Paediatric estimation issues with a focus on ART need estimates

Report of a meeting of the UNAIDS Reference Group on Estimates, Modelling and Projections held in Geneva, Switzerland, Dec 4th 2009

TECHNICAL REPORT AND RECOMMENDATIONS

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, January 2010.

Introduction

The Reference Group on Estimates, Modelling and Projections

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 1) address issues surrounding the methods used to produce estimates of paediatric infection and ART need and coverage and, 2) review the new WHO treatment recommendations and the implications of these recommendations for future estimates and, 3) to produce recommendations for updates to the Spectrum model.

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 15 experts and additionally included presentations from and additional two experts who were unable to attend (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, 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. Estimates of Paediatric ART Need and ART Coverage: Current Methods and Limitations

The objectives of this meeting were to address current issues in methods used for estimating ART need and ART coverage, to update the survival curves for HIV-infected children specific to the mode of infection (perinatal vs through breastfeeding), to discuss the new paediatric treatment recommendations and the implications of these recommendations for the Spectrum model and to identify the changes to be made to the Spectrum model for the immediate and short-term future (in time for 2009 reporting of HIV and AIDS estimates) and also for the longer-term future.

1.I Current methods in Spectrum for estimates of paediatric HIV infection

The Estimation and Projection Package (EPP) is used to generate adult incidence over time (by fitting to adult prevalence) and these outputs from EPP and the coverage of ART and PMTCT are then entered into Spectrum where the demographic data, epidemic patterns and treatment effectiveness are incorporated to generate the number of people living with HIV, the number of new HIV infections, AIDS deaths, antiretroviral treatment need, and orphans due to AIDS. To calculate HIV in children, transmission from mother-to-child (MTCT) is divided into transmission during pregnancy and birth and transmission through breastfeeding. The parameters for the probability of MTCT at birth vary depending on the drug regimen used for prophylaxis and are derived from efficacy studies of the prophylaxis regimens.

The probability of transmission through breastfeeding depends on the type of breastfeeding (mixed/exclusive) and the duration of breastfeeding. There is a new option in Spectrum which allows the manual entry of the monthly pattern of breastfeeding. Data on breastfeeding patterns are usually available from Demographic Health Surveys (DHS) with the limitation that the DHS data pertain to all women and the pattern of breastfeeding may be different in those who are HIV positive. An additional limitation is that the breastfeeding pattern in Spectrum is static and does not change over time which may not reflect the trends in individual countries.

For the 2007 estimates in Spectrum a single progression pattern was used for infected children; this progression pattern combined transmission during pregnancy and at birth with transmission during breastfeeding. After a *Consultative Meeting on Data Collection & Estimation Methods Related to HIV Infection in Infants and Children* in July 2008, modifications were made to Spectrum separating this single progression pattern into two separate survival curves by mode of infection. The curves used to generate the 2008 estimates were placeholders, pending a specific analysis of survival of children that were infected by HIV either perinatally or through breastfeeding.

1.II Comparison between modelled estimates and survey results of HIV in children

A comparison of modelled paediatric estimates from both Spectrum version 2007 and modelled estimates from the Williams model (developed for application in Zimbabwe) to survey prevalence from population-based surveys (Botswana, 2004 AIDS Indicator Survey; South Africa, HSRC Survey 2005; Swaziland, DHS 2006) was performed. It was found that the survey prevalence was generally slightly higher than the modelled estimates but there was reasonably good agreement between the modelled estimates and the survey estimates across all age groups.

A comparison was then done of modelled estimates of children 0-14 years from Spectrum version 2009 (which included the new options for PMTCT, new treatment guidelines, breastfeeding patterns and the separate progression patterns by mode of infection) compared to the survey prevalence and compared to the estimates from Spectrum version 2007. Greater differences were observed between survey prevalence and Spectrum estimates using version 2009 for South Africa and Swaziland compared to the modelled estimates from Spectrum version 2007; the Spectrum 2009 estimates were lower and often outside the confidence intervals of the survey prevalence. The results from the comparisons suggest that the survival curves currently used in Spectrum 2009 may decline too quickly and that the breastfeeding patterns might not have been captured adequately.

1.III Estimation of ART need in Spectrum

Once the new survival curves have been generated, progression patterns, from infection to ART need and from ART need to death in the absence of treatment, need to be calculated by mode of infection (perinatal vs. breastfeeding). If the survival curves are not accurate, then this can have a significant impact on the estimates. For example, if thy decline too quickly, then children will not progress to "need for ART" and this can result in inflated estimates of ART coverage

For some countries, estimates produced using Spectrum version 2009 resulted in the coverage of ART exceeding the estimated need for ART. Spectrum does not currently allow coverage of ART to be greater than 100%.

In Spectrum, the estimate of ART need among children is not explicitly based on CD4 count, CD4% or other eligibility criteria. Children newly on ART are distributed by age and sex according to '*identified need'* that is not met. 'Identified need' is the same as 'need', except it only includes children less than 1 year of age if PCR diagnosis is available. If PCR diagnosis is not available, children under 1 are still classified as 'in need', but for the modelling, children newly on ART will not be distributed into this age category. Child survival on ART is based on the consensus from the aforementioned July 2008 consultation.

1.IV Country programme data of children on ART and estimates of children in need of ART

The definition of paediatric ART coverage used in UNAIDS/WHO estimates is the number of children on ART collected from patient monitoring systems divided by the total Spectrum estimate of the number of children in need of treatment. Issues that lead to overestimates of coverage include poor quality patient monitoring systems (double counting, non-removal of deaths and loss-to-follow-up), national treatment guidelines that begin treatment earlier than Spectrum assumptions and clinicians treating patients earlier than the guidelines recommend. The challenges of estimating ART coverage arise from having no comparable data for true coverage, very few comparable data sources for the number of children on ART, no comparable data for children in need, and countries using different criteria for initiating ART.

In Swaziland, after what appeared to be reasonable estimates for 2007, the 2009 estimates of those on ART exceed the need for ART. This may be a result of the new survival curves implemented in Spectrum version 2009 but may also result from all children commencing ART immediately upon HIV diagnosis in Swaziland while the eligibility for ART used in Spectrum is based on the WHO criteria and does not include initiation of all children thus many children will commence treatment who will not have been identified as "in need" in the modelling. In the discussion, it was also recommended that the patterns of breastfeeding be examined and compared to DHS data, and if necessary, to update the breastfeeding patterns from the default values to the country-specific values.

In Namibia, estimates of children on ART were greater than the estimates of ART need for both 2007 and 2008 using Spectrum version 2009 (i.e. coverage greater than 100%). Initiation of treatment in Namibia follows WHO treatment guidelines. While there has been no formal evaluation of the patient monitoring system, individual level data are reported to the national level using unique IDs and programme data are tallied against drug consumption.

In Rwanda, coverage of children on ART exceeded 100% for 2008 using Spectrum version 2009. Rwanda has a good quality TRACnet electronic reporting system, uses unique IDs, and systematically removes deaths and loss to follow-up.

In Argentina, estimates of ART coverage in children were over 100% for 2004-2008 using Spectrum version 2009. Similarly, in the Dominican Republic, estimates of children on ART were greater that the estimates of ART need for 2008 using Spectrum version 2009. While there is limited evidence regarding the quality of the programme data, countries feel strongly that they have good quality patient monitoring systems.

2. New analyses of survival of HIV-infected children and of age-specific CD4 distribution

2.I Survival of children infected perinatally and through breastfeeding, a pooled analysis of individual data from resource-constrained settings

A 2004 analysis (Newell et al, Lancet) using data from eight studies was updated by Becquet et al using a dataset that includes data from six additional studies. The study analysed the survival of HIV-infected children in low and middle income countries in the absence of antiretroviral therapy. Separate analyses were done for children infected perinatally and for children infected through breastfeeding. The effect of background mortality on survival post-infection by time of infection (perinatally vs. breastfeeding) was investigated and model curves were fit to the net survival of each of these groups for use in updating the survival curves used in mathematical models.

Children born to HIV positive mothers were included in the analysis and Kaplan-Meier functions were used to calculate survival patterns since birth according to HIV status of the children. In HIV positive children, Kaplan-Meier functions were used to calculate survival patterns since acquisition of infection separately by timing of infection -- children infected in peri-partum, children infected in postnatal, and children infected with unknown timing of infection. The data was left-censored at the estimated time of diagnosis of HIV infection with the date of HIV acquisition calculated as the mid-way point between the last HIV negative test and the first HIV positive test, and then the estimated 24-month mortality for HIV infected and uninfected children, and the 24-month mortality for HIV infected children by timing of transmission was generated.

Net survival through adolescence

Previous methods used to create net survival curves included the assumption that all children were infected from birth due to the timing of infection not being available. Additionally, most data was taken from published papers rather than using the complete datasets. An analysis by M Marston et al updated the net survival curves using data from 12 sub-Saharan Africa sites which included timing of infection. Data is available up to 2.5 yrs of age, but at the end the sample size is very low; therefore, to extend the curve, two double Weibull distributions were fitted (based on analyses done by the Alpha network of the survival of young adults) and used to model survival through adolescent age. This method resulted in a good fit with a median survival for those infected early of one year and nine years for those infected late. These results were more optimistic, especially for those infected early, than what was previously used in Spectrum and may result in more accurate estimates

The potential caveats include all study sites being in sub-Saharan Africa and most occurring in urban antenatal clinics or large city hospitals. There may be regional differences in survival and these curves should be compared to other data available.

It was highlighted that the uninfected children included in these studies had much lower mortality than what would expected on the basis of available infant mortality estimates. As a result, net survival curves are very similar to crude survival curves, as there was little background mortality. It was discussed that because Spectrum already includes the background mortality, this might actually be beneficial.

2.II CD4 distributions in the HIV Paediatric Prognostic Markers Collaborative Study and Cross Continents Collaboration for Kids study

David Dunn, from the Medical Research Council Clinical Trials Unit presented an analysis of the CD4 count and CD4 percent age-specific distributions from two collaborative studies.

The HIV Paediatric Prognostic Markers Collaborative Study (HPPMCS) is a meta-analysis of individual longitudinal data on HIV-1 infected children enrolled in cohort studies and randomised controlled trials in USA and Europe. The objective of this study was to describe the "natural history" of perinatally acquired HIV. Data was collated on approximately 4,000 children, with 75% of data collected prior to1995, resulting in a total of ~25,000 data values. Values were censored at the onset of combination antiretroviral therapy (AZT monotherapy included) and the data was presented up to age 12 with the reported distribution of CD4 count and CD4 % by age (0-11 years).

The Cross Continents Collaboration for Kids (3Cs4kids) study is a meta-analysis of individual longitudinal data on HIV-1 infected children from 10 studies (9 African, 1 Brazilian). Most data was collected after 2000, simultaneous with ART rollout. Data was pooled on approximately 2,500 children; the median age at first measurement was 4.0 years as these were generally late diagnoses. Values were censored at the onset of antiretroviral therapy, a total of ~6,000 values, and the data was presented up to 12 years of age. Compared to the HPPMCS data, the 3Cs4kids data had greater variability in CD4 count compared to CD4 percent.

Discussion

Because countries use different treatment regimes for children (notably Swaziland and Rwanda where there are issues with the estimates of those in need for ART compared to those receiving ART), we would need to generate different eligibility curves which correspond to each different treatment regime used. This will be arduous and will become particularly complicated in the future as a result of the increasing variability in treatment regimes.

It was discussed that for children, since the time of infection is known in the model (0-1 years), it should be possible to estimate the CD4 count or CD4 percent based on age which would mean that the model could have age associated with a specific CD4 count or CD4 percent distribution and have this data in a look-up table in Spectrum. The net survival curves (generated by Marston, et al) are without ART and if the model has CD4 count or CD4 percent by age then ART eligibility by age can be determined. This CD4 based approach would not require actual CD4 count or CD4 percent but would instead use the CD4 distribution by age. It may be possible to adopt this method in the short-term and it would not require additional data inputs from the countries.

For the longer-term future, the Spectrum user would then only need to specify 2 parameters for paediatric estimates – the age eligible for ART, and the CD4 count and/or CD4 percent that defines eligibility for that age and those under age 5 (note that eligibility for those over age 5 is the same as the new eligibility for adults). Countries that use unique IDs for children on ART will already have the age data.

3. Revised WHO Recommendations

Paediatric ART

WHO produces recommendations citing both the strength of the recommendation (strong, weak, conditional), and the quality of evidence (high, moderate, low, very low) associated with the recommendation. The strength of the recommendation indicates the degree of confidence that the desirable effects outweigh the undesirable effects while the quality of evidence indicates the extent to which one can be confident that an estimate of effect or association is correct.

For the revised paediatric ART recommendations, countries are expected to adopt country-specific treatment guidelines depending on their specific setting, country data, cost, burden, targets, access, availability and resources.

The guiding principles are to do no harm, ensure access and equity, promote quality and efficiency and be sustainable.

The current strong recommendations for when to start children on ART are based on weak evidence – HPPMCS based thresholds of CD4 and CD4 % that resulted in ~5% mortality. This is a historic cohort from Europe and US so there is concern with its representativeness. Compared to the date from 3C's4kids, there were similar curves but all pushed towards greater mortality. Additionally, there is observational evidence of high mortality in children under 2 years, at any CD4 level.

The new draft recommendations can be summarised as follows:

- Start all infants irrespective of CD4 or clinical stage
  (strong recommendation, moderate quality of evidence)
- Start ART for all children 12-23 months irrespective of CD4 or clinical stage
  (*conditional/weak recommendation, very low quality evidence)*
- Start ART if presumptive severe HIV < 18 months
  (strong recommendation – moderate quality of evidence)
- Start ART for children 24- 59 months infants with CD4 abs < 750 cells/ mm^3 or CD4 percent < 25
  (strong recommendation, low quality of evidence)
- Start ART for children 5 years of age and older according to the same criteria as for adults (CD4#<350)

Prevention of mother-to-child transmission (PMTCT)

The aim of the recommendations for PMTCT is to maximise the reduction of vertical transmission, to minimise the side effects for mothers and infants, and to preserve future treatment options.

It is recommended that all pregnant women with a CD4 count <350 cells/mm^3 and those >350 cells/mm^3 with WHO Stage 3 or Stage 4 symptoms should be put on ART. Pregnant women not meeting these criteria should receive ARV prophylaxis from as early as 14 weeks gestation. There are two recommended options for ARV prophylaxis for mothers who are not eligible for ART – maternal AZT or maternal triple ARV prophylaxis. Nevirapine regimens are not recommended. For infants, the prophylaxis regimen will depend on whether the infant is breastfeeding. Effective postpartum ARV-based interventions for all HIV positive women will allow safer breastfeeding practices. The revised PMTCT recommendations will be published in March 2010.

RECOMMENDATIONS

Immediate and short-term recommendations:

- Uncap treatment coverage so that coverage can exceed 100% of the Spectrum-estimated ART need.
- Update the survival curves in Spectrum with the net survival curves produced by Marston et al.
- Generate survival curves from the HIV Paediatric Prognostic Markers Collaborative Study (HPPMCS) and compare these curves to the survival curves produced by Marston et al.
- Use the CD4 distributions by age (both CD4 count and CD4 percent) from the HIV Paediatric Prognostic Markers Collaborative Study (HPPMCS).
- Adopt an age-specific compartment approach in Spectrum (similar to what will is being implemented for adults) where CD4 count is associated with age and the age-specific CD4 count and CD4 percent distribution is generated from the HPPMCS results. This will alleviate the need to generate different eligibility curves for each different treatment regime used.
- Once these changes have been made in Spectrum, perform a detailed comparison for all countries where there were issues with the estimates of ART coverage (Argentina, Dominican Republic, Namibia, Rwanda and Swaziland), comparing the new ART needs and coverage results with the previous results
- Once the changes have been made in Spectrum, perform a detailed comparison of HIV prevalence among children between the modelled estimates and the data observed in population based surveys for the relevant countries (Botswana, Uganda, South Africa, Swaziland).
- Once the changes have been made in Spectrum, compare the new estimates to the 2008 estimates of prevalence, incidence, mortality and ART needs for all countries.
- Continue to distribute children on ART proportionately by age and sex in Spectrum, as per previous methods, for the short-term.

Longer-term recommendations:

- Countries should report ART data by age and sex for children.
- Spectrum will need to accommodate ART data by age and sex when it becomes available.
- Include estimates for children on, and in-need-of, second-line ART. Countries should report this data disaggregated by age and sex.
- Update Spectrum to include a 6th PMTCT treatment option -- dual ARV prophylaxis for the mother and ARV for the child for the duration of breastfeeding – which will be part of WHO's March 2010 PMTCT recommendations.

Appendix I: Meeting Agenda

Meeting on paediatric estimation issues with a focus on ART need estimates
Friday, December 4th, 2009

Start	Duration	Subject	Speaker
900	10	Opening remarks	Peter Ghys
910	10	Overview of meeting and expected outcomes	Kim Marsh
Session 1 - Presentations Chair: Kim Marsh			
920	15	Current Spectrum methods for estimates of HIV prevalence, incidence and mortality among children	John Stover
935	15	HIV infections among children: comparison between survey and modelled estimates	Eleanor Gouws
950	15	Discussion	
1005	15	Current Spectrum methods for estimates of ART needs among children	John Stover
1020	15	Swaziland - Programme data of children on ART and estimates of children's ART needs and ART coverage	Helen Odido
1035	15	Other countries: Country programme data of children on ART and estimates of children's ART needs and ART coverage	Mary Mahy/Paloma Cuchi
1050	15	Discussion	
1105	20	Coffee break	
1125	15	Multi-centre epideimological anlaysis of survival of children infected perinatally versus through breastfeeding	Renaud Becquet
1140	15	Development of net HIV survival curves for HIV infected children by time of infection	Milly Marston
1155	15	New recommendations for treating pregnant women and preventing HIV infection in infants	Nathan Shaffer
1210	15	Disucssion	
1225	55	Lunch	
1320	15	New recommendations of child ART eligibility by age	Siobhan Crowley
1335	15	Age-specific distributions of CD4 cell counts from HIV Paediatric Prognostic Markers Collaborative Study and Cross Continents Collaboration for Kids study	Peter Ghys on behalf of David Dunn, MRC CTU
1350	20	Discussion	-
1410	20	Coffee break	
Session 2 - Working Group Discussion and Recommendations Chair: John Stover			
1430	120	Questions 1. How should we calculate progression from infection to eligibility for treatment? 2. How should we calculate progression from eligibility for treatment to AIDS death in the absence of treatment? 3. How do we distribute new ART patients by age and sex? 4. Do we need to include second line ARV for children?	-
1630	10	Close	Peter Ghys
1640			

Appendix II: List of Participants

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