Demographic issues in modelling HIV/AIDS epidemics

Report of a meeting of the UNAIDS Reference Group for Estimates, Modelling and Projections held in Tours, France, July 25-26th 2005

TECHNICAL REPORT AND RECOMMENDATIONS

UNAIDS

The meeting of the UNAIDS Reference Group on Estimates, Modelling and Projections (the 'Epidemiology Reference Group') was organised for UNAIDS by the UK secretariat of the reference group (http://www.epidem.org) based at Imperial College London. Participants of the meeting are listed at the end of this document. The recommendations in this document were arrived at through discussion and review by meeting participants and drafted at the meeting.

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Introduction

The Reference Group

The Joint United Nations Programme on HIV/AIDS (UNAIDS) *Reference Group on Estimates, Modelling and Projections* exists to provide impartial scientific advice to UNAIDS and the World Health Organization (WHO) on global estimates and projections of the prevalence, incidence and impact of HIV/AIDS. The Reference Group acts as an 'open cohort' of epidemiologists, demographers, statisticians, and public health experts. It is able to provide timely advice and also address ongoing concerns through both *ad hoc* and regular meetings. The group is co-ordinated by a secretariat based in the Department of Infectious Disease Epidemiology, Imperial College London (www.epidem.org).

Aims of meeting

The primary aim of this meeting was to bring together experts to produce recommendations for improving the modelling of demography, which is important in making estimates and projections of HIV epidemics and the demand for anti-retroviral therapy.

Approach

The meeting featured both presentations of recent data and group discussions, which focused on specific technical issues. Presentations included comparisons of the methods used by different modelling packages, and the outputs of those packages; an analysis of the different life tables used in demographic models; modelling results of the impact of demographic change on HIV epidemiology over the course of an epidemic; urbanization, and international migration; the use of data from demographic and health surveys (DHS) and a description of data that will become available from SAVVY surveys (see Appendix I for a complete list of presentations).

The meeting was attended by 23 experts from 5 countries (see Appendix II for a list of participants). Each contributed, not only data, insights and analysis, but also worked hard to produce a set of recommendations for UNAIDS and WHO, drafted at the meeting. We would like to thank them for their hard work and attendance at the meeting.

The recommendations drafted at Reference Group meetings give UNAIDS and WHO guidance on how best to produce estimates of HIV/AIDS, an opportunity to review current approaches and also help to identify information needs (earlier reports are published on the Reference Group website www.epidem.org). They are typically drafted with an explicit timeframe for follow-up work that is subsequently reported on by the Reference Group secretariat to ensure a response to all recommendations. In this report, goals are categorised as short-term (to be achieved by end-2006), medium-term (2007-8) and long-term (next five years – i.e. by end-2010). This transparent process aims to allow the statistics and reports published by UNAIDS and WHO to be informed by impartial, scientific peer review.

Modifications to EPP and Spectrum

1. Brief overview of EPP and Spectrum

EPP/Spectrum were deliberately designed to be a 'simple' package, because, whilst it has long been recognised that heterogeneity in risk behaviour is important in determining the trajectory of the HIV epidemic in different countries and regions, the data that are required for the modelling of those heterogeneities are usually lacking. Additionally, the EPP/Spectrum package needs to be user-friendly so that it can be used globally without requiring intensive support. However, as more detailed data become available, it may be desirable to incorporate demography in a more sophisticated fashion.

EPP is only intended for making short-term projections of HIV prevalence, and not population size. Its model population is not stratified by age or sex; the HIV prevalence estimate is then used by Spectrum to make projections of HIV prevalence and incidence by age and sex.

A number of sites can be specified for the country under consideration, and each site is assumed to have a curve of the same, but each site can have a different scaling factor applied to the curve, to specify the distribution of HIV amongst the sites. The overall country prevalence curve is scaled to pass through the DHS prevalence data-point. In effect, scaling specifies the proportion of the total population that is considered to be at risk of HIV infection.

EPP's parameters are time-invariant, and so it cannot incorporate (e.g.) changes in the urban/rural distribution. The UN Population Division uses a model (abcDIM) which is similar to EPP but which allows parameters to vary over time.

Spectrum's model population is stratified by sex and age, and it considers both AIDS- and non-AIDS-mortality. Spectrum's first step is to distribute HIV infections by sex, according to an empirically-determined sex-ratio of infections which changes as the HIV epidemic matures: in the early stages of a typical HIV epidemic, most prevalent infections are found in men (in men who have sex with men (MSM), injecting drug users (IDU) and clients of sex workers), whilst later in the epidemic, most prevalent infections are found in women. It should be noted that the empirical data used to derive this pattern came from cross-sectional surveys completed at different stages of the HIV epidemic in different countries, and that there are few longitudinal data from a single country.

Spectrum uses an empirically-determined generic curve of the relationship between the sex-ratio of HIV prevalence and time since the start of the epidemic, which is scaled according to the DHS data input. The same shape of curve is assumed in both concentrated and generalised epidemics.

Rates of progression from HIV infection to death are dependent upon sex in Spectrum, with females taking longer to progress. This reflects in part the fact that females tend to be infected at younger ages than males, and that progression is slower in younger people. However, the effect of the age-at-infection on an individual's progression rate is not considered explicitly – i.e. progression rates are not age-dependent in Spectrum.

After distributing prevalent infections by sex, Spectrum then distributes them by age according to model patterns of prevalence by age. There are two patterns, one for generalized epidemics and one for concentrated epidemics. These patterns were developed by assuming a constant force of infection by age and fitting a simple transmission model to match DHS+ data for countries where it is available. The resulting patterns of prevalence by age over time were averaged across all countries with data to create the standard pattern. For concentrated epidemics the pattern was created by examining available information on the age distribution of infection in special risk groups: MSM, IDU sex workers and clients. Finally, age- and sex-specific HIV incidence is estimated from the distribution of prevalent infections.

The effect of HIV status on female fertility is considered in Spectrum: those who are HIV+ have 30% lower average fertility than those of the same age who are HIV-, with the exception of 15-19-year-olds, whose average fertility is higher in HIV+, reflecting the fact that in this age-group many HIV- individuals are not sexually active.

Non-AIDS mortality is modelled using life-tables supplied by the UN Population Division. AIDS cases are subject to competing risks of mortality – i.e. they may also die a non-AIDS death. Anti-retroviral therapy (ART) delays progression to death; cotrimoxazole delays progression to death in HIV-infected infants; prevention of mother-to-child transmission (PMTCT) is also modelled, and reduces the proportion of infants infected. Infants can receive cotrimoxazole or ART or both.

It is important to note that if ART coverage changes then this will introduce an inconsistency between EPP and Spectrum, because the former does not consider it explicitly, whilst the latter does.

2. Modifying EPP to account for temporal changes in demographic and behavioural parameters

Currently EPP does not allow incorporation of temporal changes such as urbanization or behaviour change. This means that EPP cannot reproduce a situation where HIV prevalence reaches a plateau and then declines due to behaviour change (either because individuals change their behaviour or because the most-high-risk individuals are depleted by AIDS mortality). Also, the roll-out of widespread ART will have a major impact on HIV epidemiology. Currently, the 'behaviour' parameter, ϕ, only applies to new recruits into the population, whilst having a 'behaviour' parameter that applies to the whole population would allow for more flexibility in the curve-fitting.

Recommendations were that:

- if parameters are to be allowed to vary with time then this should be only in the fitting process, and users should not be permitted to manipulate them (e.g. to prevent over-optimistic estimation of the impact of interventions);
- demographic changes should be permitted, since there are usually good data to support them;
- in the short term, an assessment be made of how common are problems in achieving acceptable fits to data in the current round of estimation, and a collection of cases of poor fitting be made, to be examined to see if they justify allowing temporal behaviour changes.

It was remarked that there is a need in advocacy for examination of 'simple' scenarios (e.g. a halving of the HIV transmission rate), without being concerned with the changes in the 'process' parameters (e.g. increases in patterns of condom use) required to achieve them.

It was suggested that a facility to make projections under different scenarios be provided, so users can compare the effect of parameter changes with the no-change scenario. It was suggested that this examination of scenarios would be better provided in Spectrum than EPP, where the impact on incidence rather than prevalence could be examined. Additionally, EPP's fits are not unique, and EPP's parameters are composites of several epidemiological processes. It was noted that model structure will be an important source of uncertainty, not just the parameter estimates.

3. Changing age-patterns of incidence used in Spectrum

Data used to calculate incidence from prevalence in Spectrum were from DHS surveys in 7 countries, and were not longitudinal. A proposed medium-term goal was to examine whether different types of epidemics have different temporal age-patterns and to examine incidence-prevalence relationships, since Spectrum calculates incidence from prevalence.

Many models do not have a not-at-risk group in the population, which EPP uses to limit the prevalence. This also means that those models cannot account for people spending a limited period of time at risk (e.g. having several sexual partners before forming a long-term monogamous partnership). However, the not-at-risk group is accounted-for implicitly in Spectrum by its use of EPP's prevalence estimate.

4. Sex-ratios of HIV prevalence and how they change during the course of an epidemic

In the 'general pattern' the female/male ratio of prevalent HIV cases is initially very low, as infection is concentrated in men, particularly injecting drug users (IDU – who tend to be mostly male), men who have sex with men (MSM), and clients of female sex workers. Although female sex workers may have a high prevalence of HIV, they are usually only a small proportion of the female population. As the epidemic matures, infection spreads to the general population and the female/male ratio rises. Ultimately, in a generalized epidemic it exceeds 1, because females may be more susceptible to infections and males typically have faster progression from infection to death, which depletes relative the number of prevalent infections in males.

Whilst no country is now in the early stages of an HIV epidemic, with the duration from infection to death being typically around 10 years, the historical pattern of incidence is affecting the current pattern of AIDS mortality.

<u>Variation in the trajectory of the sex ratio</u>
The trajectory of the sex-ratio may vary widely, both in the initial value of the sex-ratio and its final value. Variation in the relative sizes of high-risk groups of males (e.g. IDU, MSM, clients of sex workers) and females (e.g. female sex workers) affects the initial value of the sex-ratio. The degree of 'bridging' between high- and low-risk groups can also have an effect: e.g. where an epidemic is concentrated in female sex workers and their clients, if those clients also have regular female partners then there could be rapid spread into the general population, raising the female/male ratio.

However, in Thailand transmission to the wives of male clients of sex workers was slow because sexually-transmitted diseases (STDs, which promote HIV transmission) were much less prevalent in sex worker-client partnerships than in client-wife partnerships.

In South Africa, HIV risk was more generalised from the beginning of the epidemic so the sex ratio was less male-biased.

<u>Sex-ratio of incident cases is not the same as the sex-ratio of prevalent cases</u>
The sex-ratio of incident infections (which is a parameter required for incidence projection) will not the same as the sex-ratio of prevalent infections (for which there are data, as used in Spectrum) because of the effects of sex and age-at-infection on survival times of HIV+ people. Younger individuals and women have longer survival times than older individuals and men. Models that do not take account of this will underestimate the number of HIV+ females (by making them die too quickly, if incidence is ‘matched’) or will overestimate female incidence.

Sex-ratios may vary with age, but in general there will be insufficient statistical power to detect an age-effect. DHS data could be used to examine prevalence sex-ratios.

<u>Research questions</u>
Is a sex-ratio close to unity associated with rapid generalised spread of HIV? To address this question, it was suggested that AIDS-death data could be analysed by age and sex from the early stages of an epidemic, to estimate the sex-ratio of prevalent cases. Cohort-study data would be invaluable. As a short term goal, historical data and contemporary DHS data could be analysed. Another short-term goal should be validating Spectrum’s projections of AIDS cases / deaths against data. It was suggested that the five African cohort studies could look at the relationship between HIV prevalence and AIDS deaths.

A proposed medium-term goal was to identify correlates of different sex-ratios and to determine if there are there regional patterns in the trajectories of the HIV-prevalence sex-ratio. If so then DHS data from one country could be applied to another, if that country lacked its own data. However, in Kenya the female/male ratio is 1.9 whilst in Tanzania it is only 1.4, so it may be that there are not strong regional patterns.

As a long-term goal, EPP should be developed to model the sexes separately, but this requires data for men – which are currently lacking, since ANC data are used, although DHS data will become available.

4. Reconciling discrepancies in estimates

It was suggested that there is a need for general guidelines on how to reconcile discrepancies in data from different sources. However, it was questioned whether general principles can actually be derived. The need to avoid having adjustments made by in-country groups, which would lead to inconsistencies in UNAIDS’s estimates, was emphasised.

It was agreed that a medium-term goal should be the incorporation into Spectrum of standard comparative measures of rates of mortality, orphanhood, etc, in tables/graphs, that could be compared with country-specific data, to assess the validity of Spectrum’s output. Users would not be allowed to change parameters (e.g.

rates of progression of infection) to improve the fit, but it was noted that users may be tempted to make other invalid changes to try to improve the model fit.

5. Possible future development or replacement of EPP/Spectrum

It was believed by some that development of an integrated package to replace EPP, Workbook and Spectrum would be desirable, but it was recognised that this would have to be a long-term goal with extensive validation before it could replace the current approach.

Incorporation of age-structure into EPP, or its replacement, was suggested as a long-term goal. However, its robustness would need to be evaluated. Additionally, doubts were expressed over the availability of the age-structured data required to enable fitting of an age-structured model, but it was suggested that a simple model could be used for fitting, and a more-sophisticated one for projections of different scenarios. However, it was argued that, for consistency, the models used for fitting and projection need to have the same degree of complexity. It was pointed-out that one can have a sophisticated model with many parameters, but constrain them to avoid exceeding the limits of the data. However, it was noted that the Asian Epidemic Model is sophisticated and consequently difficult to apply to detailed country data – and that the model being proposed in the discussion is even more complex, which would mean that the demand for technical support for in-country teams would be enormous. It was suggested that much of the model complexity can be hidden from the user, and that there could be ‘basic’ and ‘advanced’ modes of use. A more-sophisticated model may actually be simpler to use than EPP because EPP has to be ‘forced’ to fit scenarios for which it lacks the necessary flexibility, giving as an example regional epidemics where the HIV epidemic in a particular country is being driven by international migration.

Age-structure, and how the age- and sex-specific prevalence and incidence of HIV infection are estimated from the overall prevalence estimate

1. Estimates of prevalence in those aged over 50 years

Currently, EPP provides an overall prevalence estimate for the 15-49-year-old population, with the sexes combined. Spectrum then distributes HIV infections between the sexes and amongst different age-groups, including distributing 'additional' infections in those aged >49 years. The resulting discrepancy is believed to be slight, and so for simplicity it has been ignored. As a short-term goal it was recommended that Spectrum should be modified to provide outputs for the HIV prevalence in ages 15-49 and ≥15 years, so that they may be compared. Also the total number of individuals aged >49 years in Spectrum's model population could be output. The age-structures of urban and rural populations may be significantly different.

2. Survival of HIV-positive children

EPP/Spectrum considers individuals aged ≥15 years, and this is the youngest age at which they allow HIV infection to occur. Since, in reality, some of those in the younger ages over 15 years will have acquired HIV before age 15, EPP/Spectrum will over-estimate their survival times. The abcDIM model does not have this problem because it considers all ages from birth, although there are not empirical data for the whole range of ages 0-15 years. Cohort data are now available for survival of HIV-positive children aged up to 11 years. As a medium-term goal, data from the African cohort studies should be analysed.

3. Age-effects on survival in EPP/Spectrum

Currently EPP/Spectrum do not incorporate any effects of age on survival post-HIV-infection. Incorporation of age-effects in Spectrum would be straightforward, but would then lead to inconsistency with EPP. The difficulty is that the average survival time, which is used by EPP, depends upon the age-distribution of prevalent HIV, which is only calculated by Spectrum after EPP has produced its output. Resolution of this problem would require an iterative process in which the average value used by EPP were revised in light of Spectrum's output, and then used to produce a new estimate from EPP, which would then be passed to Spectrum to produce a revised output, and the process repeated until convergence is achieved (if it does in fact occur).

A medium-term goal should be to check whether Spectrum is producing reasonable estimates of incidence by age and sex.

Modelling the impact of anti-retroviral therapy (ART) of HIV epidemiology in EPP/Spectrum

1. Requirement for a special meeting to discuss the impact of ART

There is a need for models to predict both demand for ART and the impact of ART on the HIV epidemic. It was agreed that there is a need for a special meeting of the Reference Group on ART modelling, involving experts on ART, and those involved in implementation of ART programmes, as well as modellers. (This meeting will need to consider not just the effect of ART on mortality rates of those on treatment, but also its effects on HIV-infectivity and sexual activity of patients, and potential behavioural disinhibition in the HIV-negative population, which are all factors that will affect HIV transmission.) It was suggested that Botswana would be a good location, since it has experience of implementing ART.

2. When people become eligible for ART

The criteria for ART-eligibility vary amongst countries; e.g. some use CD4-count data, whilst others use only signs and symptoms. Additionally, WHO is currently reclassifying the clinical stages of HIV infection, which will affect ART-eligibility criteria. Additionally, the speed with which ART-eligible people actually commence therapy will vary amongst countries, according to access to *diagnosis*, as well as availability of therapy. Therefore, perhaps the facility to reflect these national differences should be provided in EPP/Spectrum. Currently in Spectrum HIV-positive people become eligible for ART two years prior to their predicted death in the absence of ART. It should be noted that this is used to calculate *demand* for ART, and that the proportion of those who are eligible who receive ART is determined by the specified coverage level.

It was recommended that this implementation be made more flexible to allow for different patterns of ART provision.

3. The effect of ART on survival

Currently, Spectrum models the rate of progression from infection to death, and then estimates ART-eligibility by ‘working backwards’ from the time of death. It was recommended that this be changed, to model the rate of progression to ART-eligibility. This was how Spectrum operated originally, but it was changed due to the rate of progression to AIDS symptoms being poorly estimated. However, now that there is the need to model ART demand, this change should be made as medium-term goal. EPP also needs modification to incorporate the impact of increasing provision of ART. Change should be made, cognisant of the approach to modelling ART demand used in ASSA2002.

It is important to ensure that data collection associated with ART implementation meets modelling needs.

4. The effect of ART on HIV-infectivity

The effect of ART on HIV-infectivity is not currently incorporated into Spectrum. However it is a feature of ASSA2002.

5. The effect of ART on sexual risk behaviour

ART-recipients often have increased sexual behaviour, resulting from improvements in their health and feelings of well-being. Whether or not this results in a net increase in rates of HIV transmission depends upon the extent to which increased rates of sexual contact are counteracted by reduced infectivity due to a reduced viral load.

An important potential effect of the widespread provision of ART is *behavioural disinhibition* – an increase in risk behaviour in the population in response to the belief that HIV infection is no longer a serious medical condition, but rather one that can be readily managed. This effect may apply to both HIV-positive and HIV-negative individuals, and generally appears to be particularly apparent in the latter – which may potentially cancel-out the HIV-incidence-reducing effect of ART's reduction in HIV infectivity.

Long-term projections of the HIV epidemic

1. Modelling the demographic impact of different HIV epidemics

Modelling work presented at the meeting showed that the demographic impact of HIV can be very different when there are differences in the sexual risk behaviour of the population, in terms of partner change rates and patterns of partner choice.

In the absence of behaviour change, as an epidemic matures there is a shift in the peak age of incidence from older to younger, as the numbers of susceptible individuals in the older age-groups become depleted. Additionally, prevalence in the older age-groups can decline due to HIV-associated mortality, which occurs after a delay due the long incubation period. In a rapidly-spreading HIV epidemic, due to high rates of partner change, AIDS mortality may be initially highest in the younger age-groups, despite their having slower progression to AIDS than older individuals, due to their having higher rates of infection.

The modelling work found that the outcome was sensitive to parameters for which estimates are often lacking. Patterns of age-mixing and age-dependent rates of sexual partner change can produce widely-varying patterns of change in incidence of infection and mortality, and their age-distributions.

Risk behaviour of individuals may not simply decline monotonically from a peak in early adulthood, as is commonly assumed. Thai data suggest that older males may have higher risk behaviour than younger males. Data presented at ISSTDR meeting in Amsterdam in July 2005 on MSM in the UK, which showed that there is a peak in risk behaviour at intermediate ages, whereas in heterosexual males, peak risk behaviour occurs at younger ages. Data from the Africa Centre indicate a relatively high incidence of HIV can occur in those aged 40-50 years. The study in Kisesa, Tanzania, found that older females were at higher risk of HIV infection than intermediate-aged females.

The effects of changes in risk behaviour on the prevalence of infection are largest and seen first in the younger age-groups. Reductions in risk behaviour increase the average age-at-infection as individuals take longer to become infected.

A key area where knowledge is lacking is how rates of partner change and patterns of partner choice change in response to changes in the availability of partners caused by mortality due to AIDS, which tends to remove the most high-risk individuals from the population. From survey data we have information of rates of partner change and characteristics of chosen partners, but these are data on the *outcome* of the process of partnership formation, and do not specify the mechanism of the process itself. Partnership formation is a process of interacting supply and demand, and it is not clear how ‘compromises’ occur when the desired number of partners (and of a particular type) is not available. In MSM, rates of partner change may be affected by the number of new partners who are available.

2. The need for long-term projections

The UN Population Division has to make projections to the year 2050, whilst UNAIDS prefers not to make projections even 5 years in to the future. It was suggested that UNAIDS should attempt to make longer-term predictions, even though this is difficult. He also commented that the funding for many interventions is dependent upon their measured performance in terms of (e.g.) infections averted, which can only be assessed using mathematical models to predict the trajectory of the epidemic in the absence of the intervention. Therefore it is important to ensure that it is understood that predicted declines in HIV prevalence are occurring due to interventions, so that they are not used as the 'no-intervention' baseline for assessment of interventions.

Mortality Data

1. Comparison of demographic models' performance

Abacus/abcDIM (UN Population Division), Spectrum/AIM (Futures Group), and RUP/RupHivAids (International Programs Center) were compared to see how consistent were their projections. A detailed report can be obtained by members of the Reference Group from the website at www.epidem.org.

The main findings were that different assumptions regarding age- and sex-distributions of prevalent infections result in large differences in mortality estimates.

It was suggested that an artificial 'DHS' data set should be created using a model, and then testing how well EPP/Spectrum and other modelling approaches can recreate it.

2. Life-tables used in demographic projections

It is commonly assumed that rates of childhood and adult mortality are correlated, but this is only loosely the case[1]. Therefore it is problematic to estimate adult mortality for a country from childhood mortality data for that country and a life table from elsewhere (or to estimate childhood mortality using data on adult mortality and a life table from elsewhere). However, Timæus recommended that if one has to do this, the South model life-tables should be used for tropical Africa and the West life tables in Southern Africa. However, when estimating infant and childhood mortality from overall under-five mortality, the North tables are more likely to be appropriate.

Also there can be substantial variation in patterns of mortality amongst sub-national populations.

In some cases, the life-tables used by the UN Population Division for particular countries have been changed in response to Timæus's work. It is important to note that the life-table that is applicable to a particular country can change over time. Information on which life-table was used for each country has not been made clear in the past (it has not been North in all cases, as is sometimes assumed), but that this information can be made available. 'Spliced' life-tables (which comprise the childhood mortality pattern from one life-table and the overall mortality pattern from another) will be available in 2006.

UNICEF's demographic modelling uses different life tables, making inconsistency of its projections with UN Population Division's inevitable. Development of a common approach would be desirable.

Mortality due to AIDS and other causes

Rates of non-AIDS mortality and AIDS mortality are non-independent: those who are at higher risk of AIDS mortality are also at higher risk of non-AIDS mortality.

[1] Timæus, I. M. (1999). Mortality in sub-Saharan Africa. In: Health and Mortality: Issues of global concern. J. Chamie and R. L. Cliquet (eds.). New York and Brussels, Population Division, United Nations and Population and Family Study Centre (CBGS), pp. 110-131.

An important point that non-AIDS mortality (also called background mortality) is not mortality in the absence of HIV/AIDS, but, rather, it is the mortality of HIV- individuals in a country where HIV/AIDS is present. A high prevalence of HIV/AIDS affects the mortality of both HIV+ and HIV- people in a number of ways.

More work needs to be done to improve estimates of mortality in HIV+ and HIV- individuals. At present, mortality rates are often overestimates, because HIV-associated mortality is often added to estimates of mortality that already include all deaths of the HIV-positive (i.e. gross mortality).

3. Improvements in mortality estimates: Methods of estimation of adult mortality rates from DHS/MICS and potential for incorporation of these and of vital registration data in EPP/Spectrum to calibrate mortality

Accurate estimation of adult mortality rates from survey data is usually not possible, due to small sample sizes and under-reporting of deaths. Surveillance data may suffer less from recall bias than national survey data but are not nationally representative Currently, the only mainland sub-Saharan African country with good vital registration data is South Africa.

<u>Biases in mortality estimates from sibling histories</u>

DHS data are inadequate as they suffer both from large sampling errors and recall biases. The method used by Timaeus to extract information from them is to impose common age-patterns of AIDS mortality and non-AIDS mortality on all countries, but to allow country-specific levels and trends. This method is a complex, requiring substantial demographic expertise, and so is unsuitable for general global use by in-country teams.

Even after this, apparent increases in mortality over time could be due to omissions in sibling-history death records being more common for deaths that occurred further into the past: i.e. more-recent deaths are more likely to be recorded.

Another factor causing underestimation of mortality is that if all siblings have died then no deaths will be recorded. A paper describing a method of correction for this bias is in preparation from Harvard.

Spectrum's outputs need to be compared with empirical mortality data. Compared with the sibling history data, Spectrum has higher estimates of AIDS mortality and lower estimates of non-AIDS mortality. This may have been due to the use by Spectrum of the North life-table, which will be changed in the 2006 version.

Mortality data could potentially inform on the extent to which an increase in HIV prevalence is due to incident infections or to increased survival of HIV+ people due to anti-retroviral therapy (ART).

Due to the dynamic nature of the HIV epidemic, and the provision of prevention and therapeutic interventions, there is a need for dynamic models of mortality, which are cognisant of HIV incidence and prevalence, rather than static life-tables.

Ian Timæus commented that survey data suggest that annual numbers of AIDS deaths in men often exceed those in women, despite HIV prevalence in men being thought to be lower – a phenomenon that is only partially explained by faster rates of progression in people infected at older ages, who tend to be male, but may be a feature of the early stages of the epidemic.

Movement of people: urbanization and international migration

Movement of people within and between countries can have an important impact on HIV epidemiology – in particular if movement from a high-HIV-prevalence area increases the prevalence of HIV in a low-prevalence area. Unfortunately, data are lacking on the sizes of flows of people, and their HIV status. Models commonly assume that migrants have the same HIV prevalence as the population of their country or region of origin or their country or region of destination.

Movement of people can also alter the age-structure of populations.

1. Urbanization

The measure used by UN Population Division is the percentage of the national population that is ‘urban’, as defined by the particular country. Unfortunately there is a lot of variation in national definitions of ‘urban’, and many are vague. This makes cross-country comparisons difficult. Additionally, changes in definitions used by particular countries can also make within-country trends difficult to interpret.

Importantly, urbanization does not necessarily require movement of people: the process of development can turn a ‘rural’ location into an ‘urban’ one, and net growth rates due to reproduction alone in settled populations have often been higher in urban populations than rural ones. Movement of people into cities from rural areas has often slowed as a result of declining national economies having reduced the ‘attractiveness’ of cities.

Currently, half of the world’s population of 6.5 billion is urban. The absolute number of people living in rural areas is expected to remain roughly constant until 2030, but they will represent a declining proportion of the total population, as urban populations grow. Most of this urban population growth is predicted to occur in Africa and Asia; the Latin America and Caribbean region is already highly urbanized. Note that, in terms of absolute numbers, the African rural population is predicted to grow. Within Africa, the east is currently the least urbanized, and the south the most. India and China currently have less than half their populations being ‘urban’, but this is predicted to increase rapidly, particularly in China.

The greatest degree of urbanization is expected to occur in countries that are most affected by HIV.

It was suggested that the age-group that is at highest risk of HIV acquisition may be more concentrated in urban areas than rural ones.

EPP currently stratifies the model population into areas that are ‘urban’/’rural’/’other’, and provides stratified outputs as well as an overall national prevalence estimate. The process of urbanization can be easily incorporated into EPP. Whilst the available estimates of rates may be imprecise, it is preferable to use them than to assume a constant proportion of the population when this is known not to be the case.

It is important to ensure that the categorisation of ANC sites is consistent with that used in estimates the urban/rural distribution of the national population. A medium-term goal should be to use UN categorisation of urban/rural for both ANC surveillance sites and estimates of the population distribution.

The ‘other’ category in EPP should be used where there are better data for the major cities of a country than for other urban areas.

2. International migration

Migration can have an important impact on patterns of spread of HIV, but the data required to have a full understanding of its role are usually lacking. Although data on the age and sex of migrants are often available – and differ by type of migration – there are usually no data on the patterns of HIV prevalence of migrants, which may be different from the patterns of the ‘source’ population.

Often only the net flow is known, whilst there may be a number of different flows in different directions. In particular, it is difficult to detect the magnitude – or even the presence – of circular flows, and they may be very important in fuelling HIV transmission if they involve areas that differ in their HIV prevalence.

<u>Implementation of international migration in Spectrum</u>

In the Spectrum software package, <u>e</u>migrants are currently assumed to be HIV-negative, so emigration necessarily increases HIV prevalence in the model population. An alternative assumption would be that emigrants have the same characteristics as the rest of the population. Changing to using this alternative requires consideration of the effects on rates of disease progression and ART use.

Currently, Spectrum assumes that <u>im</u>migrants are HIV-negative, which causes an increase in the estimated incidence of infection, in order to fit to the prevalence value that is input. Again, this assumption could be changed, but consideration needs to be given to its impact.

A medium-term goal should be to implement in Spectrum the ability to specify the distribution, by age and sex, of the time-since-HIV-infection of immigrants, since this may be different from the local population. However, usually we do not know the stage of HIV infection of migrants.

New sources of data

1. HIV prevalence data from demographic and health surveys

HIV testing and knowledge of HIV status

Action is being taken to increase the extent of HIV-testing of participants in demographic and health surveys (DHS), by increasing the numbers of field staff who are trained to collect and test samples, thus reducing the workload of each individual (participants are often not at home, making repeated visits necessary). Also, there is increasing publicity promoting HIV testing in DHS. Although testing is currently anonymous, consideration is being given to whether, and how, to make results available to participants. Currently participants are encouraged to make use of voluntary counselling and testing (VCT) services.

DHS surveys have begun to ask participants if they know their HIV status, and, in general, people who know their HIV status are still agreeing to be tested in the DHS survey.

There are no plans to include questions about marital history in DHS surveys.

Biases

Men are more likely to under-sampled in DHS surveys because they more likely to be away from home.

Data on HIV prevalence from private ante-natal clinics (ANC) will be subject to different biases from estimates from DHS data.

ANC estimates may under-estimate HIV prevalence in all but the youngest age-group, due to reduced fertility of HIV+ women. (In the youngest age-group, HIV prevalence in pregnant women may be higher than in other women because pregnancy is obviously a marker of sexual activity – which is a risk factor for HIV – and many young women who are not pregnant may not have commenced sexual activity, and hence be at very low risk of HIV infection.)

DHS data may under-represent the most high-risk individuals, and so under-estimate HIV prevalence.

Sex-ratios of HIV prevalence

Sex-ratios of HIV prevalence of participants vary greatly amongst countries. Generally, HIV prevalence is higher in urban areas than rural ones. (‘Rural’ HIV prevalence in the Dominican Republic is high, being inflated by HIV prevalence in commercial plantations.)

It was suggested that, now that DHS data are becoming available, models should be developed to use those data, rather than – or perhaps in addition to – ANC data, which were what were available when the current models were developed, as a medium-term goal.

2. HIV-associated mortality data from Sample vital registration with verbal autopsy (SAVVY)

Use of the SAVVY method in Tanzania was validated by applying it to a sample of cases where the cause of death was known from hospital autopsy.

There is potential overlap with studies carried out by INDEPTH, and attempts are being made to harmonise the survey instruments.

Some vital registration sampling systems only record numbers of deaths, to estimate the proportion of deaths attributable to each cause, and so do not allow estimation of death *rates* due to the lack of denominators. However, SAVVY studies will record population sizes, too.

Data from SAVVY studies are intended to be made widely available, with release after a short delay, as with DHS data.

Diverse sources of funding are being sought, to promote the longevity of the programme.

Often it will not be possible to distinguish deaths due to TB in HIV-positives and HIV-negatives, although this may depend upon on the staff performing each study.

Summary of recommendations

The Reference Group should organise a special meeting on ART, involving experts on ART, and those involved in implementation of ART programmes, as well as modellers. This meeting will need to consider not just the effect of ART on mortality rates of those on treatment, but also its effects on HIV-infectivity and sexual activity of patients, and potential behavioural disinhibition in the HIV-negative population, which are all factors that will affect HIV transmission. It is important to ensure that data collection associated with ART implementation meets modelling needs.

Short-term goals (by end 2006)

- An assessment be made of how common are problems in achieving acceptable fits to data by EPP/Spectrum in the current round of estimation, and a collection of cases of poor fitting be made, to be examined to see if they justify allowing temporal behaviour changes in the fitting.

- Examine whether different types of epidemics have different temporal patterns in sex-ratios of prevalent infections, and whether a sex-ratio close to unity is associated with rapid generalised spread of HIV. Also examine incidence-prevalence relationships, since Spectrum calculates incidence from prevalence.

- EPP be modified to allow demographic changes to occur over time.

- Validate Spectrum's projections of AIDS cases / deaths against data.

- Spectrum should be modified to provide outputs for the HIV prevalence in ages 15-49 and ≥15 years, so that they may be compared. Also the total number of individuals aged >49 years in Spectrum's model population could be output.

Medium-term goals (in 2007-8)

- Estimate survival rates of HIV-positive children, using data from the African cohort studies.

- Examine temporal trends in age-specific incidence to determine if an age-structured model is required, and, if so, to parameterise it.

- Check whether Spectrum is producing reasonable estimates of incidence by age and sex.

- Incorporate into Spectrum standard comparative measures of rates of mortality, orphanhood, etc, in tables/graphs, that can be compared with country-specific data.

- Implement in Spectrum the facility to specify the distribution, by age and sex, of the time-since-HIV-infection of immigrants, since this may be different from the local population.

- Spectrum be given a facility to make projections under different scenarios, so that users can compare the effect of parameter changes with a no-change scenario.

- Modify Spectrum to model ART demand (i.e. numbers eligible for ART), and to model progression from infection to ART-eligibility and then progression to death, with and without ART provision, rather than working backwards from time of death in the absence of ART.

- Modify EPP to incorporate the impact of increasing provision of ART.

- Use UN categorisation of urban/rural for both ANC surveillance sites and estimates of the population distribution, to achieve consistency.

- Identify correlates of different sex-ratios and to determine if there are there regional patterns in the trajectories of the HIV-prevalence sex-ratio.

- An artificial 'DHS' data set should be created using a model, to test how well EPP/Spectrum and other modelling approaches can recreate it.

Long-term goals (by 2010)

- EPP should be developed to model the sexes separately, but this requires data for men – which are currently lacking, since ANC data are used, although DHS data will become available.

- Consideration be given to developing an age-structured model, to replace EPP/Spectrum. However, its robustness would need to be evaluated.

Appendix I: Meeting Agenda

Following an introduction by Karen Stanecki and Geoff Garnett, the following presentations were made to the group. The meeting concluded with a discussion of key topics, chaired by Geoff Garnett.

Monday 25th July	
Welcome	**Karen Stanecki & Geoff Garnett**
Session 1 (Morning)	**Chair: Peter Way**
Description of demography in EPP2, including prevalence in all aged ≥15 years versus 15-49 years	Tim Brown
Description of demography in Spectrum, including differential mortality due to ART	John Stover
Description of demography in ASSA2002	Rob Dorrington
Methods used in UN Population Division's new models	Thomas Buettner
USBC modelling methods	Tim Fowler
Comparison of demographic models	Peter Johnson
Session 2 (Afternoon)	**Chair: Rob Dorrington**
The impact of demographic change on HIV epidemiology over the course of an epidemic	Tim Hallett
Review of earlier proposals to the Reference Group for age structured models, and basis for the Reference Group's decision to develop non-age structured EPP model in 2001/2002	Geoff Garnett
Which life-tables are currently in use by UN Population Division and what was the basis for decisions to accept or reject Timæus's suggestions for recommended life tables for different countries	Ian Timæus & Thomas Buettner
Empirical data on the relationship between HIV/AIDS and demography	Basia Zaba
Urbanization	Hania Zlotnik
International migration	Peter Way
DHS prevalence data: possible bias due to low response rates; overview of distribution of HIV by age, sex and urban-rural areas; new analytic opportunities in linked DHS+ datasets to inform impact of AIDS on demography.	Ann Way

Continues…

Tuesday 26th July	
Session 3 (Morning)	**Chair: Basia Zaba**
DHS prevalence data: how they are used in Spectrum	John Stover
Methods of estimation of adult mortality rates from DHS/MICS and potential for incorporation of these and of vital registration data in EPP/Spectrum to calibrate mortality	Ian Timæus
Potential future use of SAVVY data for calibration of the level and age-distribution of mortality in EPP/Spectrum	Peter Way
Session 4 (Morning & Afternoon)	**Chair: Geoff Garnett**
Discussion of key topics	

Appendix II: List of Participants

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