Future tools for national estimates and epidemiological analyses

Report of a meeting of the UNAIDS Reference Group on Estimates, Modelling and Projections held in London, United Kingdom, 19-20 January 2010

TECHNICAL REPORT AND RECOMMENDATIONS

UNAIDS
JOINT UNITED NATIONS PROGRAMME ON HIV/AIDS
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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 (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.

Kelsey Case, London, April 2010.

Introduction

The Joint United Nations Programme on HIV/AIDS (UNAIDS) *Reference Group on Estimates, Modelling and Projections* exists to provide impartial scientific advice to UNAIDS, the World Health Organization (WHO) and other United Nations and partner organisations 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).

Aim of the meeting
The aim of this meeting was to bring together experts to discuss and review proposals for the suggested developments to the tools currently used for generating national estimates and to identify and discuss new approaches and make decisions on which methods to pursue further for both the short term and longer term in an effort to respond to the need to improve the current approach and to provide the potential to alter the future course of generating estimates.

Approach
The meeting featured presentations of recent data, presentations of proposals and group discussion. The meeting agenda is included in Appendix I.

The meeting was attended by 33 experts, nine of whom presented proposals (see Appendix II for a list of participants). Each contributed, not only data, insights, experience and analysis, but also worked hard to produce a set of recommendations, 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). This transparent process aims to allow the statistics and reports published by UNAIDS and WHO to be informed by impartial, scientific peer review.

1. Background

For the last decade UNAIDS, WHO and their partners have been using the Estimation and Projection Package (EPP), Spectrum and the 'WORKBOOK' to collate and analyse data on the extent and trends of national HIV epidemics. These programmes were initially developed when data sources were limited and often sparse, before treatment was widely available and when most HIV epidemics were still growing or recently stabilising. In response to the changing sources of data, improved understanding of HIV epidemiology and new expectations, for example, estimation of incidence, estimation of the number of people needing ART and PMTCT services, the models have been further developed, in line with a two year cycle of generating new estimates.

1.I Model evolution and key improvements over the past decade

The tools for fitting global epidemics have constantly evolved, responding to new knowledge, improved understanding, evolving surveillance and new needs. The complexity of the task required of these models has made their combined application increasingly problematic.

Estimation and Projection Package (EPP)

In 1997, the Global Estimates made by UNAIDS used Epimodel, a simple model with a 2-point gamma function fit which used point prevalence estimates for 1994 and 1997 and best fit by visual inspection. In order to accommodate additional data and fit to multiple points, EPP was created. The earliest version fit gamma functions (which plummet after the last data point) and was followed by a version with modified gamma functions. The desire to have a more epidemiologically driven model led to the development of the UNAIDS Reference Group Model, now the core of EPP, which began with four parameters and a single interface which continually developed. EPP 2005 incorporated the lessons learned over time adding post-fit calibration to adjust for surveillance data overestimating epidemics building on HIV prevalence data from national surveys, level fits and multi-site fits to address new surveillance sites artificially driving the curve downward and the choice in type of epidemic was added (either generalised or concentrated with turnover in at-risk populations) which helped flatten fits in high turnover populations.

It became evident that many curves can fit the same data thus an uncertainty interface using Bayesian melding was added in EPP 2007 which resulted in long runs, often gave only a few curves and in some cases resulted in zero incidence. At the same time, the focus was shifting from prevalence to incidence, ART access was rapidly expanding and the urban/rural population distribution was changing. As a result, EPP 2009 outputs incidence to Spectrum (instead of prevalence), IMIS (sampling around higher density of curves) was added to accelerate fits, provide more curves and better uncertainties and different models were explored to address zero incidence with phi-shift chosen as the best solution. The model was expanded to include ART and modified to allow for a changing urban/rural population distribution. The issues remaining with EPP include uncertainty in concentrated epidemics, largely related to the size of populations at-risk, population differences as a result of EPP and Spectrum using different demographic models, the need for an improved user experience that is simpler and more efficient to navigate, countries with problematic fits and countries that continue to have sparse surveillance data.

Spectrum

Spectrum was developed in 1995 and released in 1997. Inputs for Spectrum/AIM 1999 included adult HIV prevalence, progression patterns from infection to AIDS death, age distribution of HIV infections, sex ratio of HIV, reduction in the total fertility rate and a perinatal transmission rate. Since this version, input assumptions have been refined, new calculation methods have evolved, links to other datasets have been incorporated, uncertainty analysis was added and reporting functions were integrated.

The underlying demography has evolved from five year age groups (1999) to single age calculations (2001) to the EasyPoj application based on estimates from the UN Population Division (2003) with new estimates of single age mortality implemented in 2007. Prevalence and incidence have evolved from the user entering prevalence (1999) to linking to EPP for prevalence (2001) to inputting incidence from EPP (2009). The sex ratio of adult prevalence now uses the ratio of incidence and Spectrum 2009 includes an age pattern of incidence based on calculations made from DHS data. Progression patterns from infection to AIDS death for both adults and children have continually evolved as more data became available and further analyses were performed.

In 1999 there was a single probability of MTCT. This was updated to include prophylaxis, infant feeding options and the coverage of PMTCT, and then further updated to include new PMTCT options and estimates of efficacy. In Spectrum 2009 breastfeeding patterns and the age-specific effect of HIV on fertility were incorporated based on DHS analyses. Orphan and double orphan estimates have continually evolved over time based on analyses, new data becoming available and the realisation that maternal orphans were not getting counted properly in surveys. Treatment assumptions and survival on treatment have also evolved over time. In 2005 additional outputs were added including tables for adults over 15 years, regional tables and treatment need. In 2009 outputs were added for child age bands.

1.II Current and remaining difficulties with the models used for HIV estimates

In several concentrated epidemics, HIV prevalence estimates do not match reported cases and mortality estimates do not match reported deaths, even after adjusting (e.g. Mexico). Additionally, there are issues estimating prevalence in high risk groups and the size of high risk groups in concentrated epidemics. There is often a change in the size of high risk groups over time, particularly for IDU, while the input in EPP only allows one population size which leads to confusion over which population size (previous or current) to input. There is also the issue of turnover in those who move in and out of a population several times, for example IDU and prisoners. Lack of available data is consistently a problem and countries often have no idea of turnover rates or treatment coverage for high risk groups.

In EPP different fits are obtained using initial guess compared to using “EPP fit” and it is often not clear which fit should be used. Small epidemics with low HIV prevalence do not fit well and there are no uncertainty bounds for concentrated epidemics. It is particularly difficult to fit epidemics where there is a decline followed by an increase in prevalence, Uganda for example. Further, it is unclear when and how to use anchors and most countries only have data from the later years which can cause problems.

In Spectrum, treatment criteria that differs from the default WHO criteria can lead to underestimates of those *in-need* of treatment which further results in discrepancies in treatment coverage estimates. Patterns of breastfeeding may differ depending on HIV status, but the option to use survey data assumes that feeding patterns are the same regardless of status which can lead to overestimates of HIV+ infants (Botswana). Additionally, the size of the uncertainty analysis file in Spectrum can cause problems.

Questions remain over what data should be used for low-risk populations – ANC data or PMTCT data – and also how additional data available can be used as a tool for producing estimates, for example case report data and the results from prevalence among children from surveys.

Discussion

There is a separation between approaches for the short term and those for the longer term. Essential improvements will be done for the 2009 estimates and longer-term approaches will continue with beta versions produced to aid in a parallel process. In thinking of future

approaches, there is a need to separate the models from the software; Spectrum/EPP can absorb different models.

Because EPP does not include aging-out at age 50 or migration, importing incidence from EPP underestimates prevalence. For the short term an adjustment has been added in Spectrum so EPP prevalence matches the Spectrum prevalence, for the long term there will be aging out and migration in EPP. It was also noted that dramatic changes in treatment will have a profound impact on our ability to use prevalence data for estimating incidence. The addition of a prior distribution for incidence, or for an upper or lower bound added to phi-shift was discussed and it was decided that we can infer something about incidence in countries with two or more DHS surveys and that these data may be used to inform bounds for a certain time point.

There is a need and demand to have projections. Donors and countries want to have longer-term projections for planning purposes, to identify resource needs and to consider different future scenarios and the UN Population Division uses projections from UNAIDS for their future demographic projections. In order to make projections, we will first need to produce high-quality estimates.

2. Abstracts of proposals presented

To respond to the need to improve the current approach in the short term and the potential to alter the course in the longer term, proposals for suggested developments to the tools currently used and new approaches to generating national estimates were reviewed and discussed in order to make decisions on the methods to pursue further for both the short-term and longer-term future. UNAIDS operates in 2-year cycles for producing estimates. The proposals and approaches detailed below are designed either to support the 2011 round of estimates for which EPP and Spectrum will be integrated or to provide alternative methods for the later future.

2.I Mortality and incidence in South Africa, Rob Dorrington

The research covered two distinct topics. The first concerned comparing the estimates of the age distribution and total number of AIDS and non-AIDS deaths produced by the UNAIDS model for South Africa with the age distribution and numbers (corrected for under-registration) of registered deaths. This research found that the number of AIDS deaths from the model were nearly double the number identified from the registered deaths and, proportionally, up to 7-9% higher for ages 20-29 and 3-5% lower for ages 40+ than the empirical data, and showed greater change over time than the empirical data. Comparison of the number of deaths due to all causes by age suggest that the UNAIDS model exaggerates the number of deaths in the 0-4 age group and for males at most ages 20+ except 45-49, with a peak of about 10 000 extra deaths in the 25-29 age group. For females adult excess is confined to the 20-39 age range, with a peak of 15 000 excess deaths, also in the 25-29 age range. On the assumption that the total number of non-HIV deaths estimated by the model is correct the excess HIV deaths in the UNAIDS model account for much of the overall excess in the 20-34 age range but the remainder of the excess to age 44 for males and 39 for females suggests that the non-HIV mortality in the model is exaggerated in these ages.

The second topic investigated the possibility of estimating HIV incidence in the national population in South Africa by scaling the prevalence of women attending public antenatal clinics to represent the prevalence in the national population as measure by a national household prevalence survey at three time points. The research found that while the level and or trend in ratio of national to antenatal prevalence in specific age groups was uncertain it had remained remarkably constant (at around 70%) for the age group 15-49 as a whole. Using this result incidence was estimated for each year from October 2000. Incidence appears to have been between 2% and 2.5% until 2004/5 after which it has fallen gradually to around 1.5% by 2007/8.

Discussion

It was highlighted that the mortality coding in South Africa likely does not capture all HIV related deaths and it is probable that many of the deaths reportedly due to TB are actually HIV related deaths. It was also discussed that the recently updated paediatric progression patterns in Spectrum (based on more recent analyses) will likely address the issue of overestimates of deaths in children age 0-4 as the new progression patterns are longer, particularly for those infected around birth. It was suggested that the inclusion of age-specific progression patterns would result in age-specific mortality estimates that would be closer to the age pattern observed among registered deaths.

2.II Applied demographic models, *Nicolas Bacaer and Carel Pretorius*

The authors show a discrete-time age-structured HIV model where incidence depends on age and time and is computed using prevalence, turnover of sexual partners and transmission probabilities. The model is fit to the South African age-specific HIV and mortality data. The model predicts the evolution of the epidemic for the next 10 years.

Outputs such as incidence and AIDS-related mortality can also be compared with estimates obtained using EPP and spectrum.

The assumptions of this model included rapid initial growth (prevalence 1/1000 in 1986) and that the numbers of partners are under-reported with the real number twice that which people report. A transmission probability per partnership is used (no partner formation) with the assumption of 85% transmission from male to female and 50% from female to male. Condom use is included as a rate per partnership. Median survival when infected, in the absence of ART, is 10 years, but mortality is dependent upon when treatment is initiated. Treatment assumptions include ART coverage of 40% of those in need and a relative infectiousness of 1% while on ART. PMTCT was also included.

Intergenerational sex and the spread of HIV
A strong association exists between large age differences among sexual partners and high levels of HIV in many developing countries. An age- and gender-structured deterministic model was used to study the role of intergenerational sex in the establishment of major HIV epidemics. The basic reproduction number is computed as a function of the standard deviation in the age difference between partners. Simulation results suggest a standard deviation of 1.5-2.5 years is required to establish a major HIV epidemic. There is an intrinsic uncertainty attached to all partnering models when small populations are modelled, as is usually the case. A master equation and an approximating Fokker-Planck equation are derived to study fluctuations in partnering models. Variance in partner choice results in correlation between infection in different age categories. This correlation appears to be related to the critical behaviour of the model.

Discussion
Having age-specific data allows for more rigorous testing of the model. The usefulness of this age-structured model is that it is intermediate in its complexity (more complex than EPP) but the entire core of the model can fit into a single sheet. The model has advantages of a simple model and is useful for targeting specific gender/age groups. It was discussed that the model did not fit the data well at older ages (choice of partnerships to be further investigated) and that mortality when on ART would probably further decline in the long term than what is currently assumed.

2.III An age-structured model for projecting ART need in generalised epidemics, *Basia Zaba*

An age-structured model was constructed for projecting ART need for persons infected with HIV in a typical generalised epidemic. The model takes as its baseline the population structure, broken down by age, sex and HIV status based on a nationally representative serological survey.

The model uses the following inputs:

- Standard UN Population Division life table representation of background mortality for those who are not infected
- Weibull representation of age-specific mortality for those infected with HIV based on a hazard analysis of pooled mortality data collected in the ALPHA cohort studies in the pre-ART era
- Current age-specific HIV prevalence obtained from a national survey
- Age-specific HIV incidence, derived from ALPHA models fitted to current prevalence

In order to predict the number of AIDS deaths (post-ART) the model needs the following parameters:

- The ART need definition (defined in terms of number of years before the expected death that we aim to start people on ART)

- An effectiveness assumption about ART selection criteria with respect to the defined theoretical need;
- Proportion currently being treated;
- The baseline ART coverage and recruitment from those with unmet need;
- The incidence trend, which may incorporate assumptions about reduced infectivity due to the ART feedback effect.

These parameters are needed to adapt the ALPHA age-specific mortality model(s) to estimate the number of deaths of those who do not need treatment and the number of deaths of those who have an unmet need. ART programme statistics are then used to estimate the number of deaths of those receiving treatment.

The added value of this model essentially consists of providing an alternative approach bypassing the need to use bio-markers (CD4 counts, viral load) to estimate the number of those who will die if untreated. Estimating such compartmentalised risks is problematic because of small numbers, shifting criteria and uncertainty about when patients achieved a CD4 cut-off level between test dates.

Discussion
Both donors and governments want age-specific estimates of treatment need for programmes. This method is an easy way to separate out incidence and then estimate mortality from these data. The data used were from cohorts in Africa; however, the data from Uganda were quite different and it was discussed that these data may make the case that age-specific mortality will change over time as the epidemic ages. There was also a concern about the generalisability of age-specific mortality when you take it out of Africa and apply it to China for example (where there is less uncertainty about the generalisability of time from infection to death then perhaps age-specific mortality). The data presented were gross rates (they include all other causes of mortality) and thus you would need to have net rates (removing other causes of mortality) in order to use this method in different contexts. The question arose whether you could break down age-specific mortality by CD4 data and it was cautioned that there will be far more limited data if you are using CD4 count data for each age.

2.IV Assessing uncertainty in the size of at-risk populations, *Le Bao and Adrian Raftery*

In most countries in the world outside of sub-Saharan Africa, HIV is largely concentrated in sub-populations whose behaviour put them at high risk for contracting and transmitting HIV, for example, injecting drug users, sex workers and men who have sex with men. The size estimation of those sub-populations is important for assessing the overall HIV prevalence and conducting effective interventions. The authors present a Bayesian hierarchical model for making local and national size estimates of at-risk HIV populations. The model incorporates multiple commonly used data sources including mapping data, surveys, interventions, capture-recapture, estimates from other organizations, and expert opinion. This is the first statistical model for assessing the uncertainty of HIV at-risk population size with a view to improve the estimation of the uncertainty around HIV prevalence estimates in countries with concentrated HIV epidemics. The proposed model is applied to the 2004 size estimation of injecting drug users and female sex workers in Bangladesh.

Discussion
It was highlighted that there is the potential for problems when you only have data from big cities. No weights were applied based on perceived quality of the data, something that can probably be done; however, there will be a large posterior distribution when there is a large confidence interval. Data from 2001 and 2003 were used with the assumption that these data represented the same population size (i.e. population size at different times is not built in). The question was raised of how expert opinion was used and the effect of expert opinion on the estimates coming from other methods, for example multiplier method. It was

discussed that where you have both expert opinion and multiplier method you use the multiplier to verify the validity of the expert opinion and you can also use this difference to inform the variability when there is only expert opinion available. Expert opinion gave an actual estimate, not a band. The prior allowed for a bias that could allow for a factor up to 10.

2.V The effect of correlation between maternal and paediatric HIV survival on the estimation of numbers of AIDS orphans, *Leigh Johnson*

In African countries, model-based estimates of numbers of maternal orphans tend to be around 50% greater than survey estimates of numbers of maternal orphans. This study aimed to evaluate whether deterministic models exaggerate numbers of orphans by not allowing for known sources of correlation between maternal and paediatric HIV survival.

A stochastic model was developed to simulate rates of orphanhood in a cohort of mother-child pairs. In those mothers who are HIV-positive at delivery, maternal HIV viral load was assumed to be correlated with maternal survival, the probability of mother-to-child transmission of HIV and paediatric HIV survival. Maternal access to antiretroviral treatment (ART) is also assumed to be correlated with access to prevention of mother-to-child transmission (PMTCT) services and child access to ART. The model was compared with a model in which no correlation is assumed.

The proportion of children aged less than 18 who are maternally orphaned due to AIDS was estimated to be 11.0% when allowing for correlation and 11.9% when not allowing for correlation – a difference of 7.4%. ART increases the difference, while PMTCT reduces the difference. The difference is substantially greater at young ages, at 47% for maternal AIDS orphans under the age of 5 years.

Correlation between maternal and paediatric HIV survival was not significant enough, by itself, to explain the difference between model-based estimates and survey estimates of levels of maternal orphanhood. Bias in survey responses probably accounts for much of the difference.

Discussion

The main constraint was the need to make sure the survival curves are the same or roughly consistent in the two models (for both maternal survival and paediatric survival in the two models). It was discussed that there were no uncertainty bounds on the correlations, but ratios at the upper range were used thus these estimates are likely to over-estimate the true extent of the bias. Only ART during pregnancy was looked at; the bias increased with ART as a result of the correlation between ART and survival.

2.VI A microsimulation model to assess the reasonability of deterministic model approximations in South Africa, *Leigh Johnson*

Mathematical models have an important role to play in informing HIV/AIDS policy, but uncertainty regarding sexual behaviour assumptions can undermine confidence in the results of these models. While deterministic models have generally not been sufficiently detailed to make use of available sexual behaviour data, microsimulation models have generally been over-parameterized relative to the data available. A deterministic model was developed that is sufficiently detailed to make use of the sexual behaviour data available in South Africa, but sufficiently simple that all parameters can be estimated from the data. Although this model has been shown to provide a good fit to HIV and sexually transmitted infection (STI) prevalence data, as well as sexual behaviour data, a major limitation is that the model does not link individuals who are in partnerships, and this is problematic when evaluating the role of concurrent partnerships in the spread of HIV.

The objective of the proposed research is to develop a microsimulation model that can be used to assess whether the simplifying assumptions in our deterministic model are a reasonable approximation to reality. The model will be similar in structure to the deterministic model, but will link individuals in partnerships and will record each individual's exact age, rather than their five-year age group. All parameter values will be identical in the two models. The microsimulation and deterministic model estimates of the prevalence of HIV and six other STIs will be compared across a number of demographic groups. Other outputs that will be compared include the percentage reductions in STI prevalence due to improvements in STI treatment, the percentage reductions in HIV incidence due to changes in sexual behaviour, and the proportion of the population in each five-year age group. Any differences between the microsimulation and deterministic model outputs that are more than 5% of the microsimulation model estimate will be highlighted as causes for concern.

The key benefit of this work would be increased confidence in the results of the projection models that are used in South Africa, which is one of the few African countries that have sufficient data to support detailed modelling of HIV. These detailed models could serve as benchmarks in assessing whether the models that have been developed by UNAIDS produce reasonable estimates.

Discussion
It was discussed that the process was to initially compare the microsimulation results to the outputs from the deterministic model and then add additional complexity at further stages. The question was raised that if the results of the two models are the same, would this indicate whether we are getting closer to the truth or if it is simply the assumptions made that drive the results? It was highlighted that this is a valid point, one that needs to be tested as the first step. While it was noted that the microsimulation model will not be fit to data; it was mentioned that if you do fit this model to the same data that was used for the deterministic model, you could compare the different values for parameters, and also identify what different parameters can be used to achieve the same outputs and how this might result in different levels of impact of interventions. This tool could also be used to identify if the models are over-parameterised, to identify if there are redundancies and to identify parameters that can be made constant. It was discussed that you could take the results from the microsimulation model and feed them into EPP/Spectrum for comparison and that you could potentially use microsimulation to identify if the simple models are sufficient.

The question was raised as to how this could be useful for countries other than South Africa, especially given the limited available data on behaviour which is necessary for this model. It was highlighted that it can be used to assess the impact of interventions and to create future projections. Additionally, it was asked whether microsimulation might help with the Modes of Transmission (MoT) model. Because the microsimulation model includes a crude measure of concurrency, you could potentially use data coming out of this to inform the MoT model. There is also the potential for this model to inform on concurrency in generalised epidemics.

2.VII Improving tools for national estimates of HIV/AIDS, *Joshua A Salomon and Daniel R Hogan*

Cross-sectional time series on HIV prevalence among pregnant women attending antenatal clinics (ANC) and prevalence estimates from population-based Demographic and Health Surveys (DHS) are the main sources of primary data to inform national estimates of HIV/AIDS in generalised epidemics. UNAIDS, working with country analysts, currently uses the Estimation and Projection Package (EPP) to estimate and predict HIV incidence, prevalence and mortality in generalised epidemics. EPP fits a simple epidemiologic model that has 4 unknown parameters (the date the epidemic begins [*t0*], the initial force of infection [*r*], the fraction of the population at risk [*f*], and the behavioural response to the epidemic [*phi*]). While attractive in its simplicity, the EPP model may impose excessive

constraints on the shape of an epidemic (especially post-peak prevalence) due to its reliance on static values for all parameters.

A modified version of EPP was developed that allows the force of infection parameter *r* to vary over time. A curve for *r* is generated from a linear combination of third degree B-splines with a penalty applied to second differences. The difference penalty imposes smoothness on the shape of *r* over time, thus meeting the weak epidemiological constraint that changes in incidence should be gradual. Since the force of infection can change in this proposed model, the structure of the EPP model was simplified. The new model only requires two risk groups ("susceptible" and "infected"), and the behavioural parameters *f* and *phi* are dropped. Initial results were promising for the four country-regions to which the spline-based model was applied (rural Uganda, urban Uganda, urban Kenya, and urban Rwanda). It appeared to better estimate the peak, fall and levelling of prevalence in rural Uganda, urban Uganda, and urban Rwanda, compared to the EPP model. These qualitative conclusions were confirmed by the calculation of Bayes factors that suggested strong support for the spline-based model over EPP for all four country-regions. The current approach to model fitting involved Monte Carlo Markov Chain (MCMC) with correlated proposals. Although efficient, the use of MCMC required the value of t0 to be fixed (set to 1980) and had some trouble with convergence. Future work will investigate the feasibility of allowing t0 to vary, other fitting algorithms, and ways to make short-term predictions of future prevalence within the spline-based model framework.

Discussion

The splines are fit to r as opposed to prevalence; fitting to prevalence can result in negative incidence, while fitting splines to r keeps this from happening. There was a debate whether a more epidemiologically based method should be used emphasising that there are other ways to get this bounce back effect and it might be better to have an epidemiologically-based argument. However, it was cautioned that you need to be careful with the assumptions made, i.e. what the change is due to that results in the decline or incline, which can then have a large impact on future projections. It was noted that because EPP has artificial exposed/unexposed groups, the r-spline proposal seems more realistic. The objective for this model is to describe recent trends. When the data runs out, the curve follows the trend of the last data point. While you can forecast by continuing on with the same r for a year or two forward, the model requires data and there is limited scope for projection, especially more than two years. This method has not been applied to concentrated epidemics and there is a low probability that this will work well in the concentrated epidemics. There is likely not enough data (struggling to simply get r), but because there is more of a homogenous population in concentrated epidemics (less heterogeneity), it might not be necessary to have this additional flexibility in r. It was noted that the current EPP has IMIS whose convergence is self-modifying. MCMC has problems with convergence so slotting into EPP may solve the convergence problem; however, it needs to be considered for the long term how well the convergence package will work with the new models. The question was raised regarding how this model will function when ART is included, especially where treatment increases rapidly. It was discussed that there was no reason to believe, a priori, that we will be unable to continue to model this with rapidly expanded ART.

It is important to remember that these methods will be implemented by countries so they need to be simple, but this is also why they need to be well tested and robust. The next step of this proposal is to apply this method to additional countries. It was discussed that after the decline due to saturation r is really a direct force of infection thus one can draw a correlation on behaviour and STIs at the end of the curve and compare the r-spline method to behavioural data from a country with good data on behaviour and STIs (e.g. Thailand or data from the Alpha network). This comparison can also be done to test r-spline in concentrated epidemics.

3. Presentations

3.I CD4 compartment approach for modelling ART need in Spectrum

Spectrum needs to accommodate changing ART guidelines. In the past, treatment eligibility occurred at CD4 counts <200 cells/mm^3. The 2009 WHO ART guidelines for adults and adolescents recommend treatment commencing at CD4 counts <350 cells/mm^3 and anyone in WHO clinical stage 3 or 4, with countries encouraged to independently figure out the best way to achieve these guidelines. As a result, Spectrum will need to accommodate the different treatment regimes adopted. The current approach for modelling ART need in Spectrum uses progression curves (Weibull curves) with progression from infection to AIDS death in the absence of treatment, progression from infection to treatment eligibility and progression from eligibility to AIDS death. This method requires different curves for every different eligibility criteria and additionally causes problems with mortality when countries change treatment regimes. To resolve these problems and better allow for modelling ART need in the future, a new method is proposed to track those infected by CD4 compartment.

A national dataset from Kenya of CD4 distribution for those not on ART was used to parameterise the compartments. Annual AIDS mortality assumptions by CD4 compartment were obtained from the CASCADE Collaboration (for CD4 >500 cells/mm^3 and CD4 350-500 cells/mm^3), from Badri et al, 2006 (for CD4 250-350 cells/mm^3 and for CD4 200-250 cells/mm^3) and then fitted for CD4 <200 cells/mm^3. The model fit obtained for Kenya was good and the same method was used for two other countries and compared to CD4 distributions from study sites which also resulted in a reasonably good fit. The advantages of this model are that it allows easy specification of the number eligible for treatment and mortality is not affected by a change in eligibility criteria. The disadvantage is that it is based on a single national dataset and it is not known how well this method will apply to other countries.

Discussion

The benefit of this method is that you do not need to track duration since infection. It was suggested that the model results can be compared with CD4 decline models from the US and UK and the numerous published papers on how CD4 declines over time. It would also be useful to compare the transition rates between CD4 compartments used in other models, bearing in mind there are differences in how these models are set-up, particularly regarding those that allow CD4 counts to increase.

It was highlighted that there is the need to consider that different countries have different starting CD4 counts thus the decline happens in different ways. It was queried whether we know if the decline is related to starting CD4 count and pointed out that we do not have data on starting CD4 count. It was suggested that one way to do this would be to have a starting point depending on the country, then have a decline function. Alternatively, you could work backwards with the data available and not worry about those with CD4 counts above 500.

3.II Estimating incidence from prevalence surveys

The availability of more than one nationally representative, cross-sectional, HIV sero-survey in a country presents the opportunity to indirectly measure incidence. To do this, you need to evaluate the survival of HIV+ individuals from one survey to the next which is difficult because survival is strongly dependent on the distribution of time since infection (i.e. dependent on the course of the epidemic) and dependent on age. There are two proposed methods for calculating the survival of HIV infected individuals and both methods produced similar results. A comparison of the model results with data from the ALPHA network

demonstrated broad agreement of the methods with the cohort data across all age groups (within 95% confidence intervals, and for half the difference was less than 10%). A test with simulated data provided good estimates under a wide range of age patterns of incidence, sudden changes in incidence and increasing coverage of ART. To apply this method with ART you first strip out the effect of ART from the data to obtain the adjusted prevalence and then proceed as normal. The effect of ART is obtained from the total number on treatment, number in the age group, and the age distribution of those on treatment. Theta is the fraction of those HIV infected who are alive due to ART which will vary by country and over time; this parameter is difficult to estimate as it is dependent on time since ART became available and the pattern of ART scale-up.

Discussion

The usefulness of this method is using the results to inform a prior on incidence in EPP for a particular year using the 95% confidence interval. It was emphasised that all of the assumptions work better with a short time interval between the two surveys. The question arose whether it is too difficult to estimate with the inclusion of ART or if it will become too difficult as ART rapidly gets scaled up or reaches high levels in populations. It was explained that if you know who is on ART and who is not then this is a relatively robust method, but if you do not know then this can be a significant problem. The age and sex of those on treatment in public clinics is often available for this and triangulation of different data sources regarding treatment would give greater confidence.

3.III Methods to produce estimates of HIV prevalence and the number of people/percentage undiagnosed

At least three approaches exist for estimating the number of people with undiagnosed HIV. The three methods use different data thus provide independent estimates; for greatest insight the best option is to use all three methods.

1. **Estimates based on prevalence surveys**: HIV prevalence is multiplied by the population size to identify the number with HIV and the number diagnosed is subtracted to obtain the number undiagnosed. Issues with this method include how to divide categories, population size, and issues with prevalence estimates (you need the average level of risk thus if only high risk individuals are sampled to obtain prevalence, you will overestimate the number infected). The benefits of this method are that the assumptions are explicit and that it can provide up-to-date estimates.
2. **Estimates based on reported numbers of HIV diagnoses**, **back-calculation**: Before ART the aim of this method was to identify how many people must be infected, and when must they have been infected, in order to produce the numbers of new AIDS cases observed. A curve from seroconversion to AIDS (based on cohort data) was created to identify the expected number of new AIDS cases per year based on a certain number of people infected. Different assumptions for the number of people infected each year were made to calculate the number of AIDS cases by year and compared to observed AIDS cases then adjusted to obtain the best fit. From this incidence curve, you then subtract deaths to obtain the number living with HIV.

   The *revised back-calculation* method sought to identify how many people must be infected and when must they have been infected, and what must the probability of getting diagnosed have been in order to produce the numbers of new HIV diagnoses observed. A curve is created linking infection to HIV diagnosis. The number of new diagnoses is driven by testing in those asymptomatic and testing as a result of the onset of symptoms/AIDS and will differ by year with increased testing in more recent years thus this curve will change over time and will vary by location. An incidence and diagnosis rate are inferred from the number of new diagnoses; data on CD4 count at diagnosis can help with inferring the diagnosis rate. The advantages of this method are that it does not require prevalence, it is based on routine case reporting data only, it estimates an incidence curve, it provides information on predicted time

from infected in those undiagnosed and it can provide an estimate of diagnosis rates over time.

The *extended back-calculation* approach used in the US is based on the number of HIV and AIDS diagnoses, knowledge of AIDS incubation distribution and HIV testing hazards. The data required are new HIV diagnoses per year (or you have a distribution), the number diagnosed HIV/AIDS in same year and the number diagnosed HIV, no AIDS in same year. You can create distributions of the probability of HIV testing and the probability of AIDS diagnosis and then do iterations to get a "true estimate" of new infections from which you can subtract the estimated number of deaths to arrive at prevalence.

3. **Estimates based on reported simultaneous HIV/AIDS cases:** This method works backward from those presenting simultaneously with HIV and AIDS. For example, if 250 people present with simultaneous HIV/AIDS with CD4 <200 cells/mm^3 and the rate of development of AIDS for those with CD4 count<200 cells/mm^3 is roughly 25 per 100 person years, then there are approximately 1000 people with undiagnosed HIV and CD4 count <200 cells/mm^3. Alternatively, if you know the distribution of CD4 count in those undiagnosed then you can use this distribution instead of individual CD4 count to estimate the number undiagnosed. This method is well-suited for estimating the number of undiagnosed people with low CD4 count.

Methods 2 and 3 rely upon reasonably complete reporting on HIV, AIDS and death from AIDS and require surveillance systems for these events. The methods are enhanced by use of data on CD4 count at diagnosis which will not be available in all new diagnoses. It was discussed that countries in Asia, Europe, North and South America do have the data necessary to use these tools. These methods could be used to reconcile differences in estimates from EPP/Spectrum compared to reported data. Additionally, this method could be explored further with the data available in European countries and potentially ECDC might be interested in applying this method.

It was acknowledged that we do need to reconcile AIDS deaths and that we often do not know how good the data actually is for AIDS deaths. Additionally, there has been a de-emphasis by WHO on reporting AIDS deaths. It was emphasised that you need to be careful using back calculation in areas where ART was not effective ART and that this method will apply in places with good treatment coverage.

RECOMMENDATIONS

Recommendations for implementation during 2010 to support the integrated EPP/Spectrum modelling software for the 2011 round of national estimates (short term) and recommendations for the longer-term development of models (long-term).

1. EPP and r-spline

Short-term recommendations

- Further develop the r-spline method: testing for many countries and testing for concentrated epidemics.
- Further develop the r-spline method to allow for 2-5 years projection.
- Use a country where there is good behavioural data (Thailand) and compare what happens to model parameters at the very end of the r-spline method compared to the behavioural data.
- If r-spline is deemed satisfactory, implement this method in EPP for the 2011 estimates.
- Use incidence obtained by Tim Hallett's method of estimation from two cross-sectional nationally representative surveys to inform priors on the range of incidence in EPP.

Long-term recommendation

- Begin developing a replacement for r-spline; explore the use of a model to replace r-spline in the future with an equation that includes behavioural data.

2. Concentrated Epidemics

Short-term recommendations

- Finish the work on uncertainty surrounding the size of at-risk populations, completing the exercise for all risk groups in Bangladesh and incorporating uncertainty surrounding HIV prevalence estimates in these risk groups.
- Use the example of Ukraine and look at vital registration and possibly survey data of proportions undiagnosed, apply a Bayesian framework (specify a prior distribution on the "truth") and compare estimates.
- Data collection - Add one day to the country workshops (at the start) talking about data quality for all types of data, how to handle data and how to adjust the data.
- Data collection - Look into the quality of mortality data, starting with the countries which have a fairly good vital registration system and testing the level of bias, then moving on to test in countries with lower quality data.

Long-term recommendations

- Implement confidence intervals around estimates of the size of high risk groups and prevalence in high risk groups.
- Explore model development using data on the proportion of HIV infections diagnosed/undiagnosed.

3. Age Structure and ART needs estimation

Short-term recommendations

- Data collection - Collect good data (age and sex) of those on treatment.
- Make use of the additional gender and age-structured data available when fitting, and set-up the models to be able to include these data but also include default assumptions for those countries that do not have these data.
- Develop and test an age-specific, CD4 count bin structure method tracking those infected by CD4 count using a transition rate from each category based on Kenyan data of CD4 distribution and the Alpha network age-specific progression pattern. Two methods should be tested: 1) Modelling time to CD4 count of 350 cells/mm^3, or 2) Modelling from a starting CD4 count of 500 cells/mm^3. Additionally, test to see if one can get a good fit using a constant linear progression through CD4 count bins. Compare the resulting age-specific progression to death patterns to the Alpha network progression patterns.

Long-term recommendations for research

- Quantify the difference in the models with and without age-structure and the resultant impact if we ignore age-structure in the models.
- Create an age-structured model in simple functional form, fitted to the data.
- Explore survival on ART by starting CD4 category
- Explore removing time from infection altogether by obtaining age-specific prevalence from a cross-sectional survey to produce age-specific deaths and estimate treatment eligibility from time from death (by translating CD4 cut-off criteria into years before death and selection efficiency). Use this as a comparative model and for projections.
- Create an entire model de novo that is age-specific for future potential development.

4. Projections

Short-term recommendations

- Hold a future Reference Group meeting on projections to identify what features are needed for these models and to review the models currently used.

Long-term recommendations for research

- Explore models for long-term demographic projections.
- Review the tools currently used for projections (ASSA/Goals) and identify whether we are able to apply them for the longer term.
- Apply current models (Goals/ASSA) and develop new models to produce projections for specific interventions and to explore programme impact on the spread of infection, incorporating the impact of interventions and changes in behaviour.
- Identify a funding source to develop proposals for new models developed specifically for longer-term projection that can include age-structure, interventions and behaviour.

Appendix I: Meeting Agenda

Meeting Agenda: Future Tools for National Estimates and Epidemiological Analyses
London, January 19-20th, 2010

Tuesday, January 19th

Start	Duration	Subject	Speaker
Session 1 - Introduction Chair: Geoff Garnett			
900	10	Opening remarks	Peter Ghys
910	10	Introductions	
920	15	Fitting global epidemics. From Epimodel to EPP 2009: an historical perspective	Tim Brown
935	15	Evolution of Spectrum 1999-2009	John Stover
950	15	Current and remaining difficulties with the models used for HIV estimates	Karen Stanecki/Paloma Cuchi
1005	10	Discussion	
1015	15	Working group discussion - outline of desired model components and sources for input	Geoff Garnett
Session 1 - Proposals Chair: Brian Williams			
1030	20	Coffee break	-
1050	25	Proposal: Age-specific mortality and incidence - Model comparison of results from ASSA2008 vs Spectrum	Rob Dorrington
1115	15	Discussion	
1130	25	Proposal: Applied demographic models	Nicolas Bacaer/Carel Pretorius
1155	15	Discussion	-
1210	25	Proposal: An age-structured model for projecting ART need in generalised epidemics	Basia Zaba
1235	15	Discussion	
1250	55	Lunch	
Session 1 (continued) Chair: John Stover			
1345	25	Proposal: Assessing uncertainty in the size of at-risk populations	Adrian Raftery/Le Bao
1410	15	Discussion	-
1425	20	Proposal: A microsimulation to validate AIDS orphan estimates	Leigh Johnson
1445	15	Discussion	
1500	20	Coffee break	
1520	20	Proposal: A microsimulation model to assess the reasonability of deterministic model	Leigh Johnson
1540	15	Discussion	
1555	25	Proposal: Modifications for EPP	Dan Hogan/Josh Salomon
1620	15	Discussion	
1635	25	Group discussion, all proposals	
1700	5	Close	Geoff Garnett

Wednesday, January 20th

Start	Duration	Subject	Speaker
900	15	Summary of Day 1	Geoff Garnett
Session 2 - Presentations Chair: Josh Salomon			
915	15	Spectrum updates - CD4 compartment approach for modelling HIV infection in adults	John Stover
930	10	Discussion	
940	15	Estimating incidence from prevalence surveys	Tim Hallett
955	10	Discussion	
1005	20	Coffee break	-
1025	20	Methods to produce estimates of HIV prevalence and the percentage undiagnosed	Andrew Phillips
1045	20	Methods to produce estimates of HIV prevalence and the percentage undiagnosed in the US	Rick Song
1105	10	Discussion	-
Session 3 - Group discussion and consensus on future tools Chair: Geoff Garnett			
1115	15	Discussion questions	
1130	75	Working group discussion	
1245	60	Lunch	
1345	75	Working group discussion	-
1500	20	Coffee break	-
1520	60	Working group discussion	-
1620	30	Consensus, recommendations and forward direction	
1650	10	Close	Geoff Garnett

Appendix II: List of Participants

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