Improving parameter estimation, projection methods, uncertainty estimation, and epidemic classification

Report of a meeting of the UNAIDS Reference Group on Estimates, Modelling and Projections held in Prague, Czech Republic, November 29th – December 1st 2006

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.

Dr Peter White, London, March 2007.

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).

Aim of the meeting

The aim of this meeting was to bring together experts to produce recommendations on a range of topics, including methods of parameter estimation; development of estimation and projection tools; interpretation of HIV prevalence in general population surveys in generalised epidemics and mixed concentrated/generalised epidemics; trends and alternative data sources; and the relationship between epidemic categories and transmission dynamics.

Approach

The meeting featured both presentations of recent data and group discussions, which focused on specific technical issues. Presentations and discussion topics are listed in Appendix I.

The meeting was attended by 31 experts from 12 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). This transparent process aims to allow the statistics and reports published by UNAIDS and WHO to be informed by impartial, scientific peer review.

Estimation and projection tools and parameter estimates

1. Survival of HIV-infected patients on antiretroviral therapy (ART) in lower and middle-income countries (LINCs): a systematic review

In the context of the scaling up of programmes offering ART to HIV-infected patients in LINCs, few data are available so far on survival after treatment initiation. A systematic review of published reports on survival among HIV-infected patient on ART in LINCs, especially those reports investigating the factors associated to mortality in adults and children, was conducted.

Three readers independently extracted data from articles that were selected after screening of PubMed™ up to October 2006 and abstracts of the 2004-2006 international and US HIV/AIDS Conferences. Observational cohorts and clinical trials were eligible as long as the studies took place in LINCs. The details recorded included patients demographic characteristics, baseline CD4 count, survival estimate and factors associated to mortality on ART.

For adult patients, a total of 24 articles were included in this review among 177 screened. Twelve months after starting ART, the probability of survival ranged from 0.74 to 0.94. It was generally lower in patients starting ART with CD4<50 cells/µl (range 0.67-0.91). The factors associated to poorer survival were low CD4 count<200 (14 reports out of 14 studying this factor), advanced WHO stage 3 and 4 (9/11 reports), low body max index (4/6 reports), low haemoglobinaemia – with different cut-off values (5/6 reports), male gender (3/7 reports) and poor adherence (1/1 report). The incidence rate of death was higher in the first three months following the initiation of ART (from 5.1 to 37.3 per 100 person-years among five reports). In children, only four articles could be included among 23 originally selected. The six-month survival after ART initiation varied from 0.91 to 0.95. A low CD4 percentage was associated to poorer survival on ART.

ART treatment programme in LINCs have survival rates comparable to those reported in developed countries in the early phase of ART introduction 10 years ago. However, the frequency of patients lost to follow-up in the reviewed articles is of serious concern to fully interpret their findings. Furthermore, little or no data were available on survival according to the different first-line drug regimens prescribed and the treatment switches that occurred in the first year on ART.

There are a number of gaps in our knowledge including causes of HIV-associated death in children and the effect of HIV subtype on mortality. More data need to be collected on the causes of loss to follow-up, since the rate is comparable to the rate of confirmed HIV-mortality, meaning that if loss to follow-up is commonly due to HIV-mortality then this rate could be much higher than currently estimated. Work is needed on the survival of patients on second-line therapy.

The meeting recommended that for modelling the survival of patients on ART in LINCs, the above survival probabilities for adults and children be considered, as well as additional data that were expected by February 2007, including on the survival probability during a second year of ART. Due consideration should be given to the impact of losses to follow-up on estimated survival probabilities.

2. Estimates of the time from ART eligibility to death in the absence of ART

To monitor progress towards universal access and targets set by countries we need to know not only how many people are receiving antiretroviral treatment (ART), but also how many people are in need of treatment.

The World Health Organization (WHO) recommends ART for HIV infected people with a CD4 cell count <200 cells/µl, for those in clinical stage III with a CD4 cell count < 350 cells/µl, and for those with a diagnosis of WHO stage IV disease. Current UNAIDS/WHO estimates of the number of people in need of treatment are based on a median survival time from infection to death of 9 years and the assumption that adults with advanced HIV infection who fit eligibility criteria for treatment would die of AIDS in about 2 years if not treated.

A literature review of estimates of the survival time from ART-eligibility to death in LINCs published 1990-2005 was conducted. There was large variation in the time from CD4 count <200 cells/µl to death and from 200-350 cells/µl combined with stage III disease to death. Modelling based on the results from the review and data from the Swiss HIV cohort study suggests an estimated 2.9 years from CD4<200 cells/µl to death, and an estimated 2.7 years from 200/µl <CD4<350/µl combined with stage III disease.

Two community-based assessments of ART eligibility were used to explore assumptions of time from ART eligibility to death of 2 and 3 years respectively. In Orange farm, South Africa, 11.4% and 17.1% of HIV-infected adults respectively were estimated to be in need of ART compared to 9.5% observed in the study based on an eligibility criterion of CD4<200/µl. In Karonga district, Malawi, 17.7% and 25.4% of HIV-infected adults respectively were estimated to be in need of ART compared to 24% observed in the study based on an eligibility criterion of CD4<200/µl or clinical WHO stage III or IV.

The Reference Group recommended that the time from ART-eligibility to death be increased to 3 years (8 years post infection onset with median life expectancy of 11 years).

3. Towards improved uncertainty bounds: implementation of of Bayesian melding in EPP

At the Reference Group meeting in Glion, Switzerland, in July 2006 it was decided to use Bayesian melding for uncertainty assessment in EPP, subject to the resolution of some outstanding issues. Progress was reviewed at an interim subgroup meeting in London in October 2006, where it was agreed that the best single estimate from Bayesian melding was the maximum a posteriori (MAP) estimate. Bayesian melding has been implemented in EPP for generalised epidemics (work is on-going for implementation for low-level or concentrated epidemics). This is an additional feature and EPP can continue to be used for curve-fitting as before. For Bayesian melding the user specifies ranges of values for the different parameter values and can specify constraints on the plausible range of prevalence outputs, speed of epidemic, etc. Although computing power requirements are increased, the process is still acceptably fast on computers that are available to most country teams.

The Reference Group recommended that the default priors should be:

- t_0: uniform (1970, 1990)
- f_0: uniform (0, 1)
- r: uniform (0, 15)
- φ: logistic (100, 50)

Fitted parameter values from the last round of estimation should be collated and examined to determine if other prior distributions should be recommended.

The advanced user should be allowed to alter all of the priors, and the plausibility limits on prevalence, etc. These features should be accessible via an "advanced" button. There is a need to develop recommendations for adjusting priors.

At least 200,000 samples should be taken from the priors, and at least 10 unique plausible curves should be generated for resampling weighted by likelihood. If the initial sampling of 200,000 does not produce 10 unique plausible curves then the user should be given the option to do more initial sampling. For efficient memory use, curves with zero likelihood should not be stored since they will not be selected resampling anyway. It was recommended that adaptive sampling for priors, to improve efficiency, be investigated.

To account for uncertainty in prevalence estimates from individual ANC sites, it was recommended to have both beta-binomial and probit estimation, with probit being the default. The capacity to change this setting should be an "advanced" option.

For combining data from different areas of a country, the current approach should be used for the time being, but further work needs to be done, including considering how to combine data from multiple countries.

4. Other changes to EPP

Other changes already made to EPP or proposed for implementation include: improvements to the fitting algorithm; modifications to increase the speed of execution; implementation of a 'review' mode for projections; adding the possibility of allowing the epidemic growth rate parameter, *r*, to change through time; changes in approaches to calibration of national surveys; implementation of antiretroviral therapy; and other user interface changes.

5. Changes to Spectrum

The Spectrum software package is being updated in several ways to support the next round of estimates. These changes include:

(i) a revised demographic projection module developed in consultation with UN Population Division, US Census Bureau and University of Cape Town;
(ii) revised AIDS module which segregates the population into HIV categories (not infected, asymptomatic, in need of treatment, on first line ART, in need of second line ART, on second line ART, on co-trimoxazol) and tracks duration in each state;
(iii) new patterns of progression that define progression from infection to need for treatment, from need for treatment to AIDS deaths without ART, from first-line ART to need for second-line, and from second-line ART to AIDS death;
(iv) possibility to enter data for up to three national surveys on the age and sex distribution of prevalence;
(v) new ways of setting ART targets;
(vi) new procedure to estimate the uncertainty around estimates.

There are various options for estimation of ART need under different scenarios.

It was commented that the option to specify different PMTCT programmes with different efficacies should be provided.

Sex-differentials in the distribution of age at infection are not universal. In generalised epidemics, females are usually infected at younger ages than males, through sexual transmission. In concentrated epidemics with sexual transmission this will also be the

case, but in concentrated epidemics in injecting drug users, e.g. in Russia, it may be males who are infected at younger ages. This is important since survival time post-infection decreases as age-at-infection increases, and female survival is usually assumed to be longer than male survival due to this age-at-infection effect.

Although factors such as HIV subtype, CD4 count, 1st- or 2nd-line ART affect survival, these factors are implicitly accounted-for in the current survival rates. Furthermore, at present there are too few data to determine how survival rates would be affected - and too few data from individual countries to know which survival rate estimate to use. Therefore the current system is satisfactory at present.

6. Survival of untreated HIV+ individuals: report from a meeting of the Alpha network

Few reliable measures of survival following HIV infection are available for developing country populations because of the difficulties of identifying suitably large numbers of sero-converters and following them up over time.

Eight longitudinal observational studies pooled data on new HIV infections, person-years of follow-up and deaths. Four of the studies are community-based: Masaka and Rakai in Uganda, Kisesa in Tanzania and Manicaland in Zimbabwe; two are occupational cohorts: South African miners and Thai military recruits; and two are clinic based cohorts: Thai blood donors and Haiti STI clinic patients. An effort was made to use uniform definitions of exposure and censoring. Kaplan-Meier survival functions were computed for each site, and Weibull curves fitted to extend the observed values to obtain estimates of median survival age. Comparisons were made of survival times for males and females and for people infected before and after age 30. Observed survival patterns were adjusted for background mortality based on mortality patterns for uninfected persons drawn from the same populations.

Studies contributed observations on over 3,500 sero-converters with a total of 18,000 person-years of follow-up, and a maximum follow-up time of 13 years. Proportion alive 7 years after infection ranged from 54% (Thai blood donors) to 72% (South African miners), directly observed median survival times were available for 5 sites and ranged from 7.4 years (Thai blood donors) to 10.5 (South African miners), when Weibull fits were used to extend the observation range the upper range for the median estimate was even higher, with the Kisesa cohort (Tanzania) predicting a median survival time of 11.4 years. Apart from the Thai blood donor cohort, sites with enough data to contrast survival time by age at infection showed significantly shorter survival for those infected at older ages. Contrasts by sex were less marked, in Kisesa and Rakai where women appeared to have a survival advantage this could be explained by earlier age at infection. Adjustment for age at infection sharpened the difference between the African cohorts on the one hand, and those from Thailand and Haiti. Net survival adjustments calculated for studies that had survival data for uninfected controls suggested that notable differences remained between the study populations after allowing for background mortality, though statistical tests for these differences have not yet been developed.

The results above should be viewed as provisional, since the studies have different rules for follow-up of those who leave the study population, and measure sero-conversion times with varying precision because of different frequencies of serological testing. More work is under way to estimate the effect of resulting biases and to adjust for these where possible. Some of the survival contrasts may be due to virulence of different strains of HIV that dominate these populations.

The Reference Group recommended that median survival of HIV+ individuals should be increased to 11.5 years for females and 10.5 years for males for all countries with generalised epidemics. For Thailand, where subtype E dominates, the default

median life expectancy should remain 9 years. These recommendations should be reviewed in the light of new evidence as it becomes available.

7. Diverse age patterns in HIV incidence rates in Africa

Few direct measurements of HIV age-specific incidence are available for general populations. Estimates based on back-calculations from prevalence are unreliable, particularly at older ages, due to HIV-related mortality.

Four longitudinal community-based observational studies (Masaka – Uganda, Kisesa – Tanzania, Manicaland – Zimbabwe and Hlabisa – South Africa) pooled data on new infections and person-years at risk, using uniform definitions of exposure and censoring. Kaplan-Meier curves for age-cumulated infection risk at each study site were calculated. Instantaneous hazard functions were smoothed using centrally weighted moving averages. Sites with longer time series of data categorised results by decade of observation. Age-specific rates were normalised to a value of one at the first maximum, and ages re-calculated relative to this peak age.

Peak incidence rates ranged from under 1% (Masaka) to over 10% (Hlabisa). Peak ages clustered around 29 (males) and 24 (females), with slightly older distributions in Southern Africa. On the normalised scales the build-up of incidence by age prior to the peak, appeared remarkably uniform for females, slightly less so for males whose broader peaks are harder to locate precisely. At ages following the peak, patterns are more diverse, though widening confidence intervals due to lower values of person-years observed at older ages reduce the significance of differences between sites. In East African sites secondary peaks emerge at older ages for males and females after 2000.

Broadening of incidence age schedules over time runs counter to expectations of gradual elimination of risky behavioural traits at older ages. Secondary peaks may be due to high infection rates among divorced and widowed persons who become relatively more numerous as the epidemic progresses.

It is important to note that the lifetime risk of HIV acquisition (the proportion of individuals who will acquire HIV at some time in their lives) can be much higher than the prevalence of infection (i.e. the proportion of individuals with HIV at a point in time) due to earlier death of HIV-positives.

It was recommended that the age-incidence patterns from these studies be compared with Spectrum patterns.

Interpretation of HIV prevalence in general population surveys in generalised epidemics

1. Comparison of country-level ANC prevalence and survey prevalence in countries with generalised epidemics

Estimates of HIV in countries with generalized epidemics are generally based on data collected over time from women attending antenatal clinics. In recent years, several countries have also conducted national population based surveys (including Demographic and Health Surveys) in which HIV testing has been included in an attempt to obtain more representative estimates of HIV prevalence. Results from national surveys can be combined with data from antenatal clinic surveillance to determine the relationship between them. Time trends in HIV prevalence obtained from antenatal clinic surveillance can then be scaled to determine time trends in the general population.

Estimates of HIV prevalence from population based surveys were compared with estimates based on antenatal clinic surveillance for countries in sub-Saharan Africa in which national surveys have been conducted. Ratios of HIV prevalence in surveys relative to prevalence based on antenatal clinic surveillance were calculated to determine adjustment factors for urban and rural settings. These adjustment factors can be used to correct ANC estimates in countries where population based surveys have not been carried out.

For most countries with generalised epidemics ANC prevalence exceeds the general-population prevalence. Bias may have a geographical component: e.g. a study in Ethiopia found that prevalence in the general population was higher closer to ANC sites.

2. Comparing observed and projected paediatric HIV prevalence estimates, Uganda 2004

National paediatric HIV prevalence estimates are usually estimated indirectly by triangulation of adult HIV prevalence estimates, mother-to-child transmission probabilities and paediatric HIV disease progression tables. In Uganda, a large population-based sero-behavioural survey was conducted in 2004/5 that sampled both adults and children (aged 0-59 months) and collected blood for HIV testing, thus providing an opportunity to compare the paediatric HIV prevalence as observed in the survey with a projected estimate using adult HIV prevalence data from ANC surveillance and from the 2004/5 survey. The survey's response rate among females was 89% and analysis of non-response data suggested that bias due to non-response likely was minimal. 10,561 adults and 9,540 children were tested for HIV; the weighted adult HIV prevalence was estimated at 6.4%. In EPP, HIV prevalence data from ANC surveillance were input and a HIV prevalence curve over time was obtained. HIV prevalence was calibrated with the UHSBS-based HIV prevalence estimate for 2004. In Spectrum, census data, PMTCT programme data and the EPP-derived HIV prevalence data were input; the probability for MTCT was estimated at 25% without intervention, and at 17% with nevirapine (coverage in 2004: 8%). The Spectrum-default paediatric HIV progression table was used. The number of children under five years (denominator) and the number of HIV-infected children under five (numerator) was obtained, resulting in a HIV prevalence of 0.9% among children, compared to 0.7% as measured directly in the survey. Lowering the MTCT rates to 19% (and 15% with nevirapine) in Spectrum would result in a projected paediatric HIV prevalence of 0.7%, similar to that observed in the survey. Alternatively, a more rapid progression to disease and death in HIV-infected children may achieve a similarly lower HIV prevalence.

This study did not indicate any fundamental problems with Spectrum and does not require any modifications to be made. Where availability of data allows, more comparisons such as this should be performed.

3. Recommendations (generalised epidemics)

- All national surveys should do an analysis of bias introduced by non-participation, and should record at least the age and sex of non-participants; ideally more information would be collected.
- For calibration in EPP, adjusted prevalence estimates should be used for each sub-population, where available.
- Further research is needed into adjustment factors for high-risk groups that are likely to be under-sampled (e.g. FSW). It may be a function of the baseline HIV prevalence. Studies should be on-going so that recommendations can be kept up to date as data availability increases.
- For countries with generalised epidemics that do not have national survey data, ANC prevalence should be adjusted based on the ANC:survey prevalence ratio, separately for urban and rural areas. The range of variation in the observed ANC bias should be discussed in training workshops so that countries are aware of the importance of the effect. Users should be able to alter the adjustment factor.
- There is a need to consider the ANC-uptake rate in the particular country to see how this affects the relationship between household and ANC prevalence. The characteristics of those attending ANC in countries with a national survey should be investigated, so that these characteristics may be used to derive the relationship in countries without survey.
- Children should not be included in national surveys for the purpose of monitoring HIV prevalence since the information gained does not justify the cost involved.
- Estimation of uncertainty for countries without survey should use data from countries that do have national survey and ANC data to scale EPP fits. The distribution of differences between probit(survey) and probit(ANC) needs to be examined, with the best estimate being based on the average difference. If a parametric distribution fits the data then the adjustment factor can be resampled from that distribution; otherwise it should be drawn from the observed data (each country with equal probability).

Do household-based general-population surveys in concentrated epidemics underestimate HIV prevalence?

1. Background

There is concern that in concentrated epidemics (including in epidemics with relatively high prevalence levels, e.g. of up to 2%) household-based prevalence surveys may under-represent high-risk groups and hence underestimate HIV prevalence. A session addressed this question by looking at some particular cases.

2. Overview of comparisons of HIV prevalence in household surveys and ANC in south India

In India, HIV Burden is estimated using sentinel surveillance data. Its ability to reflect HIV status in the community is frequently debated. Some independent research groups undertook Community/household surveys, to determine the population based estimates of HIV prevalence, in some parts of South India. This presentation attempts to compare results of household surveys with those obtained through sentinel surveillance in the respective areas in the corresponding years. Wherever possible, sampling techniques used, profiles of recruited population and non-response rates of the household surveys were considered. Out of six household surveys conducted so far, the results of the NFHS-3 are not available yet and the results of the remaining five surveys will be presented.

In 1999-2000, Kang et al (2005) tested 2870 individuals aged 15-40 years, drawn from 88 villages (block) of Vellore district by cluster sampling. Response rate was 87.7% in urban areas and 94.8% in rural areas. Overall prevalence was 1.01% (Rural – 0.66% and Urban – 1.4%). There was no antenatal site for surveillance in Vellore district in 1999. Prevalence of HIV in the State was in 1999 was 1.6%. An antenatal site was established in that district in 2001 and the observed prevalence in that year was 0.8%. However, if adjusted for urban rural distribution of the study sample, it worked out to be 1.3%.

Thomas et al (2002), in a household survey of 1981 individuals (1157 women and 824 men of 15-45 years of age) selected by cluster sampling, observed 1.8% prevalence of HIV in three randomly selected districts of Tamil Nadu in 2001. Among women, the observed prevalence was 2.1. Out of these, only one district had antenatal site in 2001 and, therefore, the results were compared with overall prevalence of the state which was 1.4%. However, the selected sample had rural bias (urban: N=566, P=0.8%, Rural: N=1415, P=2.2%) as against the predominantly urban population in sentinel surveillance (urban=2397, rural=1600). After adjusting for the rural urban distribution, the prevalence works out as 1.36%.

In a third survey conducted by APAC in 2003, among 1318 individuals drawn from six districts of Tamil Nadu, HIV prevalence was observed to be 0.7%. As per sentinel surveillance, median prevalence was 0.75% and mean prevalence was 1.0%. However, when the pooled prevalence for the six districts surveyed was 1.5%. Following rural urban adjustment also, the prevalence remains as 0.8%.

In 2004, household survey was conducted in three randomly selected blocks of Bagalkot district of Karnataka, covering a population of 6700 persons in the age range of 15-49 years (Moses et al, 2006). Overall prevalence of HIV in this population was 2.9%. Corresponding pooled prevalence in two antenatal sites in the district was 2.6%. (Bagalkot 2.7%, Jamkhandi 2.5%).

In 2004, a household cluster survey was conducted in Guntur district of Andhra Pradesh in which 12,617 individuals in the age range of 15-49 years was conducted. Response rate was 91.2%. Overall prevalence rate was observed to be 1.7%. Corresponding prevalence among 800 antenatal mothers covered in two sentinel sites in the district was 2.5% (Guntur 3.5%, Narasaraopet 1.5%).

3. Issues in the estimation of HIV/AIDS burden and related mortality in India

The estimated number of HIV infections in India has been on sharp increase since the first reported case in 1986 and crossed 5 million in 2003. The programme planners started focussing their attention to the care and support of the HIV infected as well as on the social and economic burden due to the impact of the epidemic. For implementation of such programmes, estimates of number of deaths, orphans and vulnerable children due to AIDS, number of children and adults needing treatment etc. has become the essential requirement. However, these estimates are largely dependent on the estimated number of HIV infections (which has always been under increasing scrutiny, and criticised as too high, too low or simply the result of political expediency) and the impact of treatment programmes.

The current exercise aims to compare the AIDS deaths estimated by spectrum when basic prevalence estimated with different assumptions are input. The assumptions have been reviewed on the basis of behavioural surveillance data and other information available from literature. Current assumptions used for estimation in India are aggregated for states at three levels of epidemic stages while they are highly variable across the states. Hence the current model tries to adjust the population according to their exposure to infection and adjust the prevalence to the exposure level. For example, prevalence observed from STI patients are on the higher side as they are referred to the STD clinic at advanced stage of infection.

UNAIDS's Estimation and Projection Package has two different models for generalised and concentrated epidemic countries. However, both the models are not fully appropriate for India because (i) HSS in India is not carried out separately for urban and rural areas to use the generalised model and (ii) Prevalence and population size for all high risk groups are also not available for all states. Hence, state-specific assumptions for size of risk groups and adjustment on prevalence for respective risk groups are likely to provide more-realistic estimates.

4. The HIV/AIDS epidemic in India: force, growth and mortality

Spread of the HIV/AIDS infection continues to be a global concern as the epidemic has established itself in the general population in many countries. However, the extent of real burden is still anybody's guess though every country tries to arrive at a number based on incomplete observed prevalence. Current method of estimation of HIV burden in India applies the observed prevalence to the estimated population of the respective risk groups directly and the model based estimation assumes an initial value of transmission parameters to fit the curve by iteration. However, the results vary for different initial values.

The current exercise aims (i) to estimate the transmission rate (force of infection) between two high risk behaviour groups and from bridge population to general population using observed prevalence, (ii) to estimate the growth of the epidemic using the force of infection and (iii) to estimate the mortality due to AIDS.

The methodology involves obtaining the growth of HIV prevalence within risk groups using either regression method or probability distribution. Assuming that the observed prevalence in each risk group at a point of time is independent and is a

representative random sample of the total infections in particular risk group, the rate of spread of the infection between groups over time can be obtained. Using the growth rate within risk groups and transmission rate (force of infection) between risk groups, the number of infections over time is obtained. Mortality due to AIDS is obtained applying Weibull probability of incubation and death.

5. Is the HIV burden in India being overestimated?

HIV burden among adults in India is estimated officially by direct extrapolation of annual sentinel surveillance data from public sector antenatal and sexually transmitted infection (STI) clinics and some high-risk groups. The validity of these extrapolations has not been systematically examined with a large sample population-based study.

13,838 persons age 15-49 years from 66 rural and urban clusters were sampled using a stratified random method to represent adults in Guntur district in the south Indian state of Andhra Pradesh. The sampled persons were interviewed and provided dried blood spots which were tested for HIV antibody, antigen and nucleic acid to estimate HIV prevalence. This prevalence estimate for Guntur was compared with the estimate derived from sentinel surveillance data. Plausible correction factors for the sentinel surveillance data were determined from these data, and applied to the four major HIV states in India (Andhra Pradesh, Maharashtra, Karnataka and Tamil Nadu) to examine the impact on the overall HIV estimate for India.

12,617 persons, 91.2% of the sampled, gave a blood sample. Adjusted HIV prevalence was 1.72% (95% confidence interval 1.35-2.09%); men 1.74% (1.27-2.21%), women 1.70% (1.36-2.04%); rural 1.64% (1.10-2.18%), urban 1.89% (1.39-2.39%). HIV prevalence was 2.58% and 1.20% in persons in the lower and upper halves of a standard of living index (SLI). Among women who were pregnant during the past 2 years, the 21.1% who utilised antenatal care in large public sector hospitals that participate in sentinel surveillance had an over-representation of the lowest SLI quartile (44.7%) and 3.61% HIV prevalence versus 1.08% in the rest; HIV prevalence was higher in the former even for the same half of SLI (lower 4.39%, upper 2.63%) than in the latter (lower 1.06%, upper 1.05%) due to referral of HIV positive/suspect persons by private practitioners to public hospitals. The sentinel surveillance method (HIV prevalence: antenatal clinic 3%, STI clinic 22.8%, woman sex workers 12.8%) led to an estimate of 112,635 (4.38%) 15-49 years old persons with HIV in Guntur district, which was 2.5 times the 45,942 (1.79%) estimate based on our population-based study. Application of conservative correction factors derived from this study reduced the 2005 official sentinel surveillance based HIV estimate of 3.7 million 15-49 years old persons in the four major HIV states in India to 1.5-2.0 million, which would drop the official total estimate of 5.2 million 15-49 years old persons with HIV in India to 3-3.5 million.

The official method used in India led to a gross overestimation of HIV burden in Guntur district. The reasons for this, in the order of importance, were addition of substantial extra HIV estimates from STI clinics, the common practice of referral of HIV positive/suspect persons to public hospitals, and a preferential use of public hospitals by lower socioeconomic strata. Plausible and cautious extrapolation of these trends suggests that India is likely grossly overestimating its HIV burden with the current official sentinel surveillance based method. This method needs revision.

6. Variability in HIV prevalence, risk behaviours and size of core groups in Karnataka, a southern Indian state

The observed variations in the prevalence of HIV, risk behaviours and size of the groups at risk at the regional or state level in India masks important small area variations which exists at the district and sub-district level. The HIV prevalence among antenatal women in Karnataka varies substantially by district, ranging from less than 0.05% in Haveri and Dakshina Kannada to a prevalence greater than 2% in 6 contiguous districts in the North. The estimated number of female sex workers (FSWs) and men who have sex with men (MSM) per 1,000 adults in these high-prevalence districts is 8 or higher.

The sub-district variations were studied using the data from the district of Bagalkot. There are an estimated 7,280 FSWs in Bagalkot district (17.1 per 1,000 adult males), with 87% living and working in rural areas. The relative size of the FSW population varies from 9.6 to 30.5 per 1000 adult males in the six sub-district administrative areas (Talukas). FSW populations are highly clustered; 15% of the villages account for 54% of all of the rural FSWs. The degree of clustering is similar across all of the Talukas (Gini coefficient ranging from 0.45 to 0.47). Talukas with fewer and larger villages have larger clusters and more FSWs overall. The proportion of men reporting previous sexual relations with an FSW was highest (18%) in the Taluka which also had highest number of FSWs per 1000 adult males. General population HIV prevalence is highest in the Taluka with the highest relative FSW population.

Estimates of populations affected with HIV should take into account these small-area variations. Programmes should be scaled up to reach FSWs in rural areas, and should focus on those districts and sub-district areas with large concentration of FSWs. More research is required to determine the distribution of FSWs in rural areas in other regions of India.

7. Maharashtra and Tamil Nadu AVAHAN studies: size of group and HIV prevalence for groups with high risk behaviour and their relation to HIV prevalence in the community survey

The objectives were to review the availability and comprehensiveness of data on HIV prevalence, size and risk behaviour among high risk groups in Andhra Pradesh and Tamil Nadu and to explore question of whether household surveys are likely to miss members of high risk groups. Many organisations assisted in this process, including AIDS Prevention and Control Project, APSACS, ASCI/HIV/AIDS Alliance/INSP, Avahan Project Partners, India National AIDS Control Organization, Resource Center for Sexual Health & HIV, Tamil Nadu AIDS Initiative (TAI)/Voluntary Health Services, and USAID.

High-risk groups have only recently been included in sentinel surveillance. Although they may represent only a small proportion of the total number of HIV-infected persons, they represent a much larger proportion of the force of infection and so it is important to have effective monitoring. There is potential for substantial ‘bridging’ between risk groups, with many MSM having male casual and commercial sex partners, as well as wives. In addition many FSW have husbands. FSW may be under-represented in household surveys because many are not at home when surveys are conducted, even though some FSW are home-based.

8. Recommendations (low-level and concentrated epidemics)

- Population surveys should be adjusted for groups that are not sampled or under-sampled. The method of adjustment requires development, which requires information on: the (i) total size of high risk groups; (ii) proportion of each high risk group missed in the survey; (iii) HIV prevalence in each high risk group; (iv) measured prevalence in the survey.
- It is recommended that if ANC prevalence is <1% then a survey should not be performed, but if such data are available then they should be used.
- Surveys should perform an analysis of non-participation bias.
- For estimates in countries with an epidemic like India, the Workbook method should be used, with EPP used for comparison for research. A consultative meeting is required to estimate sizes of high-risk groups and their HIV prevalence.
- Prevalence trends in countries with an epidemic like India should be estimated by applying Workbook retrospectively, additionally informed by an analysis of trends in consistent surveillance sites. The trend should be calibrated using data from the adjusted national household survey. AIDS-related mortality should then be estimated using Spectrum.
- Uncertainty estimation requires data on risk group sizes and HIV prevalence from household surveys. For countries without these data, recommended ranges need to be based on a meta-analysis of published literature.
- To determine trends, prevalence point estimates and ranges from each round of estimation are required. A logistic, or double-logistic, curve should be fitted, as appropriate, and then input into Spectrum.

Trends and alternative data sources

1. Estimating incidence from prevalence

HIV prevalence data are much more common than data on incidence, yet clearly the two types of data are closely related. Incidence data are needed to determine the current rate of spread of the HIV epidemic, since prevalence is determined by past infection and mortality rates and therefore it would be useful to be able to derive reliable estimates of incidence from sequential prevalence data

Three alternative mathematical approaches were investigated, based on:
(i) demographic accounting in a real cohort;
(ii) variable growth rate methods for cross-sectional age groups; and
(iii) synthetic cohort methods for time points and intervals.

The methods were validated by applying them to the Kisesa HIV observational cohort study, where incidence rates can also be measured directly. Currently most countries' national survey data are from a single survey, requiring additional "steady state" assumptions to be made even though these are known to be historically unrealistic. When data from additional surveys are available better estimates will be possible.

Further work includes developing the synthetic cohort method to work simply with repeated surveys; validating all three methods in as many cohort studies as possible; developing model representations for mortality by age among HIV-positives; testing the sensitivity of the methods to different assumptions about mortality and changing incidence levels; applying the methods to national survey data (assuming stability) and comparing with Spectrum's incidence estimates.

It was commented that ART will have an important impact on mortality but that national surveys do not routinely collect the data required to make adjustment for this.

2. Report of 5th Meeting of the WHO/AFRO Technical Network on HIV/AIDS and STI Surveillance network

The fifth meeting of the WHO/AFRO Technical Network on HIV/AIDS and STI Surveillance network was held in Harare, Zimbabwe in September 2006. One of the objectives of the meeting was to determine the areas of synergy between unlinked anonymous testing (UAT) in antenatal clinic (ANC) sentinel surveillance and prevention of mother-to-child transmission (PMTCT) of HIV programme data. Specifically, the meeting sought to

- summarize current evidence on the use of PMTCT data for HIV surveillance; and
- build consensus and make recommendations on the conditions required to use PMTCT data for HIV surveillance.

The meeting reviewed the experiences of Kenya, Uganda, Zimbabwe and Thailand.

The meeting concluded that there was a good rationale for using PMTCT programme data for surveillance in lieu of UAT sentinel surveillance. However, based on the experiences discussed during the meeting, it appears that at present PMTCT programme data cannot replace UAT surveillance for estimating HIV prevalence in many countries.

The meeting recommended that steps must be taken to assess the feasibility of using PMTCT programme data for surveillance and, if feasible, to take the necessary steps for preparing for this transition. The assessment must be conducted in all PMTCT sites and should assess both the PMTCT programme and UAT surveillance.

The key elements to assess include:

UAT surveillance:
- Sampling for UAT surveillance
- Is left-over blood from all sampled UAT clients collected for HIV testing?
- Quality of HIV testing and laboratory QA/QC programme
- Number of UAT sites compared to PMTCT sites
- Stock-outs and human resource issues

PMTCT programme:
- Data quality
- Ease of abstracting data from PMTCT sites for surveillance
- HIV test uptake in PMTCT sites
- Ratio of HIV prevalence in test refusers to test acceptors in dual sites
- Comparison of PMTCT HIV prevalence to UAT HIV prevalence in dual sites
- Quality of HIV testing and laboratory QA/QC programme
- Stock-outs and human resource issues experienced at the site

Based on the assessments, HIV prevalence from PMTCT programme should be compared to HIV prevalence from UAT. The effect of participation bias on the PMTCT HIV prevalence should be estimated and adjusted.

A source of bias increasing ANC estimates may be the reservation of testing kits for individuals judged to be at higher risk of infection when those kits are in short supply. It was recommended that the place of residence of women using ante-natal clinics be recorded since HIV+ women will be attracted to those clinics that offer PMTCT, biasing the estimated prevalence upwards.

3. Analysis of 15-24 year old ANC clinic data as a proxy for trends in HIV incidence in the most-affected countries

In 2001 the UN General Assembly made a Declaration of Commitment to reduce HIV prevalence among young people (aged 15 to 24) by 25% in the most affected countries by 2005, and to reduce it by 25% globally by 2010. To assess whether these goals have been reached there is a need to assess prevalence trends among 15-24 year olds in countries. Improved methods of analysing trends in ANC prevalence are being developed. In the past, trends in the median prevalence of multiple sites have been used. Superior approaches, performing a “regression by site”, or using mixed-effects statistical models, are being developed.

Epidemic classification: transmission dynamics and epidemiological categories

1. Report on Practical Guidelines for Prevention recommendations: revised classification of epidemics

UNAIDS/WHO described a three-category classification of epidemics in the Second Generation HIV Surveillance guidelines of 2000. During 2006, UNAIDS has been developing "Practical Guidelines for Prevention".

The three-category classification was believed to have led to poor prevention planning in some cases. In addition, it was felt that an additional category would be useful. A four-category classification has been now proposed for prevention planning, clarifying the definition of concentrated epidemics, and adding a category for "hyper-epidemics". This would apply to countries where HIV is firmly established in the general population with sexual transmission, including non-commercial casual sex and concurrent partnerships, sufficient to sustain a large epidemic independent of sub-populations at higher risk of infection.

Problems identified with the current classification system include the ANC prevalence = 1% guideline division between concentrated and generalised epidemics being misinterpreted as a rigid threshold requiring a change in the nature of prevention activity if it is crossed. It was suggested that it may be desirable for a new system to avoid specifying numerical guidelines, or giving ranges, to avoid this problem. However, it was also pointed-out that countries often want simple, clear, unambiguous guidance. Whilst it is desirable for each country to understand its epidemic in detail to design a corresponding response, this is often not possible.

When planning prevention programmes, it is incidence that is most informative, because it indicates how new infections are occurring. However, incidence data are less common than prevalence data. Prevalence reveals the history of the epidemic, which may be different from its future. Prevalence informs on treatment need and predicts mortality patterns.

The Reference Group strongly recommended that the proposed introduction of a "hyper-epidemic" category should not be made, as there are risks of undesirable mis-interpretation potentially encouraging complacency in countries whose epidemic is not severe enough to enter that category. Specifically, the meeting agreed:

- there is a major risk of encouraging complacency in countries with serious (particularly generalised) epidemics that are not categorised "hyper" or equivalent; and
- further categorisation of generalised epidemics based on prevalence measures alone does not indicate who is becoming newly infected, and is therefore not useful in guiding prevention interventions.

Instead it was recommended that a more effective approach to improving prevention advice would be to identify more clearly the risk-groups in which new infectious are occurring to guide targeting of intervention actions. This should be pursued by supporting workshops in countries that focus on describing the modes of transmission using existing spreadsheet and other computer-based models. These workshops should be additional to existing surveillance & estimation workshops, since they require sufficient time to provide the necessary training.

2. Comparing incidence in Thailand from AEM and the UNAIDS Modes of Transmission model

The incidence measures from the Asian Epidemic Model (AEM) and other sources were compared with the estimates from the UNAIDS Modes of Transmission model. Limitations of both approaches were explored and the potential problems applying the workbook at national level were discussed. AEM is designed for epidemics that are driven by commercial sex and injecting drug use in an Asian context and it has succeeded in predicting prevalence trends, including through capturing temporal trends such as the increase in condom-use in commercial sex, and changes in transmission patterns such as the increasing importance of transmission from former clients of sex workers to their wives. The Workbook model is not able to capture time-trends since it is intended for short-term analysis of immediate prevention needs.

3. Modes of Transmission model

The Modes of Transmission Model was used in the last round of estimates training to get people thinking about where most new infections occur and to provide a tool for estimation. The model uses information on the size and prevalence by risk group available from the workbook coupled with information on number of partners, condom use, and STI prevalence by risk group plus assumptions about the probability of transmission to estimate the number of new infections by risk group. The model has the potential to be very useful in stimulating a focus on sources of infection but needs more time for training and implementation than was available in past workshops. It was recommended that consideration be given to running workshops dedicated to using the MoT model, rather than including it in the standard training workshops.

4. The contribution of commercial sex work to HIV transmission in a maturing, widely-disseminated epidemic: the case of Zimbabwe

The contribution of different risk factors (including membership of and contacts with core groups) to HIV transmission can differ by type and stage of epidemic. Thus, closer characterization of epidemics may aid the design of timely/effective interventions. The likely contribution of commercial sex work to past and contemporary levels of HIV transmission in Zimbabwe was estimated.

Data from a large-scale general population cohort in eastern Zimbabwe on recent levels and changes in the extent of HIV risk associated with commercial sex were analysed. A mathematical model was used to explore the contribution of commercial sex to past trends, to the current scale of the epidemic, and to contemporary HIV transmission.

The proportions engaging in commercial sex declined between 1998 and 2005 for both men (15% to 5%) and women (3% to 2%) and the risk associated with involvement in commercial sex was found to reduce for women (age-adjusted POR, 5.3, 1998-2000; 4.6, 2001-2003; 2.8, 2003-2005; test for trend, $p<0.0001$). Between 1998 and 2003, HIV incidence was 4.4% and 1.5% in women engaging and not engaging in commercial sex, respectively [age-adjusted IRR, 3.1 (1.4-6.7)] and 8.3% of new infections (PAF) in women could be attributed to commercial sex. Engaging in commercial sex showed a positive but non-significant association with incident HIV infection in men [1.6 (0.9-3.0), $p=0.14$]. PAF tends to exaggerate the contribution of a risk factor when the occurrence of the factor in the population is reducing over time. However, model simulations indicate that, in the case of commercial sex work in Zimbabwe, this limitation may be outweighed by the exclusion of secondary infections.

Quantification of the contribution of commercial sex work to widely-disseminated HIV epidemics is not straightforward. Preliminary findings suggest that commercial sex work almost certainly played a critical role in determining the scale of the HIV epidemic in Zimbabwe. The extent of commercial sex activity and, in women, the associated risk of infection has reduced in recent years. However, it probably continues to play a substantial role in onward transmission of infection.

Past and future work of the UNAIDS Reference Group on Estimates, Modelling and Projections

1. Background

The objectives of the Reference Group are to

- streamline the interpretation and communication of data and understanding of the epidemiology HIV;
- regularly review and disseminate available evidence and opinions on the predicted scale of the HIV epidemic and its impact; and
- endorse or provide methods and parameter estimates for projections of the future HIV epidemic globally.

The Reference Group seeks to balance practicality and scientific rigour, to make recommendations based on the best-available evidence. To do this it organises international meetings of experts to advise on topics of contemporary relevance which will impact upon HIV epidemiology and estimation of HIV incidence and prevalence, typically 2-3 times per year. Meeting reports are published online at www.epidem.org. Numerous scientific papers have been written by attendees at Reference Group meetings and published in the peer-reviewed literature, including in leading journals such as Science, Lancet, and AIDS.

The Reference Group advises on development of the estimation and projection software packages used by UNAIDS to estimate the national and global burden of HIV: i.e. EPP, Spectrum, and Workbook. Topics addressed by past meetings include the course of different HIV epidemics; approaches to estimation of mortality and orphanhood; use of ANC data to monitor trends; approaches to estimation of uncertainty; the use of the BED assay for estimation of incidence; PMTCT regimens; impact of ART on survival; estimation of ART need (incl. paediatric); urbanisation; (male) circumcision; and causes of declines in HIV prevalence & incidence where they have been observed.

Rather than having a formal membership, meeting participants are invited to attend meetings where their expertise is relevant. More than 100 individuals have attended meetings since 2000, including from WHO, UNDP, US Census, US State Department, World Bank, CDC, Futures Institute, UNICEF, The Global Fund, and many health ministries and universities worldwide. A Secretariat based at Imperial College London coordinates the activities of the Reference Group.

2. Future work

The Reference Group recommended that attention be given to the following topics:

- Estimation of the age-distribution of HIV incidence.
- Improving orphanhood estimates for generalised epidemics and deriving estimates for concentrated epidemics. (Work has been done on this with data from South Africa.)
- Prevalence trends analysis: developing methods to determine if an apparent decline is statistically significant.
- Using data on HIV-discordance within sexual partnerships from DHS+ and other household surveys, etc to inform on transmission modes and dynamics.
- Analysis of the relative importance of different modes of transmission in specific countries to gain insight into general patterns and processes.

Appendix I: Meeting Agenda

Wednesday November 29th

Start	Duration	Subject	Speaker
900	20	Opening remarks	Peter Ghys
Session 1 - Estimation and projection tools and parameter estimates. *Chair: Rob Dorrington*			
920	20	Survival of HIV-infected patients on antiretroviral therapy (ART) in lower and middle-income countries (LINCs): A systematic review	Francois Dabis
940	20	Estimates of the time from ART eligibility to death in the absence of ART	Eleanor Gouws
1000	20	Disussion	-
1020	*30*	*Coffee break*	-
1050	20	Towards improved uncertainty bounds: current status of Bayesian Melding in EPP	Tim Brown
1110	20	Outstanding issues regarding Bayesian melding in EPP	Adrian Raftery
1130	20	Other changes to EPP	Tim Brown
1150	20	Updates to Spectrum	John Stover
1210	40	Discussion	-
1250	*75*	*Lunch*	-
1405	20	Survival of untreated HIV+ individuals: report from Alpha network	Basia Zaba
1425	20	Diverse Age Patterns in HIV Incidence Rates in Africa	Basia Zaba
1445	45	Discussion	-
1530	*15*	*Coffee break*	-
Working-group discussions: Uncertainty estimation and Default patterns of incidence and AIDS mortality. *Chair: Peter Way*			
1545	50	Working groups	-
1635	40	Reporting back	-
1715		Close	-

Thursday November 30th

Start	Duration	Subject	Speaker
Session 2 - Interpretation of HIV prevalence in general population surveys in generalised epidemics. *Chair: Meade Morgan*			
900	20	Comparison of country-level ANC prevalence and survey prevalence in countries with generalised epidemics	Eleanor Gouws
920	15	Comparing observed and projected paediatric HIV prevalence estimates, Uganda 2004	Wolfgang Hladik
935	20	Discussion	-
Session 3 - Interpretation of HIV prevalence in general population surveys in "mixed concentrated/generalised" epidemics. *Chair: Meade Morgan*			
955	10	Overview of comparisons of HIV prevalence in household surveys and ANC in South India	DCS Reddy
1005	10	Estimation of HIV/AIDS burden and Related Mortality in India: Some Issues	Arvind Pandey
1015	10	HIV/AIDS Epidemic in India: Force, Growth and Mortality	Mariamma Thomas
1025	10	Discussion	-
1035	*30*	*Coffee break*	-
1105	20	Is the HIV burden in India being overestimated?	Lalit Dandona
1125	20	Variability in HIV prevalence, risk behaviours and size of core groups in Karnataka, a southern Indian state	BM Ramesh
1145	25	Discussion	-
1210	15	Maharashtra and Tamil Nadu AVAHAN studies: size of group and HIV prevalence for groups with high risk behaviour and their relation to HIV prevalence in the community survey	Tobi Saidel
1225	15	Senegal, Burkina Faso, Mali: exploring adjustments to the HIV prevalence measured in the survey, based on size and HIV prevalence of relevant groups with high risk behaviour	Karen Stanecki
1240	20	Discussion	-
1300	*75*	*Lunch*	-
Working-group discussions: interpretation of data. *Chair: John Stover*			
1415	90	Working groups	-
1545	*20*	*Coffee break*	-
1605	40	Reporting back	-
1645		Close	-

Friday December 1st

Start	Duration	Subject	Speaker
Session 4 - Trends and alternative data sources. *Chair: Neff Walker*			
830	15	Estimating incidence from prevalence	Basia Zaba
845	15	Report of 5th Meeting of the WHO/AFRO Technical Network on HIV/AIDS and STI Surveillance network	Emil Asamoah-Odei
900	10	Methods for analysis of trends in HIV prevalence in young persons	Rob Lyerla / Ray Shiraishi
910	15	Discussion	-
Session 5 - Know Your Epidemic: Transmission dynamics and Epidemiological Categories. *Chair: Neff Walker*			
925	20	Report on Practical Guidelines for Prevention recommendations: revised classification of epidemics	Peter Ghys
945	15	Comparing incidence in Thailand from AEM and the UNAIDS Workbook	Tim Brown
1000	15	Modes of Transmission Model	John Stover
1015	10	Discussion	-
1025	*20*	*Coffee break*	-
1045	15	The contribution of sex work in Manicaland, Zimbabwe	Simon Gregson
1100	10	Discussion	-
Session 6 - The Reference Group: past and future work. *Chair: Nick Grassly*			
1110	15	Review of the past work of the Reference Group	Peter Ghys
Working-group discussions: interpretation of data. *Chair: Nick Grassly*			
1125	65	Working groups	-
1230	30	Reporting back	-
1300		Close	-

Appendix II: List of Participants

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