PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

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EPIDEMIOLOGICAL AND STATISTICAL ASPECTS OF THE AIDS EPIDEMIC: INTRODUCTION

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In 1988, a government working party studied estimates of incidence and prevalence of numbers of acquired immunodeficiency syndrome (AIDS) cases. They investigated a series of epidemiological, statistical and mathematical problems associated with predicting trends in incidences of AIDS.

This paper introduces a series of papers that give a fuller and more technical exposition of the appendixes of that working party report. The papers provide a brief background to the current state of knowledge on the epidemiology of the infection and the disease; a deterministic model for human immunodeficiency virus (HIV) transmission in the male homosexual community in England and Wales is introduced. Back-projection methods are studied in two papers, following the distribution of the incubation period of the disease. The concept of minimum size of the epidemic is introduced. Mathematical functions to describe the spread of HIV infection are refined by using past trends in the incidence of AIDS to estimate values for some parameters.

Survival times for AIDS patients from the point of diagnosis are considered and evidence for changes in male homosexual sexual behaviour is studied; lag-time from the point of diagnosis to the report of the case is also examined. There is a comparative analysis of the AIDS epidemic in various European countries. The incubation period of HIV in patients with haemophilia A and B infections and the problems associated with making predictions for different at-risk groups or small sub-groups based on geographical area are discussed.

Reasons for fluctuation between the number of reported cases from month to month are provided.

In March 1988 a small working party was established by the Chief Medical Officers of England and Wales. The working party reported 'on predictions, for a 2–5 year period, in England and Wales, of incidence and prevalence estimates for numbers of live cases of acquired immunodeficiency syndrome (AIDS) and, where adequate information is available, of other human immunodeficiency virus (HIV)-associated conditions, on the number of deaths and on the overall numbers of HIV-infected individuals; and considered the means for updating such predictions, and to make recommendations'. (HMSO 1988).

The members of the working party were: Sir David Cox (Chairman); Professor R. M. Anderson; Dr Anne M. Johnson, Senior Lecturer in Epidemiology, Academic Department of Genito–Urinary Medicine, University College and Middlesex School of Medicine; Professor M. J. R. Healy, London School of Hygiene and Tropical Medicine; Dr Valerie Isham, Department of Statistical Science, University College London; Professor A. D. Wilkie, Consulting Actuary, Messrs R. Watson and Sons; Dr N. E. Day, Director, MRC Biostatistics

Unit, Cambridge; Dr O. N. Gill, Consultant Epidemiologist, PHLS Communicable Disease Surveillance Centre; Dr Anna McCormick, Consultant Epidemiologist, PHLS Communicable Disease Surveillance Centre; Secretariat: Dr Gillian Greenberg, Senior Medical Officer, Department of Health; Mrs Hilary Hillier.

The members of the working party investigated a series of epidemiological, statistical and mathematical problems associated with making predictions of future trends in the incidences of AIDS and infection with the etiological agent of the disease, the human immunodeficiency virus type 1 (HIV-1). The final report, which was published in November 1988, contained a series of appendixes giving brief details of parts of the research that underpinned the major conclusions in the main body of the text. We felt that the work outlined in these appendixes required fuller and more technical exposition so that public health workers, epidemiologists, medical and scientific researchers in the U.K. and other countries could assess in more detail the methods, assumptions and associated problems that surround the issue of making predictions about future trends in the incidences of AIDS and HIV infection.

This issue contains eleven papers that describe various aspects of the research, ranging from studies of the transmission dynamics of HIV, via epidemiological work on temporal changes in patterns of sexual behaviour, to statistical studies of the relation between AIDS incidence and the number of people infected with HIV, and the survival-time distribution of AIDS patients. The research reported in these papers was completed over the 5–6 month lifespan of the working party and hence much of it is preliminary in character and highlights problems as opposed to solutions. However, we feel the field is of sufficient practical and scientific importance to merit the publication of these contributions within a single issue.

The problems that surround making predictions about future trends in AIDS incidence are somewhat daunting. Indeed, if practical consideration did not demand the provision of such information (however tentative in character) for health care planning, scientific judgement alone would argue for extreme caution in the production and interpretation of projections.

The reasons for this are at least threefold. First, the disease and its etiological agent have only recently been diagnosed (AIDS was first characterized in 1981 and the virus HIV-1 isolated in 1983). Although progress in understanding the basic biology of the virus, in particular the structure and function of its genome, has been rapid, much remains uncertain about key processes that determine transmission within communities of people. Epidemiological data have accumulated slowly, largely because of the very long (and highly variable) incubation period (the period from first infection to the diagnosis of the disease AIDS). Current estimates based on transfusion associated cases and infections in injecting drug users (IDUS) and male homosexuals suggest a median period of 8–10 years. The implication of this is that epidemiological data will only accumulate slowly over decades of longitudinal study of infected persons and cohorts. In addition, one of the primary routes of transmission is via sexual contact. This poses additional problems for epidemiological study, given the sensitivities of individuals, societies and government bodies to open discussion and investigation of the behavioural characteristics that influence transmission via this pathway. Epidemiological uncertainties therefore limit the accuracy of projections based on mathematical models of transmission within populations, even within a particular at risk group (e.g. male homosexuals), let alone between and within the different groups that are at risk from infection and disease.

The second reason concerns the quality of the epidemiological data upon which projections into the future are based. In England and Wales we benefit from a good infectious disease

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reporting system, based at the Public Health Laboratory Service Communicable Disease Surveillance Centre at Colindale. However, the very nature of the disease and its temporal relation with the point of first infection, implies that current reports of the incidence of the disease AIDS represent infection events that happened, on average, several years ago. They therefore represent only a small fraction of the total number of people currently infected with HIV. Data on the prevalence of infection in different risk groups, and in the general population, are very limited at present. Good data on both the incidence of disease and infection would greatly enhance our ability to project into the future. One of the major recommendations of our report, therefore, was to instigate, as a matter of urgency, studies to improve understanding of the number of people currently infected with the virus. Shortly before the publication of the report, the U.K. Government announced that it saw neither legal obstacle nor ethical objection to anonymous screening. The Medical Research Council has been invited to submit proposals for studies based on anonymous and named testing. Although these steps fall short of a large scale random survey of the general population, they represent a significant step towards improving the quality of the epidemiological data base, taking account of the many practical and ethical problems that surround screening for HIV infection. Linked to the need for data on the prevalence of HIV infection as well as the incidence of AIDS, is the need for large scale, longitudinal studies of sexual behaviour both in particular risk groups and the general population. Even with good data on HIV prevalence in samples of individuals drawn from particular risk groups, projection requires knowledge of the size of the at risk population. One of the appendixes to the report discussed the problems of estimating the numbers of persons infected with HIV from the information currently available and concluded that the uncertainties involved were considerable. Information on the size of the risk groups, especially those most at risk, homosexuals and IVDUs, is scant, and the existing studies on seroprevalence in these populations are likely to be biased because all rely to a greater or lesser extent on self-selected samples. Applying the available information, the report concluded that the number infected by the end of 1987 was probably between 20000 and 50000, though it could plausibly lie outside this range. Our ignorance of the numbers of those within each risk group, without which more precise estimates cannot be made, can only be abated by large scale detailed studies of behaviour. The implementation of such research was a further recommendation of the report.

The third problem area is intimately linked with the other areas. It concerns the influence of education and publicity on patterns of behaviour, and hence infection with HIV, during the course of the epidemic in the U.K. A brief comparison of epidemiological trends in the United States of America and the U.K. suggests that the virus began to spread somewhat later in male homosexual and drug injecting communities in Europe than in those in North America. The knowledge of what was happening in the U.S.A., linked with the extensive publicity and education campaign mounted by the government in the U.K. in 1986, appear to have resulted in significant changes of behaviour amongst certain at risk groups, particularly male homosexuals, in England and Wales around 1984–85. These changes are thought to have had an impact on the rate of spread of the virus, but we are ignorant, in quantitative terms, of the temporal pattern of change in either the incidence of new HIV infection or sexual behaviour. Given our ignorance of many key epidemiological parameters, making projections is difficult enough in the absence of secular temporal trends. The problem is made much more difficult by unknown temporal changes in certain key parameters.

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In the face of such uncertainty it is essential to try to synthesize conclusions from a variety of approaches to making predictions about future trends. This is apparent in the papers in this issue. It is organized as follows. The first paper by Anderson *et al.* provides a brief background to the current state of knowledge on the epidemiology of the infection and the disease. The paper then addresses the problem of formulating a deterministic mathematical model of HIV transmission in the male homosexual community of England and Wales, which incorporates distributed incubation and infectious periods plus heterogeneity in sexual activity. Parameter estimates are, where possible, based on empirical information and sensitivity analyses are performed to assess the significance of variation in parameter assignments and changes in sexual behaviour. This paper is followed by one by Wilkie in which a similar approach is adopted using actuarial models to follow the history of cohorts of people. It has the added refinement of age structure, but the simplification of homogeneity in sexual behaviour.

The next two papers, by Isham and Day & Gore, adopt a different approach, based on back projection of the number infected with HIV on the basis of current data on the incidence of AIDS. This approach, which uses convolution methods, requires information (or assumptions) on the distribution of the incubation period of the disease (e.g. Weibull or gamma in form). Projections can be made into the future provided a further set of assumptions is made concerning the incidence of new HIV infections over the period of the projections. The 'minimum size' of the epidemic can be estimated if one assumes that all transmission ceases at the present time point and that projections of future cases of AIDS are based on current and past history of the number infected with the virus. The fifth paper by Cox & Medley adopts a further approach that is arguably the most practically useful with respect to making short term projections over one to a few years ahead. It relies on the choice of a mathematical function (perhaps based on studies of simple mathematical models of epidemic processes) and the estimation of its parameters from past trends in the incidence of AIDS. Taking account of the distributed (and time varying) delay between diagnosis and report, these estimates can be used to make projections into the future. The linear–logistic function appears at present to provide a reasonable description of past events. Interestingly, simple mathematical models of HIV transmission incorporating distributed incubation and infectious periods or heterogeneity (or both) in sexual activity generate an epidemic curve that is well described by the linear–logistic model.

The remaining papers address specific epidemiological or statistical issues: Reeves considers the survival times of AIDS patients from the point of diagnosis, and formulates a simple model for the distribution. Johnson & Gill weigh the evidence for behavioural changes in different at risk groups over the past ten years, thereby addressing one of the key problems surrounding projection. McCormick examines age stratified reports of mortality among males and females in England and Wales during the period of the AIDS epidemic to assess whether or not there is any evidence for under-reporting of AIDS associated mortality. A comparative study of the rate of growth of the AIDS epidemic in various European countries is provided by Mariotto. Darby & Doll examine the distribution of the incubation period in patients with haemophilia A and B via longitudinal studies. Finally, Cox & Davison examine the problem of making projections for different at risk groups or for small sub-groups based on geographical areas.

It is important to stress the preliminary nature of many of the reported studies, and the great uncertainties involved in making projections. The original report was written in the summer of 1988, and was based on cases of AIDS and HIV infection reported up to June 1988. We now

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have the benefit of a further 9 months' data and it is interesting to see whether this alters the general conclusions of the report. The number of cases of AIDS reported by June 1988 had already shown some signs that the early exponential growth had given way to a phase of much slower and more linear growth (table 1). Although there is considerable fluctuation in the numbers of reported cases from month to month, and even from quarter to quarter, it is now apparent that the number of reports each quarter increased relatively slowly between the middle of 1987 and the end of 1988. A similar pattern has occurred in other countries, notably the F.R.G., France and Australia.

TABLE 1. MONTH OF REPORTED AIDS CASES IN ENGLAND AND WALES

	year							
month	1982	1983	1984	1985	1986	1987	1988	1989
January	—	1	5	11	12	57	51	64
February	—	1	2	12	15	51	57	52
March	2	0	5	11	21	26	78	83
April	—	0	2	17	6	19	28	—
May	—	5	4	5	24	40	76	—
June	—	1	3	10	25	73	49	—
July	—	2	5	19	59	53	68	—
August	—	2	9	8	20	68	59	—
September	—	6	11	14	16	54	62	—
October	—	3	10	16	49	49	67	—
November	—	1	8	14	21	45	61	—
December	—	4	9	14	22	53	51	—
total	2	26	73	151	290	588	707	199

There are several possible explanations for this. In their paper, Anderson *et al.* suggest that a slowing down in the rate of growth of new cases is consistent with a model of the epidemic in male homosexuals in which the average number of sexual partners is assumed to be sharply reduced after 1985. This model would predict an epidemic that peaks in 1989–1990, and is consistent with between 10000 and 15000 homosexuals being infected at the period of peak incidence; this is at the bottom end of the probable range of values suggested by applying estimates of seroprevalence to estimates of the size of the homosexual population. Under this, relatively optimistic assumption, the peak of the epidemic for homosexuals has almost been reached, though the number of cases might still go on rising slowly for some time after 1990 because of cases arising in the heterosexual and drug-using communities.

A further possibility is that the flattening in the number of reported cases is an artefact, caused by what the Americans have called 'reporting fatigue', i.e. an increasing tendency to late reporting or to not reporting at all. However, there is no evidence that reporting lags are lengthening and the fact that a similar phenomenon has occurred in other countries, with identical timing and to a very similar degree, makes this seem an unlikely explanation.

A third possible situation is that treatment with the drug zidovudine (AZT) may prolong the incubation period for those to whom it is administered before the onset of AIDS, in addition to prolonging survival time among those with AIDS. Zidovudine started to be used quite widely in this country around the end of 1986. The effect would be a once and for all lengthening of the average incubation period for those given zidovudine, though by how much is very uncertain, causing a lateral shift in the incidence curve. If this is the explanation, then the numbers of cases will start to rise again more rapidly once this effect has worked through. This

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theory would explain the similar flattening in reports of new cases in other countries. It is worth noting that in France the most recent figures show a return to faster growth towards the end of 1988 (although the epidemic there has rather different characteristics from that in this country and the numbers of new cases were rising faster in France than in England and Wales before the levelling off occurred in both countries in 1987).

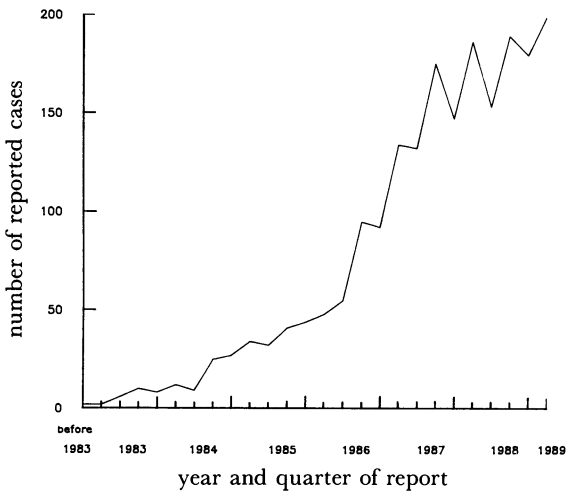

FIGURE 1. New cases of AIDS reported to the Communicable Disease Surveillance Centre by March 1989 for England and Wales.

All these uncertainties highlight the need to: (*a*) continuously update projections as data and biological understanding improve; (*b*) develop better methods for projection, perhaps based on seeking simple mathematical functions that approximate the patterns generated by complex transmission models; (*c*) refine techniques for parameter estimation taking account of the variability that seems to pervade the pattern of HIV infection and disease, both at the individual and population levels and, most importantly; (*d*) encourage the acquisition of better and more extensive epidemiological and behavioural data via nationally coordinated research programmes.

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