Technical Review of Spectrum

April 2012

Report of a meeting of the UNAIDS Reference Group on Estimates, Modelling and Projections held in Boston, MA, USA, 2 April 2012

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, May 2012

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 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.

Aim of the meeting

The aims of this meeting were:

1) To review and make recommendations for a revised method for curve fitting in the Estimation and Projection Package (EPP) component of Spectrum.

2) To address technical issues that have arisen and to make recommendations for improvement for the 2013 version of Spectrum to be used for the next round of Global HIV/AIDS estimates and projections.

Approach

The meeting featured presentations of model simulations, recent data and analyses and presentations and discussions of ongoing work, combined with group discussion. The meeting agenda is included in Appendix I.

The meeting was attended by 22 experts; each contributed, not only data, simulations, insights, experience and analyses, but also worked to produce a set of recommendations, drafted at the meeting. The list of participants is included in Appendix II

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.

Technical Review of Spectrum

The purpose of this technical meeting was to review the progress made on issues identified at the October 2011 consultation[1] and make decisions to further enhance the tools that will be used for the next round of estimates. The main objectives were to decide on a revised method of curve fitting to use in the EPP component of Spectrum and to review and discuss new data and analyses and identify how this information could be used to improve Spectrum.

1. Replacement for r-flex

Following review of the curve fitting in EPP at the Reference Group meeting in October, 2011, two modifications were proposed to replace the current r-flex model – the more flexible fitting method adopted for Spectrum version 4.0:

1. Mean-shift model – A refined r-flex model which imposes some common structure on r(t), the simple random walk, and uses more informative prior distributions.
2. Hybrid force of infection model – Dan Hogan's spline method to obtain the in-sample fit combined with Le Bao's random walk method for the projections.

Both methods were tested on approximately 30 countries and the results were reviewed considering fit, the projection and speed.

Mean-shift model

The mean-shift model imputes a systematic mean structure on the change in r(t). This method was found to provide better estimation compared to EPP classic, perform better out-of-sample than both EPP classic and r-flex, and was faster than r-flex with smoother incidence and mortality curves. The benefits of this approach are that the parameters are easy to identify and interpret, and information can be shared across sub-regions (hierarchical model for provincial estimates).

Hybrid force of infection model

The hybrid force of infection model is a hybrid model that combines the strengths of the spline (in-sample) and the random walk (out-of-sample projection). Compared to the spline model, the hybrid method stabilises incidence trajectories beyond the data, thus avoiding the rapid changes in incidence that occurred even though prevalence remained the same. The hybrid model was also tested on concentrated epidemics and found to work fairly well.

Discussion

A hierarchical model would be useful for some countries with good data. For the future, a hierarchical model will likely be the way forward but this is definitely a substantial increase in complexity. In order to be better prepared in the future, the research on the hierarchical model should continue. However, in the first instance, both of the refined approaches should be implemented in EPP and when more research and results are available, we can consider incorporating the hierarchical model.

Recommendations for the short term

- Test the mean-shift method for use with concentrated epidemics. *Le Bao, April 2012*
- Implement Le Bao's mean-shift method and Dan Hogan's hybrid force of infection model in EPP. *EPP team to code both by July 1, 2012*

Recommendations for the medium term

- **Methods to use for concentrated epidemics:** Compare the results from the mean-shift and hybrid force of infection model when applied to concentrated epidemics.
  Reference Group meeting, September 2012
- **Hierarchical model:** Further research and work on development of a hierarchical model applicable for both concentrated and generalised epidemics, and for both within country applications (e.g. estimates at the provincial level) and cross-country application.
  Le Bao to continue this research, review progress at Reference Group meeting, September 2012

2. Spectrum 2013

The following details the current issues identified and under review which pertain to Spectrum, and the consensus recommendations derived at this meeting.

2.1 Regional patterns for mortality on ART

Regional patterns for mortality on ART are now included in Spectrum, predominantly based on the data from the IeDEA Consortium. However, more information is needed to identify what is driving the different patterns and whether these are real or an artefact of the adjustments made.

Recommendation: Continue to assemble the data, request other data sources and review.
Follow up: IeDEA is awaiting Malawi and other southern Africa data
Follow up: UNAIDS to request Western Europe and US data
Review at Reference Group meeting, September 2012

2.2 Paediatric patterns for mortality on ART

The IeDEA Consortium also has data for paediatric mortality on ART thus the question arises whether paediatric patterns for mortality on ART should be incorporated in the same manner as for adults. The caveat of this is that the only adjusted data are for east Africa; the southern Africa data has crude adjustments.

Recommendation: Review the paediatric data from IeDEA, and in particular the east Africa data which are the best data we are likely to be able to get at this time. Implement after review and use with caution.
Follow up: Constantin Yiannoutsos to provide the data
Review at Reference Group meeting, September 2012

2.3 Mortality with and without ART

In Spectrum, if a country changes the treatment eligibility criteria to >350 CD4, then mortality of those on treatment can be greater than those not on treatment. This occurs as a result of the estimates for mortality on ART at these greater CD4 counts, which are based on a limited number of people from the IeDEA Consortium who are likely not representative of the broader population as they are being treated outside the normal treatment criteria. If Spectrum is used as intended (treatment criteria ranging from 200-350) then this is not a problem; however, some countries are doing hypothetical projections at these higher CD4 counts.

Recommendations:

- For countries under the eligibility criteria, continue to use the data from IeDEA Consortium.
- If countries change the eligibility to >350 CD4, then use an extrapolation instead.
- Extrapolated estimates of survival of people on ART to be developed, extrapolating from categories of people with CD4 counts at start of ART of <200 or of <350.

Follow up: John Stover and Constantin Yiannoutsos to develop and review extrapolated values
Review at Reference Group meeting, September 2012

2.4 Impact of adult cotrimoxazole on mortality

In agreement with WHO recommendations,[2] more low- and middle-income countries are increasing the coverage of cotrimoxazole prophylaxis for HIV-related infections, commonly in conjunction with ART, which has been demonstrated to have a strong impact on reducing mortality in the short term.[3] This raises the question whether we need to incorporate this additional impact in Spectrum. While we are unsure how much of the impact of cotrimoxazole is already included in the ART impact quantified, we would expect a relationship between coverage and mortality thus we may be able to tease this out if we compile all of the available information.

Recommendation: Review data from Rwanda, Uganda and other countries that recommend cotrimoxazole for adults as they initiate ART.

Follow up: Constantin Yiannoutsos to identify whether this could be an explanation for the lower mortality rates in East Africa, and derive estimates of survival for people on ART not receiving cotrimoxazole, as well as estimates of the specific effect of cotrimoxazole on survival.
Review at Reference Group meeting, September 2012

2.5 CD4 progression parameters in Spectrum

Following recommendations from the October 2011 Reference Group meeting[1], multiple sources of data were reviewed in order to better understand CD4 progression and to use this information to improve the parameters currently used in Spectrum (obtained through model fitting). Recent data from the Africa Centre, IeDEA Consortium, University of WA, and the published data from CASCADE were reviewed and discussed and a plan for further work was established.

Recommendations: Thorough review of all available data and new data as it emerges, including e-ART Linc, IeDEA, Africa Centre, UW and Uganda AIS.

Specific analyses recommended:

- Attempt to reproduce Africa Centre results in Spectrum.
  Follow-up: John Stover, Till Barnighausen
- Approach CASCADE to fit J Eaton's compartmental model directly to data. Also consider necessary changes in mortality needed for this approach.
  Follow-up: UNAIDS to approach CASCADE group
  Follow-up: Jeff Eaton, Constantin Yiannoutsos & John Stover to do modelling, analyses and implementation in Spectrum for review
- Review Uganda AIS data when available
  Follow-up: Futures Institute

Review and compare all results at Reference Group meeting, September 2012

2.6 Age pattern of incidence

In Spectrum, estimates of HIV among those over 49 years of age are significantly less than survey estimates which illustrate an uptick in prevalence in older age groups. Data from South Africa also illustrated very high prevalence in older age groups, as did Manicaland data where it was found to be associated with widowhood/divorce. Similarly, Basia Zaba's age patterns of HIV incidence from Kisesa data, 1994-2004 also indicated this trend.

Recommendations: More information on the potential increase in prevalence in older age groups is needed; it is possible that this uptick in prevalence in older age groups may have been missed as result of the lack of surveillance data that includes older populations.

Specific recommendations:

- Analyse non-response by age as the first step, then further research and analysis on the potential for an increase in incident infections in older age brackets.
  Follow-up: UNAIDS to analyse non-response of people aged 50+ in national surveys. ALPHA network to conduct further analyses of age specific incidence with focus on 50+ ages
- Create an inference about the average pattern of incidence rates across the available data sources (these should be quite similar but there is a potential for differences across countries).
  Follow-up: Futures Institute
- Use a new incidence pattern by age and sex in Spectrum that incorporates the increase in older age groups.
  Follow-up: Futures Institute
- Surveys should incorporate older age groups in order to collect data and gain a better understanding of what is occurring.
  UNAIDS to advocate for this recommendation

Review results at Reference Group meeting, September 2012

2.7 PMTCT ISSUES

1) PMTCT outputs in Spectrum

Users often have difficulty finding the PMTCT outputs in Spectrum, currently found under the *Children 0-14* tab.

Recommendation: Move PMTCT outputs to a separate grouping/tab to aid the user *Follow-up: Futures Institute*

2) PMTCT BF prophylaxis defaults

There is currently limited information for how countries are implementing the new PMTCT treatment guidelines, Option A and Option B, particularly for prophylaxis during breastfeeding. As a result, most countries leave these inputs blank in Spectrum as the data are not available. It would be useful to have default values that could be used in the absence of data.

Recommendation: Gather data available and consult experts in this area and review.
Follow-up: UNAIDS, Mary Mahy
Reference Group meeting, September 2012

3) PMTCT need

There are reports of countries having both under- and over-estimates of need for PMTCT in Spectrum compared to the country data available.

Recommendations:

- Triangulate the data available to identify discrepancies. Check need for PMTCT estimates and ART need estimates.
- Consider adjusting the fertility discount for countries where there are very different fertility patterns and prevalence levels between the rural and urban areas.

Follow-up: UNAIDS
Review at Reference Group meeting, September 2012

2.8 Effect of pregnancy on HIV incidence:

More data is needed to identify whether there is a clear, quantifiable, effect of pregnancy on HIV incidence.

Recommendation: Consult additional analyses from Alpha Network and review at an expert consultation.
Reference Group meeting, September 2012

3. EPP

The following details the current issues identified and under review which pertain to the EPP component within Spectrum, and the consensus recommendations derived at this meeting.

3.1 Spectrum-EPP transition:

Even after exploring ways of changing the rate of HIV+ individuals exiting at age 50 over time in EPP, Spectrum and EPP do not produce the same prevalence for a given incidence curve. The next step is to test with Spectrum passing the age-incidence pattern to EPP in the first instance and review if this can solve the problem of different age patterns and aging out too quickly.

Recommendations:

- Test and review
- Maintain the calibration as needed

Follow-up: Futures Institute and EPP team
Review at Reference Group meeting, September 2012

3.2 Population configuration

Several countries have expressed that *transgender* should be included as a subpopulation on the configuration page in EPP. This is something that can easily be added in EPP

Recommendation: Add transgender as a population on the configuration page in EPP.
Follow-up: EPP team to implement

3.3 Curve-fitting in EPP

We now have five different methods for curve fitting in EPP: Workbook fits, EPP classic, R-flex, the new mean-shift method, and the hybrid force of infection model (modified spline method).

Recommendation: Maintain all 5 methods for curve fitting in EPP for now.
Review performance at Reference Group Meeting, September 2012

3.4 Selection of the best-fit curve

Using the best-fit curve is not ideal, particularly for the projections where prior A is a random walk and thus the choice for best fit is arbitrary.
Recommendation: Use the mean or median of the entire projection as opposed to the single best curve.
Follow-up: EPP team to implement
Review results at Reference Group Meeting, September 2012

3.5 Revised ART apportionment

A new method was proposed for ART proportioning within EPP. All projections are first calculated without ART, then need is taken from non-ART projections and used to apportion treatment. Refitting then occurs with the new ART allocations. This is an improved method but it doubles the fitting time and thus should possibly only be done for the national level projections.

Recommendation: Implement the new method for ART apportioning and review the results
Follow-up: EPP team to implement
Review results at Reference Group Meeting, September 2012

3.6 Populations in concentrated epidemics

For subpopulation distribution in concentrated epidemics, countries are inputting the population sizes of key populations as the national estimates of these populations when the input actually requires the population sizes in the absence of an AIDS epidemic. This is problematic because when the AIDS mortality is added, it can greatly decrease the size of these populations, particularly for IDU which has additional IDU mortality as well. Countries are already struggling to simply obtain current

national level size estimates and the vast majority of countries do not have the population data required. This raises the question whether a different population model should be used for concentrated epidemics.

Recommendation: Implement a full version of the method proposed by Tim Brown that decreases population size in the receiving populations. Test and review the overall national effects on 3-4 full concentrated epidemic projections.

Follow-up: EPP team

Review at Reference Group Meeting, September 2012and decide whether to incorporate in the 2013 version

4. Underlying demography and populations

The following details the specific underlying demography and population issues identified as a result of ongoing model testing.

4.1 HIV+ kids 15-17 years

Infected kids seem to disappear after age 15 and do not appear to show up in 15-17 age bracket (with and without ART).

Recommendation: Review progression from children (age 14) to adults (age 15) and the 15-17 year outputs.
Follow-up: John Stover and Peter Johnson
Review at Reference Group Meeting, September 2012

4.2 Age distribution of new infections

When new infections in the 5-year age groups are divided into single age years (using Beers Method), it is observed that the distribution of new infections can have very abrupt transitions between age years with some years having negative numbers of new infections. This should be corrected.

Recommendation: Split 5-year data into single years and make sure it never goes negative; create smoother transitions.
Follow-up: John Stover and Peter Johnson
Review at Reference Group Meeting, September 2012

4.3 Age-specific Mx: There seem to be artificial lumps in the age-specific mortality transitions.

Recommendation: Use calendar year instead of Spectrum year for these transitions.
Follow-up: John Stover and Peter Johnson
Review at Reference Group Meeting, September 2012

4.4 Sex differential in non-ART mortality

The current methods used assume there is no sex differential in non-ART mortality (based on cohort data which suggests that after you adjust for age there is no sex difference[4]); however, when on ART we use higher mortality rates for males. We are unsure whether this difference is behavioural or biological.

Recommendation: Review assumptions for no sex differential in non-ART mortality, but on ART, higher mortality for males.
Follow-up: Alpha Network and Futures Institute
Review at Reference Group Meeting, September 2012

4.5 Orphan calculations

The current methods used in the orphan model require a stable epidemic and do not work properly when epidemics are rising/falling. UNICEF and PEPFAR still use the orphan calculations thus this should be revised. Detailed tracking of mothers and children are a first step to fixing this model.

Recommendation: Re-build the orphan model
Follow-up: Futures Institute and Peter Johnson
Follow-up: OGAC to fund the work to overhaul the orphan model
Review progress at Reference Group Meeting, September 2012

5. Guidance and Documentation

The following details the issues identified and the consensus recommendations derived at this meeting which pertain to creating and providing guidance documents to assist countries in the estimation process.

5.1 Data issues and model validation

More emphasis is needed for the necessity and importance that countries critically review all data, in detail, before inputting these data into Spectrum and EPP.

Recommendation: Develop a guidance document for data issues and validation
Follow-up: EPP team to develop

5.2 Sub-national estimates

There is a growing demand to produce sub-national estimates and thus countries will need guidance on how to create these estimates and projections and the data required in order to do so.

Recommendation: Develop guidance document on sub-national estimates, pool experiences of how countries have done these estimates and provide user recommendations.
Follow-up: UNAIDS and Futures Institute

5.3 File sharing

Countries often do not include the resample results when sending their documents to UNAIDS.

Recommendation: Change the terminology of the prompt (*"Do you want to include your resample results?"*) to make it clear that these files need to be included.
Follow-up: Futures Institute will amend

Appendix I: Meeting Agenda

Start	Duration	Subject	Speaker
830	*30*	*Continental breakfast available*	-
900	10	Opening remarks and introductions	Peter Ghys
Session 1 -Spectrum: R-flex and r-spline (Chair: Geoff Garnett)			
910	30	R-flex: Review of modifications made and summary of results (fit, projections, speed)	Le Bao
940	15	Discussion	-
955	20	R-spline: Review of modifications made and summary of results (fit, projections, speed)	Dan Hogan
1015	15	Discussion	-
1030	30	Group discussion: Recommendation for method to adopt, considering: *- How do the model fits compare between methods? Model fits for generalised vs concentrated epidemics?* *- How do the projections compare between methods? And in situations of scare data, out-of-sample?* *- How do the fitting times compare?*	
1100	*20*	*Coffee break*	-
Session 2 - Spectrum & EPP: Review of ongoing workand outstanding issues (Chair: Adrian Raftery)			
1120	20	Futures Institute Team: Current status, new additions, (CMX for adults?), work in progress, outstanding issues , time table	John Stover/Carel Pretorius
1140	10	Discussion	
1150	15	Futures Institute Team: Incidence patterns and proposed changes to match 50+ survey prevalence	John Stover/Carel
1205	10	Discussion	
1215	20	EPP Team: Current status, new additions, work in progress, outstanding issues, time table	Tim Brown
1235	10	Discussion	-
1245	15	EPP: Populations in concentrated epidemics	Tim Brown
1300	10	Discussion	-
1310	*50*	*Lunch*	-
1400	20	Global AIDS Estimates: Review of specific country issues and problems identified during the final preparation of national estimate and projection files	Karen Stanecki
1420	15	Discussion	-
Session 3 - Model Testing (Chair: Peter Ghys)			
1435	20	Priortiy list of issues identified during model testing	Peter Johnson
1455	15	Discussion	-
1510	*20*	*Coffee break*	-
Session 4 - Spectrum: New data available for CD4 count and CD4 progression (Chair: Josh Salomon)			
1530	15	CD4 progression: Review of further comparison of Lodi et al (CASCADE data) to Spectrum	Jeff Eaton
1545	10	Discussion	-
1555	15	CD4 progression: Review of data available from Africa Centre	Till Barnighausen
1610	10	Discussion	-
1620	15	CD4 progression: Review of new data available from home-based testing in Uganda and South Africa	Ruanne Barnabas
1635	10	Discussion	-
1645	15	CD4 progression: Review of new data available from IeDEA Consortium	Constantin Yiannoutsos
1700	20	Group discussion: Recommendations for CD4 progression parameters in Spectrum	-
Session 5 - Timeline (Chair: Peter Ghys)			
1510	15	Timeline	Group
1525	10	Wrap-up and close	Peter Ghys

Appendix II: List of Participants

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2. Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults: recommendations for a public health approach. Geneva: World Health Organization Department of HIV/AIDS; 2006.

3. Suthar AB, Granich R, Mermin J, Van Rie A. Effect of cotrimoxazole on mortality in HIV-infected adults on antiretroviral therapy: a systematic review and meta-analysis. Bull World Health Organ. 2012 Feb 1;90(2):128C-38C.

4. Zaba B, Marston M, Crampin AC, Isingo R, Biraro S, Barnighausen T, et al. Age-specific mortality patterns in HIV-infected individuals: a comparative analysis of African community study data. AIDS. 2007 Nov;21 Suppl 6:S87-96.