some models of other acute bacterial diseases[2]. However, this was not considered necessary to be done for the requirements of the present model, but it could be done if desired.

5. MATHEMATICAL AND COMPUTER FORMULATION OF THE MODEL

The successive cohorts passing through the model should be identifiable by age and length of stay in the various epidemiological classes. In order to permit the use of the model with vaccination at any age and in the same time to keep at a minimum the required size of the computer central processor, the time unit was fixed at 1 year for age and at 1 month for stay in epidemiological classes. The mathematical expression of the epidemiological classes takes the form of a two-dimensional matrix $x_{ik}$ ($i, j$), where $i$ is the age in years and $j$ the duration of stay in the class in number of months; the subscript $k$ refers to the individual epidemiological classes identified in the flow chart of Fig. 1. With these values the maximum size of $i$ is 80 (80 years of age), and of $j$ 120 (10 years of stay in class $x_k$). To simplify the mechanism of computerization, the time interval used for calculation of the modification undergone by the system was also fixed at 1 month.

The numerical contents at time $t + 1$ of each epidemiological class $x_k$ ($i, j$) was calculated on the basis of (i) its contents at time $t$ and (ii) the in-flow from and the out-flow to all classes involved, as indicated by Fig. 1, and in quantities determined by the respective
coefficients $R_{ij}$. An appropriate computer program was written in FORTRAN IV language to repeat the iterative process as many times as necessary to simulate the dynamics of the infection for a predetermined number of years. The subscript $j$ of the matrices $x_{ij}$ was increased by one unit after each iteration (1 month), while the subscript $i$ was increased after every 12 iterations, corresponding to an age updating of 1 year.

The system is considered to be solved for a given set of parametric values when the contents of all the matrices $x_{ij}$ cease to be modified by further iterations. The model then represents an epidemiological situation of stable endemicity in the population. The number of computer runs required to reach this situation depends on the appropriateness of the initial values entered in the model. An ad hoc computer program was written to generate these values, and a trial-and-error method was used to speed up convergence towards the solution of the system. The results obtained at the end of each run were tentatively written on magnetic disk and used as the new initial values for the next run, if they were judged satisfactory; this disk-to-disk reading/writing procedure was continued until desired stable situation was reached.

Details on the computer program system are given in Appendix A.

6. APPLICATION OF THE MODEL IN SIMULATIONS

The previous model[1, 2] proved suitable for the study of disease trends and the effects of public health interventions on general population and their cost-effectiveness. The present model, in view of its age structure, can be applied in addition to the study of (i) the trends of typhoid within various age-groups and (ii) the effects of interventions applied to specific age-groups.

6.1. Validation of the model

To be valid, the model should be able to simulate the dynamics of the disease at a given level of endemicity as observed under natural conditions in real life.

The validation of the present model was aimed at proving, in view of its age structure, its ability to simulate the natural course of the disease and the effects of interventions on the dynamics of typhoid fever in the specific age-groups.

With the age-group values selected for the force of infection (Table 1), it was possible to produce simulated age profile morbidity close to the field data obtained in Chile and Santiago* in the course of recent decades, as shown on Table 3 and Fig. 2 which are self-explanatory.

The simulation is based on a population of 6,080,440 individuals generated by successive annual cohorts of 100,000 newborn exposed to estimated age-specific mortality rates leading to the survival values of Chile, 1969–1970. Table 2 demonstrates the good agreement between the observed and the simulated life table survivals at given ages.

The distribution of this population according to epidemiological classes and age-groups is given in Table 4 for the simulated stable endemic level characterized by the age-specific typhoid morbidity and mortality shown in the last two columns of this table.

The relative proportional distribution of susceptibles, infectious and resistants within each age-group is shown in Table 5 for the same stable endemic situation. The shift of aging population from susceptibility to resistance can be seen from this table. The trend is however inverting itself after 35 years of age, although the proportion of infectious carriers continue to grow up with age as expected. The increase in proportion of susceptibles is linked with a decrease in resistance, and both phenomena are due to the low

Table 3. Average annual reported and simulated age specific incidence of typhoid fever per 100,000 population (Chile 1950-1974, Santiago 1968-1976)

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>10.7</td>
<td>29.6</td>
<td>24.6</td>
</tr>
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<td>1-4</td>
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<td>42.9</td>
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<tr>
<td>5-9</td>
<td>72.1</td>
<td>111.8</td>
<td>129.4</td>
</tr>
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<td>10-14</td>
<td>103.5</td>
<td>160.2</td>
<td>178.8</td>
</tr>
<tr>
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<td>174.1</td>
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<td>163.0</td>
</tr>
<tr>
<td>25-34</td>
<td>59.2</td>
<td>85.8</td>
<td>101.3</td>
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<tr>
<td>35-44</td>
<td>30.7</td>
<td></td>
<td>50.5</td>
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<tr>
<td>45-54</td>
<td>17.0</td>
<td>27.8</td>
<td>30.2</td>
</tr>
<tr>
<td>55-64</td>
<td>10.2</td>
<td></td>
<td>22.1</td>
</tr>
<tr>
<td>65+</td>
<td>6.0</td>
<td></td>
<td>14.5</td>
</tr>
<tr>
<td>All ages</td>
<td>55.8</td>
<td>84.4</td>
<td>80.4</td>
</tr>
</tbody>
</table>

* From information given by Cvjetanovic in his report on typhoid and its control in Chile (1978), internal WHO document.

Fig. 2.

level of force of infection operating over the age of 35 years (Table 1). The lower disease incidence in advanced ages (Table 4) is therefore not only the result of resistance acquisition through infection, but also a consequence of the reduced force of infection.

The model was validated with data collected in Chile* which is considered as representative of certain range of developing countries. However, some other countries may have significantly different age structure. In such case the population structure and mor-

Table 4. Simulated population distribution according to epidemiological class and age-group for a stable endemic level of typhoid fever

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Susceptible $x_1$</th>
<th>Infected $x_2$</th>
<th>Temporary carrier $x_3$</th>
<th>Permanent carrier $x_4$</th>
<th>Short resistant $x_5$</th>
<th>Long resistant $x_6$</th>
<th>Total population</th>
<th>Annual incidence rate$^b$</th>
<th>Annual death rate$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>92,199</td>
<td>10</td>
<td>6</td>
<td>5</td>
<td>89</td>
<td>—</td>
<td>92,300</td>
<td>24.6</td>
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<tr>
<td>1-4</td>
<td>364,837</td>
<td>67</td>
<td>40</td>
<td>124</td>
<td>642</td>
<td>1073</td>
<td>366,783</td>
<td>42.9</td>
<td>0.9</td>
</tr>
<tr>
<td>5-9</td>
<td>445,409</td>
<td>252</td>
<td>151</td>
<td>683</td>
<td>2399</td>
<td>6722</td>
<td>455,616</td>
<td>129.4</td>
<td>2.6</td>
</tr>
<tr>
<td>10-14</td>
<td>429,200</td>
<td>340</td>
<td>204</td>
<td>1820</td>
<td>3327</td>
<td>18,972</td>
<td>453,863</td>
<td>178.8</td>
<td>3.6</td>
</tr>
<tr>
<td>15-19</td>
<td>416,338</td>
<td>330</td>
<td>197</td>
<td>2999</td>
<td>3221</td>
<td>27,963</td>
<td>451,048</td>
<td>174.1</td>
<td>3.5</td>
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<td>20-24</td>
<td>411,128</td>
<td>306</td>
<td>183</td>
<td>4120</td>
<td>2995</td>
<td>28,809</td>
<td>447,541</td>
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<td>25-29</td>
<td>408,846</td>
<td>227</td>
<td>136</td>
<td>5013</td>
<td>2226</td>
<td>26,123</td>
<td>442,571</td>
<td>122.4</td>
<td>2.4</td>
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<tr>
<td>30-34</td>
<td>408,986</td>
<td>146</td>
<td>87</td>
<td>5595</td>
<td>1436</td>
<td>20,421</td>
<td>436,671</td>
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<tr>
<td>35-39</td>
<td>406,961</td>
<td>100</td>
<td>60</td>
<td>5891</td>
<td>982</td>
<td>13,711</td>
<td>427,705</td>
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<td>40-44</td>
<td>400,720</td>
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<td>47</td>
<td>6053</td>
<td>769</td>
<td>9200</td>
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<td>45-49</td>
<td>387,910</td>
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<td>34</td>
<td>6062</td>
<td>553</td>
<td>6820</td>
<td>401,435</td>
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<tr>
<td>50-54</td>
<td>371,994</td>
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<td>55-59</td>
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<td>60-64</td>
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<td>212,673</td>
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<tr>
<td>75-79</td>
<td>147,784</td>
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<td>4</td>
<td>2559</td>
<td>66</td>
<td>798</td>
<td>151,218</td>
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</tr>
<tr>
<td>Total</td>
<td>5,815,933</td>
<td>2056</td>
<td>1231</td>
<td>65,675</td>
<td>20,046</td>
<td>175,499</td>
<td>6,080,440</td>
<td>80.4</td>
<td>1.6</td>
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</tbody>
</table>

$^a$ With the age specific monthly values of force of infection shown in Table 1.
$^b$ Per 100,000 population of the corresponding age-group.
$^c$ As identified in the flow chart of Fig. 1.
Table 5. Proportional distribution of epidemiological status according to age group

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Susceptible $x_1$</th>
<th>Infected and carrier $x_2 + x_3 + x_4$</th>
<th>Resistant $x_5 + x_6$</th>
<th>Total</th>
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<td>99.9</td>
<td>0.0</td>
<td>0.1</td>
<td>100</td>
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<tr>
<td>1-4</td>
<td>99.5</td>
<td>0.1</td>
<td>0.4</td>
<td>100</td>
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<td>5-9</td>
<td>97.8</td>
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<td>2.0</td>
<td>100</td>
</tr>
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<td>10-14</td>
<td>94.6</td>
<td>0.5</td>
<td>4.9</td>
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<td>15-19</td>
<td>92.3</td>
<td>0.8</td>
<td>6.9</td>
<td>100</td>
</tr>
<tr>
<td>20-24</td>
<td>91.9</td>
<td>1.0</td>
<td>7.1</td>
<td>100</td>
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<tr>
<td>25-29</td>
<td>92.4</td>
<td>1.2</td>
<td>6.4</td>
<td>100</td>
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<td>30-34</td>
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<td>45-49</td>
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<td>1.8</td>
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<td>1.4</td>
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<td>1.2</td>
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<td>0.8</td>
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<td>1.7</td>
<td>0.7</td>
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</tr>
<tr>
<td>75-79</td>
<td>97.7</td>
<td>1.7</td>
<td>0.6</td>
<td>100</td>
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</tbody>
</table>

| Total            | 95.6              | 1.2                                 | 3.2                 | 100   |

* For the stable endemicity level simulated in Table 4 before introduction of any prevention programme.

6.2. Simulation of control measures

The effects of feasible immunization and sanitation programmes on specific age-groups were simulated, using as base line the population and an initial endemicity level typical for several developing countries.

6.2.1. Immunization. The effectiveness of vaccine used in simulations was based on the results of the recent field trials with newly developed live oral vaccine[5]. The effectiveness of the vaccine was taken as 95%, and the duration of protection was fixed at 5 years. Any other values can, however, be used in the model.

The impact of various continuous immunization programmes over 25 years on the crude annual incidence rate (in total population) with 75% and 90% coverage of eligible individuals of specified age (1-21 years) is shown on Figs. 3a and 3b, which are self-explanatory. Immunization schedule was fixed at age 1, 6, 11, 16, and 21 years. This means that it takes 5 years to cover all persons between 1 year and 25 years of age.* For this reason and also because the protection conferred lasts 5 years, the decrease of the incidence is relatively rapid during the first 5 years, and then it is slowed down during further immunization maintenance period (for the next 20 years). Figure 3 shows that for obvious reasons higher coverage and more frequent booster doses give better results.

The immunization of specific age-groups with higher initial incidence rates and higher force of infection does contribute obviously relatively more to the decrease of the crude

* Individuals are vaccinated when they reach the ages stipulated in the immunization scheme. Depending on the duration of the programme, a proportion (equal to the coverage rate) of individuals can therefore be revaccinated several times.
incidence rate in the population than the immunization of the specific age-groups with lower endemic incidence rates (see Figs. 3a and 3b). Figure 4 clearly indicates that already after 5 years of continuous immunization of specific age-groups (at 1, 6, 11 and 21 years) with 90% coverage the incidence below 25 years of age has greatly decreased. Further application of immunization affects as well to some extent older ages, as shown on Fig. 4. Such immunization programmes also bring the changes in the distribution of epidemiological states by age-groups. Table 6 shows the distribution of epidemiological states
in the specific age-groups 5 years after application of the above intensive immunization programme. It is interesting to compare this distribution with the epidemiological age structure observed before the application of the programme of immunization, as displayed in Table 5. In the general population this immunization scheme leads to the decrease of the proportion of susceptibles (from 95.6% to 65.5%) and of the proportion of infectious

Table 6. Proportional distribution of epidemiological status by age-group 5 years after introduction of continuous immunization programme

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Susceptible $x_1$</th>
<th>Infected and carrier $x_2 + x_3 + x_4$</th>
<th>Resistant $x_5 + x_6$</th>
<th>Immunized $x^*$</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>14.5</td>
<td>0.0</td>
<td>0.1</td>
<td>85.4</td>
<td>100</td>
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<tr>
<td>1-4</td>
<td>14.4</td>
<td>0.0</td>
<td>0.2</td>
<td>85.4</td>
<td>100</td>
</tr>
<tr>
<td>5-9</td>
<td>14.2</td>
<td>0.1</td>
<td>1.0</td>
<td>84.7</td>
<td>100</td>
</tr>
<tr>
<td>10-14</td>
<td>14.1</td>
<td>0.3</td>
<td>3.3</td>
<td>82.3</td>
<td>100</td>
</tr>
<tr>
<td>15-19</td>
<td>14.2</td>
<td>0.6</td>
<td>5.2</td>
<td>80.0</td>
<td>100</td>
</tr>
<tr>
<td>20-24</td>
<td>14.6</td>
<td>0.8</td>
<td>5.5</td>
<td>79.1</td>
<td>100</td>
</tr>
<tr>
<td>25-29</td>
<td>93.0</td>
<td>1.1</td>
<td>5.9</td>
<td>—</td>
<td>100</td>
</tr>
<tr>
<td>30-34</td>
<td>93.7</td>
<td>1.3</td>
<td>5.0</td>
<td>—</td>
<td>100</td>
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<tr>
<td>35-39</td>
<td>95.2</td>
<td>1.4</td>
<td>3.4</td>
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</tr>
<tr>
<td>40-44</td>
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<td>1.5</td>
<td>2.4</td>
<td>—</td>
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</tr>
<tr>
<td>45-49</td>
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<td>1.6</td>
<td>1.8</td>
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<tr>
<td>50-54</td>
<td>97.0</td>
<td>1.6</td>
<td>1.4</td>
<td>—</td>
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</tr>
<tr>
<td>55-59</td>
<td>97.3</td>
<td>1.6</td>
<td>1.1</td>
<td>—</td>
<td>100</td>
</tr>
<tr>
<td>60-64</td>
<td>97.4</td>
<td>1.6</td>
<td>1.0</td>
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<td>100</td>
</tr>
<tr>
<td>65-69</td>
<td>97.5</td>
<td>1.7</td>
<td>0.8</td>
<td>—</td>
<td>100</td>
</tr>
<tr>
<td>70-74</td>
<td>97.6</td>
<td>1.7</td>
<td>0.7</td>
<td>—</td>
<td>100</td>
</tr>
<tr>
<td>75-79</td>
<td>97.7</td>
<td>1.7</td>
<td>0.6</td>
<td>—</td>
<td>100</td>
</tr>
<tr>
<td>Total</td>
<td>65.5</td>
<td>1.1</td>
<td>2.7</td>
<td>30.7</td>
<td>100</td>
</tr>
</tbody>
</table>

*Age at vaccination: 1 year, 6 years, 11 years, 16 years and 21 years. Vaccination coverage: 90% of eligible individuals each year.
(from 1.2% to 1.1%). All together, the resistants and the immunized represents 33.4% of the total population. while before vaccination 3.2% only of the population was resistant.

6.2.2. Sanitation. The effectiveness of sanitation varies according to the quality and extension of the specific measure implemented (food sanitation, excreta disposal, health education on environmental and/or personal hygiene). For the sake of illustration, we used some values within the range of field observations[1, 2, 6].

The effect of sanitation depending on its characteristics is simulated by (i) decreasing appropriately the force of infection, thus lowering the exposure risk of susceptibles, and/ or (ii) reducing the transmission rates from the infectious individuals* (classes \( x_2 \), \( x_3 \) and \( x_4 \)), thus eliminating certain proportions of them from the infective process.

The simulation of the effect of 10 years sanitation programme with 2% and 5% annual decrease of (i) the force of infection and (ii) the transmission capacity of infectious are shown in Fig. 5. The relatively higher efficacy of the decreasing transmission capacity of the infectious (classes \( x_2 \), \( x_3 \) and \( x_4 \) of Fig. 1) in comparison with the simple reduction of the force of infection is due to the fact that the first mechanism acts immediately on several epidemiological classes \( (x_2, x_3 \) and \( x_4 \)), while the second acts slowly: It starts by affecting class \( x_2 \), and only after a delay of 1 to 4 months it acts on the other classes \( (x_3 \) and \( x_4 \)). It is important to note that the relatively rapid decline of incidence resulting from sanitation is slowed down but not stopped after the discontinuation of the programme.

6.2.3. Combined control programmes. There are varieties of possible combinations of sanitation, immunization and other control measures, which could be applied in many different ways to various age-groups and at different times.

One of such combined control programmes consists of sanitation (namely food control at school canteens covering children between 6 to 16 years of age) and of 95% coverage immunization of children at age 6, 11, and 16 years with 95% effective vaccine protecting

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* By application of a lower proportion of infectious individuals in the computation of the coefficient of transfer \( R_{1,2} \).
for 5 years. The effectiveness of food sanitation programme is assumed to be only partial, leading to a one-third reduction of the force of infection.

Figure 6a displays the simulated effect of 10 years application of these two combined control measures on age specific incidence rates of typhoid fever. While important decreases of incidence are observed in the age-groups under 20 years, only slight effects are noted on the older population. The relative impact of these two measures on crude incidence rate in the general population is shown on Fig. 6b. It can be seen that the effect of vaccination is much more important than that of food sanitation at school canteens.

The relative effectiveness of single and of combined measures for the control of typhoid incidence is shown in Table 7 by age-groups. Figure 6b and Table 7 demonstrate that the
two combined measures are more effective than any of them alone. However, the advantage of their combination is relatively small. If the cost-effectiveness of single and combined measures would be analyzed, it is probable that the combined programme would not prove to be the most cost-effective[1, 2].

However, if other values would have been assigned to the effectiveness and coverage of these measures, their effect on morbidity (and cost-effectiveness) would have changed. This shows the importance of precise assessment of the effectiveness and costs of the control measures, as the results of the simulations obviously depend on them.

7. OTHER USES OF THE MODEL

The model can simulate the natural trend of typhoid fever and the impact of different control programmes under a variety of particular conditions.

Epidemic mechanism of the natural course of infection can be studied by this age-structured model, in particular the way the population dynamics may affect this mechanism.

The birth rate and the age specific death rates are reflected in the structures of the population and thus in the prevalence of epidemiological states and classes by age-groups, which determine the disease dynamics.

Potential benefits of researches aimed at the development of new specific control measures (e.g. vaccines and other preparations for disease control, and specific sanitary measures such as disinfection techniques, etc.) can be assessed by the model.

The trends of typhoid and the appropriate strategy to be applied for its control in a country or an area can be assessed by the model. In our earlier publication[2] we have demonstrated and fully described the unique mechanism in the natural history of typhoid, namely the threshold of the endemicity. Once this threshold is reached, the self-limiting process begins leading to the gradual extinction of typhoid by continuous decline of the incidence[2].

The model thus allows to distinguish between countries and areas with stable endemicity and those with the trends of constant decline, resulting from the low or continuously decreasing force of infection. The model permits to estimate the necessary inputs for the control programmes based on immunization and/or sanitation to achieve the crucial threshold, enabling the transit from the state of stable endemicity to the one of continuous decline.

Cost-effectiveness and cost-benefit analyses of various control programmes and public health strategies can be based on the simulation of such programmes[1, 2]. The application of cost-effectiveness analysis relies on the techniques used in determining the costs of control measures and the total social cost of the disease and health, and the social benefits.
of control programme[7]. As the costs vary from place to place and change with time, cost-effectiveness analyses should always be done in close relation with the actual situation in area and population concerned at the time of such analysis.

Because the cost of immunization for higher coverage can be assumed to increase exponentially at a rate inversely related to the population cooperation, it is quite possible that an improvement of the coverage (e.g. from 75% to 90%) may not be cost-effective. The situation is of course different if the increased coverage can lead to the start of the decline in the endemicity. Cost-effectiveness analysis of alternative or combined preventive programmes may also be envisaged to explore possible benefit of improved population coverage.

There is obviously a need for reliable data on the disease incidence and the knowledge of epidemiological patterns in various parts of the country. Since general information and global estimates cannot serve as a sound basis for the formulation of an appropriate control
strategy and public health programme aimed at the control or elimination of typhoid in the country.

Epidemiological investigations and surveillance can be facilitated by use of the model, e.g. for the assessment of the reliability and the consistence of the data on morbidity rates, carrier and resistance states, etc.

The above is not an exhaustive list of the possible model uses.

8. DISCUSSION

This model, although based essentially on the data collected and used for formulation of the previous model[1, 2], differs from it in several respects. The main peculiarity of the present model is its ability to simulate the natural course of typhoid fever and the effect of interventions in age-specific groups of population.

Both models are equally suitable for simulations of all control programmes having for target the general population rather than individuals belonging to particular age categories. Special investigations on certain epidemiological classes less sensitive to dynamic changes in the model can, however, only be simulated with the previous model, as these classes were not included in the new model for reasons explained in Section 2.

The reliability of model simulations and predictions depends on the accuracy of the input data. Therefore, collection of reliable data for use in the model is of paramount importance. While basic data for use of the previous model were limited to crude morbidity and population size, in case of the present model it is necessary to have reliable data on specific age-group morbidity and on the age structure of the population. The importance of precise data on the effectiveness of control measures cannot be overemphasized.

Seasonal patterns of the disease can be simulated if necessary by altering appropriately the force of infection according to the seasonal prevalence of the disease.

The age structure of the population is controlled by the model and can therefore be modified whenever necessary by changing adequately the parametric survival rates without alteration of the computer program itself. However, to simulate new individual or combined intervention measures not yet included in the model, it might be necessary to alter some instructions of the computer program or to insert new statements in it. Such alterations should be carried out with the assistance of well-experienced persons having good knowledge of epidemiological modelling and electronic data processing.

The successful usage of the model in public health practice depends on (i) the clear definition of the problem and of the proposed strategy for solving it, (ii) the reliability of input data and (iii) the proper simulation techniques and the correct interpretation of the results. The use of the model and the exploration of its potentialities is greatly facilitated by the collaborative team work of epidemiologists, mathematicians and computer technologists.

Acknowledgement—The authors gratefully acknowledge the support provided by a grant from the Diarrhoeal Disease Control Programme. World Health Organization. They also wish to thank two referees for their helpful suggestions.

REFERENCES


* Requests for computer program listing should be addressed to Mr. H. Dixon. Epidemiological and Statistical Methodology. World Health Organization. 1211 Geneva 27. Switzerland.


**APPENDIX A: THE COMPUTER PROGRAM SYSTEM**

The computer program system is made up of distinct blocks performing specific processing functions as described below and shown in the program flowchart (Fig. A1). Appropriate blocks are combined and decision functions activated as required to perform a particular computer job.

**Block A**

From an input of 10,000 newborns each year, block A generates a stationary population by applying age-specific survival rates to the successive cohorts up to 80 years of age. The population is then distributed into the epidemiological classes $x_i (i, j)$.

Although arbitrary, the initial distribution into epidemiological classes is based on available information on the natural history of the disease and the probable parametric values for the level of endemicity concerned. Tentative age-curves worked out for the susceptible, infected and resistant populations are used to make a quantitative breakdown of each age group into these categories.

**Block B**

Block B calculates the number of individuals from each age who must move from one epidemiological class to another in each unit of time (1 month), and executes all the transfers accordingly, using the appropriate coefficients $R_{s,i}$. It also calculates and cumulates the number of cases and deaths from the contents of the classes $x_i (i, j)$. The suffix $j$ of all classes is then updated by one unit. This function can be considered as the core of the program system, since it is the simulation operator of the model.

**Block C**

Block C implements the intervention programmes. In case of immunization it transfers the individual eligible for vaccination from class $x_{i1} (i, j)$ into class $x_{i-1} (i, j)$, the vaccine effectiveness and the population coverage being duly taken into account in the process. For sanitation improvement, appropriate modifications are introduced in the mechanism of infection transmission.

**Block D**

At the end of each year, block D updates the age (suffix $i$) of all epidemiological classes $x_i (i, j)$ by one unit [except for class $x_8 (i, j)$]. This is done by applying the same survival rates already used to generate the basic population. This block also calculates the sum over age of the various epidemiological classes.

**Block E**

Block E prints out crude data on the size of the population and its distribution into the main epidemiological classes. Through this information it is possible to monitor the rate at which the simulation process is converging towards the final stable level.
Block F

Block F calculates and prints out on an annual basis all information (age-specific absolute numbers and rates) of interest for studying the transmission of infection and evaluating the impact of the simulated intervention programme on the dynamics of the disease.

Block G

After each iteration, block G writes the contents of all the computer memories used to store the matrices $x_i (i, j)$ into magnetic disk. This permits interruption of the system-solving computation and assessment of the converging power of the initial values generated by block A, without losing the stage so far reached in the process towards stability.

Block H

This function reads the contents of all cells of the epidemiological classes $x_i (i, j)$ as stored on disk. It makes it possible to restart the iterative computation needed to solve the system or to read from disk the solved matricial values for a given level of endemicity when the model is used for simulation purposes.
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C---

C--- INITIAL VALUES

C--- CREATE INITIAL POPULATION

C--- AGE DISTRIBUTION (END OF YEAR OF AGE 1-90)

C--- BREAK BY EPIDEMIOLOGICAL CLASS

C--- READ CREATED POPULATION

C--- WRITE (8Fi, 0)

C---
Epidemiological model of typhoid fever with age structure

Compiler language source code.
0154  \( x_1(VAC_1) = x_1(VAC_1) \cdot (1.0 - EFF \cdot CV) \)
0160  \( x_1(VAC_1) = x_1(VAC_1) \cdot (1.0 - EFF \cdot CV) \)
0161  \( x_1(VAC_1) = x_1(VAC_1) \cdot (1.0 - EFF \cdot CV) \)
0162  \( x_1(VAC_1) = x_1(VAC_1) \cdot (1.0 - EFF \cdot CV) \)
0163  \( x_1(VAC_1) = x_1(VAC_1) \cdot (1.0 - EFF \cdot CV) \)
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0165  \( x_1(VAC_1) = x_1(VAC_1) \cdot (1.0 - EFF \cdot CV) \)
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0168  \( x_1(VAC_1) = x_1(VAC_1) \cdot (1.0 - EFF \cdot CV) \)
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0171  \( x_1(VAC_1) = x_1(VAC_1) \cdot (1.0 - EFF \cdot CV) \)
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0201  \( x_1(VAC_1) = x_1(VAC_1) \cdot (1.0 - EFF \cdot CV) \)
0202  \( x_1(VAC_1) = x_1(VAC_1) \cdot (1.0 - EFF \cdot CV) \)
0203  \( x_1(VAC_1) = x_1(VAC_1) \cdot (1.0 - EFF \cdot CV) \)
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0209  \( x_1(VAC_1) = x_1(VAC_1) \cdot (1.0 - EFF \cdot CV) \)
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0216  \( x_1(VAC_1) = x_1(VAC_1) \cdot (1.0 - EFF \cdot CV) \)
0217  \( x_1(VAC_1) = x_1(VAC_1) \cdot (1.0 - EFF \cdot CV) \)
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0219  \( x_1(VAC_1) = x_1(VAC_1) \cdot (1.0 - EFF \cdot CV) \)
0220  \( x_1(VAC_1) = x_1(VAC_1) \cdot (1.0 - EFF \cdot CV) \)
0221  \( x_1(VAC_1) = x_1(VAC_1) \cdot (1.0 - EFF \cdot CV) \)
0222  \( x_1(VAC_1) = x_1(VAC_1) \cdot (1.0 - EFF \cdot CV) \)
Epidemiological model of typhoid fever with age structure

\[ \begin{aligned}
    &AX_2(I) = AX(I) + E(X) \\
    &AX(I) = AX_2(I) + \text{CASE}(I) \\
    &\text{CASE}(I) = \text{CASE}(I) + \text{NEW}(I) \\
    &\text{NEW}(I) = \text{NEW}(I) + \text{RANDOM}(I) \\
\end{aligned} \]
Epidemiological model of typhoid fever with age structure

0345  \[ D_{w} = 80 \text{ } K_t = 1,10 \]
0346  \[ a = 25 - K \]
0347  \[ D_{t} = 9t \text{ } J_t = 1,3 \]
0348  \[ x_{31} = x_{13} + x_{22} + x_{30} + x_{40} + x_{50} + x_{60} + x_{70} \]
0349  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0350  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0351  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0352  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0353  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0354  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0355  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0356  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0357  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0358  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0359  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0360  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0361  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0362  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0363  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0364  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0365  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0366  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0367  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0368  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0369  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0370  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0371  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0372  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0373  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0374  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0375  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0376  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0377  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0378  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0379  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0380  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0381  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0382  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0383  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0384  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0385  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0386  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0387  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0388  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0389  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0390  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0391  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0392  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0393  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0394  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0395  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0396  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0397  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0398  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0399  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0400  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0401  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0402  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0403  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0404  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0405  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0406  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0407  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0408  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0409  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0410  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0411  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0412  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0413  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
0414  \[ x_{51} + x_{10} = x_{31} + 1,2 \]
0415  \[ x_{31} = \frac{x_{31} + 1,2} {x_{13} + 1,2} \]
C---
10 CONTINUE
I+1 WRITE(5,2)6
J+1 WRITE(6,10)X1,X2,X3,X4,X5,X6,X7,X8

C--- WRITE CREATED POPULATION AT END OF RUN
C
I+1 WRITE(6,207)X1(I),X2(I),X4(I),X5(I),X6(I),X7(I),X8(I),X9(I),X10(I),X11(I),X12(I),X13(I),X14(I),X15(I),X16(I),X17(I),X18(I),X19(I),X20(I)
2(I) WRITE(6,207)X1(I),X2(I),X4(I),X5(I),X6(I),X7(I),X8(I),X9(I),X10(I),X11(I),X12(I),X13(I),X14(I),X15(I),X16(I),X17(I),X18(I),X19(I),X20(I)
STOP
5 300 STOP