Incidence & EPP/Spectrum

Report and recommendations from a meeting of the UNAIDS Reference Group on Estimates, Modelling and Projections held in Barcelona, Spain, 9 October 2013

REPORT & RECOMMENDATIONS

The meeting of the UNAIDS Reference Group on Estimates, Modelling and Projections was organised for UNAIDS by the 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.

Kelsey Case, October 2013

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.

Meeting Objectives

The specific objectives of this meeting were to:

1) Review the performance of current incidence assays available and discuss assays in the near future pipeline.

2) Review and discuss new methods for incorporating data from incidence assays within the model fitting in EPP.

3) Review and discuss the detection of significant declines in incidence.

Approach

The meeting featured presentations combined with group discussion to generate consensus recommendations. The list of participants is included in Appendix I and the meeting agenda 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, provides an opportunity to review current approaches and also helps 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.

Incidence assays and their application within the EPP framework

There are many different incidence assays currently in development and there has been substantial progress in recent years with many countries planning on using these assays to test for recent infections in those found HIV positive through national surveys. It is important that data from these assays will be able to inform estimates generated in the near future and are able to be incorporated into the tools currently available.

CEPHIA: Update on incidence assay performance results, *Gary Murphy*

The Consortium for the Evaluation and Performance of Incidence Assays (CEPHIA) is a large collaboration with Public Health England (PHE), Blood Systems Research Institute (BSRI), University of California, San Francisco (UCSF) and the South African Centre for Epidemiological Modelling and Analysis (SACEMA). The initial 3-year project was to develop a specimen repository and perform systematic (and independent) evaluation of the current incidence assays. CEPHIA 2 is now funded to support biomarker discovery and collect other sample types.

A Target Product Profile table (TPP) has been developed and revised over time for what is required for a cross-sectional incidence assay (e.g., sample type, shelf life, mean duration of recent infection [MDRI], false recent rate [FRR], etc.) and what is both acceptable and ideal performance for these specifications. The CEPHIA repository currently has over 6,000 specimens and diverse panels for evaluation of performance. Assays under evaluation:

1. LAg (newish CDC assay)
2. Less-Sensitive Vitros
3. BED
4. BioRad Avidity (plate based, likely to take over from BED in US for national programme)

The assay data are evaluated for their performance with all specimens and with the challenge specimens removed. Note that the specimens do not reflect the reality in a particular population; they have been selected to help understand how the assays perform in specific challenge settings.

Brief overall performance summary for detecting recent infections:

- BED: Major problems
- L-S Vitros: Problems even without challenge specimens
- LAg: Appears to perform well once the challenge specimens are removed
- BioRad: Appears to perform pretty well

Summary from FRR challenges:

- Treatment and viral load (undetectable) are both substantial challenges
- Early treatment has profound effect on ability of all assays to classify recent infections
- Subtype D performs poorly on most incidence assays

Overall, no assay currently fulfils all TPP acceptable criteria but they are getting closer. All assays have high FRR in ART suppressed individuals which is particularly important when considering use of these assays at the population level. No single test alone is likely suitable at the population level; however, the use of an algorithm with low viral load as a marker of non-recency may be effective. New assays currently in the pipeline include the Geenius assay (results soon) and the Architect Avidity assay which demonstrated improved FRR challenge panel results. The CEPHIA group is receptive to the needs of researchers and would like to further develop a coordinated approach.

Discussion: It was discussed that algorithms exploring the combination of LAg with VL are underway and should be available early next year. CEPHIA is also rapidly trying to get dried blood spot samples

for evaluation. These samples have the potential to get a false result fairly easily but have not been thoroughly tested. It will be 18 months before CEPHIA has enough dried blood samples to conduct a proper analysis. For use of this information to inform estimation in EPP, the essential information includes the FRR at a population level (weighting the challenge sets to what is observed in the population) and also with and without viral load exclusions and treatment.

Recommendation: UNAIDS and the Reference Group to work with CEPHIA on defining the TPPs and generating recommendations for the calibrating parameters for specific incidence assays.

Use of incidence assays within the EPP framework, *Le Bao, Alex Welte, Hilmarie Brand*

The Estimation and Projection Package (EPP) in the AIM module of Spectrum fits an epidemiological model to surveillance data. At any given time, EPP calculates the size of the uninfected population, the size of the infected population and consequently, the prevalence rate and the incidence rate. The likelihood has previously only been defined for the prevalence rate; however, with data from incidence assays that test for recent infection, this information can also be incorporated into the estimation process by adding the additional log likelihood for the incidence data to the EPP log likelihood. Alternatively, the prior distribution of prevalence and incidence can be defined based on the incidence assay data likelihood, which leads to the same result (unless incidence is close to 0, in which case this approach will not work thus the former approach used).

Simulation 1 (no DHS, consistent incidence): Fit model as normal, simulate the incidence assay data (FRR=2.5%, MDRI=150 days, and N=5,000) and then refit with this additional information included.
Results: When the data from the incidence assay are in agreement with incidence in EPP, the trajectories are quite similar (minimal effect), but the confidence intervals are narrower.

Simulation 2 (no DHS, inconsistent incidence): Same approach as above but doubling and halving incidence from EPP and widely varying the sample size.

Results: When incidence assay data and EPP incidence are not in agreement, prevalence and incidence change more dramatically in relation to the sample size, with extremely large sample sizes essentially forcing prevalence and incidence to go through the assay data. The confidence intervals are also narrower.

Simulation 3 (including DHS)**:** Including time series DHS data results in less dramatic changes in the trajectories.

Discussion: It is relatively simple to incorporate incidence assays in the EPP framework. This will result in extra computing time especially when the assay data are inconsistent with incidence in EPP, but it may be possible to implement a likelihood interpolation (instead of doing all integrations to correct true likelihood and approximate likelihood) to make this more efficient. However, the national survey data will still drive the trajectory until the assay sample sizes are huge and the false recent rates at the population level are greatly decreased. The FRR assumptions utilised in the simulations (2.5%) are much lower than the current performance of these assays on population level samples. Future additional considerations include use of these assays in EPP with sub-national epidemics and in concentrated epidemics and the use in countries with a real incidence dataset.

Recommendations:

- **Test doubling incidence, declining incidence and sample sizes in-line with what will be expected from national surveys.**
- **Move forward with incorporating the possibility for including data from incidence assays into the EPP fitting approach.**

Follow-up: Le Bao, Alex Welte

Detecting significant declines in incidence

One of the Millennium Development Goals is to *reduce sexual transmission of HIV by 50%* by 2015. As a result of this goal and country targets in line with this goal, countries and the global community are interested in having tools that allow the estimation of these declines in incidence. In the 2013 Global Report, UNAIDS also reported on countries with incidence declining by 50%. This is a topic of contemporary interest and has also been recently addressed by the HIV Modelling Consortium.

Update from the HIV Modelling Consortium: HIV incidence declines meeting, *Tim Hallett*

The September 2013 HIV Modelling Consortium meeting on incidence declines conducted detailed investigations into EPP and Spectrum to identify if declines in incidence could potentially be over- (or under-) stated. While there were no major findings that would contradict the results, a few areas have been identified for further follow-up and research:

- Overestimation of numbers on ART, will result in incidence driven lower and may occur due to over-reporting, not accounting for loss to follow-up, and in EPP because there is more ART included than there should be (should only be those 15-49 but all adults are included).
- Natural dynamics and heterogeneity in susceptibility which may explain incidence declines in the absence of behaviour change.
- Fragile Network Syndrome, theory that there is little redundancy in a network thus a small decline has a large effect.
- Age-structured models which more fully captures the change and variability in patterns of infection over time among different age groups.

The HIV Modelling Consortium will put a call out for work in these areas and will report back on preliminary findings next year.

Methods in Spectrum for detecting significant declines in incidence, *John Stover*

In the *Tools* section of Spectrum there is an *incidence analysis* tool which calculates significant declines in incidence and is what is used by UNAIDS to identify countries with significantly declining incidence in the 2013 Global Report. For each country, 1000 draws in incidence (incidence curves) are evaluated. The user selects the time period for the analysis, the percentage decline, and the percentage cut-off for inclusion. For the Global Report, the analysis was from 2000-12, countries with a 50% decline and 95% of all curves had to decline by the percentage specified.

It was discussed that the quality of the country file is not fully incorporated in this analysis and it might be useful to review in more detail the files from the countries with significant declines and pressure test these findings, perhaps as part of the HIV Modelling Consortium work.

Recommendation: Consider reviewing countries with significant declines and "pressure test" these declines in a formal panel. Follow-up: UNAIDS, Reference Group.

Trends in incidence in low and middle income countries, *Karen Stanecki*

Review of incidence trends among key populations across regions and comparisons of estimated new infections among risk groups from Spectrum to those estimated using the Modes of Transmission model. This information will be used to inform the 2015 report. It was discussed that more stringent criteria are needed for this analysis (e.g. defining criteria for a trend) in order to be able to make statements. By 2015 it is likely that only a few strong assertions will be able to be made regarding the directions of trends in key populations, and for many regions and more general or cautious statements will need to be made.

Recommendations:

- **Investigate the files in more detail (data entered, curve fitting, trends) but first define criteria for inclusion in the detailed comparison. Generate rules to classify the strength of the trend with a score.**
- **MoT vs EPP: Compare population sizes and compare prevalence levels**

Follow-up: UNAIDS, *April 2014*

Appendix I: List of Participants

Le Bao
Penn State
State College, Pennsylvania, USA

Tim Brown
East-West Center,
Honolulu, Hawaii, USA

Kelsey Case
Department of Infectious Disease Epidemiology
Imperial College London, UK

Anindya De
US Centers for Disease Control & Prevention
Atlanta, USA

Geoff Garnett
Bill & Melinda Gates Foundation
Seattle, WA, USA

Peter Ghys
UNAIDS
Geneva, Switzerland

Simon Gregson
Department of Infectious Disease Epidemiology
Imperial College London, UK

Tim Hallett
Department of Infectious Disease Epidemiology
Imperial College London, UK

Mike Isbell
Consultant
New York, NY USA

Mary Mahy
UNAIDS
Geneva, Switzerland

Kim Marsh
Consultant
Edinburgh, Scotland

Bradley Mathers
University of New South Wales
Sydney, Australia

Gary Murphy
Public Health England
London, UK

Ryosuke Omori
Weill Cornell Medical College
Ar-Rayyān, Qatar

Katrina Ortblad
Institute for Health Metrics & Evaluation
Seattle, WA, USA

Robert Puckett
East-West Center
Honolulu, Hawaii, USA

Keith Sabin
UNAIDS
Geneva, Switzerland

Karen Stanecki
Consultant
Arlington, VA, USA

John Stover
Futures Institute
Glastonbury, CT, USA

Ard van Sighem
Stichting HIV Monitoring
Amsterdam, Netherlands

Alex Welte
SACEMA
Stellenbosch, South Africa

Peter Young
Contractor
Mozambique

Appendix II: Meeting Agenda

Incidence and EPP/Spectrum

Wednesday, October 9th, 2013

Incidence assays and their application within the EPP framework (Chair: Tim Hallett)			
1220	20	Update on performance of incidence assays currently available; update on incidence assays in the pipeline and likely benefits of these assays	Gary Murphy, *Public Health England*
1240	10	*Questions and discussion*	
1250	*70*	*Lunch*	-
1400	25	Use of incidence assays within the EPP framework	Le Bao & Alex Welte
1425	15	*Questions and discussion*	-
1440	30	**Discussion & recommendations for use of incidence assays within the EPP framework**	ALL
Detecting significant declines in incidence (Chair: Peter Ghys)			
1510	15	Update from the HIV Modelling Consortium meeting - recommendations	Tim Hallett, *Imperial College London*
1525	10	Methods currently available in Spectrum for detecting declines in incidence	John Stover, *Futures Institute*
1535	20	Discussion	ALL
1555	5	Final comments and closure	ALL
1600		Close	-