Methods and assumptions for estimates of children in need of treatment for HIV

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TECHNICAL REPORT AND RECOMMENDATIONS

UNAIDS

Methods and assumptions for estimates of children in need of treatment for HIV

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Present: Siobhan Crowley, Geoff Garnett, Peter Ghys, Charles Gilks, Eleanor Gouws, Chika Hayashi, Kirsty Little, George Loth, Rob Lyerla, Karen Stanecki, John Stover (by telephone), Peter White.

Presentations were received from Peter Ghys, and Kirsty Little, who presented initial demographic modelling work done with Marie-Louise Newell (referred-to hereafter as the "N&L model").

Introduction

There is a need to estimate numbers of children requiring co-trimoxazole and ART treatment globally, regionally and at the country level for programme planning. Globally this number will be between 510,000 (the annual number of AIDS deaths in children) and 2.2 million (the estimated number of children living with HIV). Development of the Spectrum model to make the necessary estimates of the demand was discussed.

Key parameters for estimating demand for paediatric HIV treatment are:

(i) prevalence of HIV amongst women of child-bearing age;
(ii) fertility rates of HIV+ women of child-bearing age;
(iii) rates of transmission from HIV+ mothers to their children (which are affected by coverage and effectiveness of PMTCT programmes);
(iv) mortality rates of HIV+ children with and without moderate-severe disease (MSD), and the impact of co-trimoxazole and ART on these rates;
(v) rates of progression to MSD of HIV+ children and the impact of co-trimoxazole and ART on these rates;
(vi) coverage of co-trimoxazole and ART treatment.

Many of these parameters will be age-specific, and many data are currently unavailable, so estimates often have to be based on expert opinion and data from different parts of the world.

Mother-to-child transmission (MTCT) rates

These are very variable, with reported figures typically in the range 12%-45%. In the N&L model, the following values were used: breastfeeding, without PMTCT intervention: 30%; breastfeeding, with PMTCT intervention: 20%; without breastfeeding, without PMTCT intervention: 20%; without breastfeeding, with PMTCT intervention: 10%.

Mortality rates

Children whose mothers are HIV+ have higher mortality rates, even if the children themselves are HIV-. It was assumed that there are regional differences in the

mortality rates of HIV- children, but not HIV+ children, because HIV infection dominates mortality rates.

Mortality data for HIV+ children in resource-limited settings are lacking. Mortality data up to age 5 are available in Newell et al. 2004. For older ages, the N&L model assumes annual mortality rates of 0.3% and 9% in HIV- and HIV+ children, respectively. For mortality of MSD cases, it was assumed that the age-dependency of mortality rates would have the same shape as in Chintu et al. 2004 (i.e. highest for the youngest age-groups, then constant beyond age 4) but that the actual values would be higher. Mortality rates were estimated by assuming that in the absence of treatment 95% of children will have developed MSD by age 10 years, although many will not be alive by age 10 years. Mortality in the 1st year was not allowed to exceed 90%.

The mortality data are for a cohort comprising both those infected neonatally and those infected in the first few months of life. The effect of the precise age of infection cannot be distinguished.

Neonatal mortality can account for up to 30% of infant deaths, and a typical mortality rate for the first month of life would be 10%. However, in the "birth cohort" data that were available at the meeting, the mortality rate for the first month of life was less than 1%, suggesting that affected neonates were in fact excluded from the data or prevented through study conditions. This is acceptable in analyses, provided those neonates are also excluded from the fertility rate data. It is important to ensure that there is consistency between the fertility rate and mortality rate data. If the fertility rate data consider all live births and the mortality rate data consider only those children who survive (e.g.) the first few weeks of life, then a correction factor needs to be applied, which would reduce the projected numbers of children in all age-groups by a constant factor (e.g. 10%). Relatively little neonatal mortality is likely to be HIV-attributable.

Impact of co-trimoxazole

In high-HIV-prevalence regions, all children born to HIV+ mothers should be prescribed co-trimoxazole until their HIV status is known (in most countries, this is not before 18 months), and then continued for those who are HIV+. Reported expert opinion is that provision of co-trimoxazole reduces mortality in the first year of life of HIV+ children by 60% and at later ages by 32%-57% (Chintu et al. 2004). The duration for which co-trimoxazole is effective is not known, but Chintu et al. (2004) reported no decline in effectiveness over a 2-year period, but did not have data beyond that period. Whether the effectiveness of co-trimoxazole depends upon the age at which provision begins is not known: Chintu et al. (2004) did not detect an age-effect, but few children under 1 year of age were included in the study. The N&L model assumes that the effect of co-trimoxazole is due to prevention of progression to MSD, and that it has little effect on mortality in MSD individuals, reducing it by only 20%.

Impact of ART

An immediate effect of providing ART to the general population is an increase in HIV prevalence due to reduced mortality. This includes women of child-bearing age, and the fertility of those HIV+ women is increasing, which increases the numbers of children born to HIV+ mothers. However, another effect of giving ART to mothers is to reduce rates of mother-to-child transmission (MTCT). Models need to take account of all three of these effects.

The HIV status of children born to HIV+ mothers cannot be determined by simple antibody testing before 18 months, due to the presence of maternally-derived antibodies. Since children will only be prescribed ART after a diagnosis of HIV infection, this means that, in many settings, many HIV+ positive children under 18 months will die before they are eligible for ART. Implementation of testing to allow diagnosis of HIV infection in children under 18 months, allowing early treatment, will increase the number of children eligible to receive treatment, and, by reducing mortality rates, it will increase the duration of treatment of those children. The impact will be setting-specific because it will depend upon the availability of testing and the willingness of parents to have their children HIV-tested, as well as the prevalence of HIV in mothers. Fassinou et al. (2004) reported that the effectiveness of ART in children in resource-limited settings is similar to that in developed countries, with an estimated one-year survival probability of 91%.

Recommendations

1) Modelling the number of children in need of treatment

For advocacy, model estimates are required to show the burden of disease and mortality, and the potential impact of interventions. Until there is interest in the programme, there will not be the data available for more sophisticated modelling work required for detailed programme planning. Model scenarios should consider the impact of provision of co-trimoxazole alone, AZT alone, and both co-trimoxazole and AZT.

The effect of testing to allow pre-MSD diagnosis of HIV infection in young children (<18 months old) is an important question for modelling to address because it will increase the number of children eligible to receive treatment, and increase the average duration of treatment.

The initial N&L model assumes that population size, age-structure, HIV prevalence and mortality rates have been stable over time, and so predicts equilibrium numbers of children requiring treatment assuming that treatment has been absent or present (with an unchanged regimen) for 10 years. Future models will allow HIV prevalence in mothers and treatment availability to change over time.

In most age groups, there will be a mixture of recent and long-term MSD cases, who will have different prognoses. Current mortality rate data will be an average of these different mortality rates. The effect of the introduction of treatment provision will be dynamic, because it will increase survival of HIV+ children, including those with MSD, and so will (e.g.) increase the proportion of those in a given age category who have long-term – rather than recently-developed – MSD. Hence the average mortality rates will change.

These dynamics are important during roll-out. Additionally, if diagnosis of HIV infection in children under 18 months is introduced and ART is provided to those who need it, then progression rates will change. Also co-trimoxazole will affect rates of progression to MSD. A model incorporating age- and weight-stratification is needed. However, initially, projections of the impact of paediatric treatment can only be made in the short term, due to lack of data on the impact of the intervention.

Whereas the N&L model considers children aged up to 10 years, Spectrum considers those aged up to 15 years, and so needs estimates of mortality rates up to this age, although empirical data are lacking. Mortality estimates for ages 11-15 will be derived from an extension of the N&L model. A complication when modelling children over 10

years of age is that their risk of acquiring HIV other than from their mother becomes non-negligible in many settings.

There needs to be the capacity to specify age-variation in the proportion of children requiring co-trimoxazole and ART who receive it, due to the frequent lack of facilities for diagnosis of HIV infection before 18 months.

The required model outputs are the number of children exposed to HIV and the number infected; and the total number requiring co-trimoxazole and ART by age, and the number of those who became eligible for treatment that year. Model results should be output in both aggregated and disaggregated form. The latter give more detail for programme planning, but the former are more suitable for advocacy, because they are easier to interpret and because the numbers of individuals are larger.

2) Modelling weight distributions of children in need of treatment

The weight of the HIV+ patient is important in terms of drug formulation as well as dosage. In general, it is not possible to use adult formulations in individuals <25kg, and many patients are severely underweight due to malnourishment. The demand for 'paediatric' formulations needs to be estimated, to persuade pharmaceutical manufacturers to being producing them. As well as expressing requirements for ART in children by age category, it should also be expressed by weight category, when further work has made this possible. This is complicated because provision of therapy results in rapid weight gain (e.g. Fassinou et al. 2004).

Current implementation in Spectrum

Since there is still some discussion going on about the detailed age pattern of mortality with and without treatment, we have implemented a simple version. This works just like the adult ART in Spectrum by using a simple proportion of those on treatment surviving until the following year. There are three inputs:

- percent of children on cotrimoxazole surviving to the next year;
- percent of children on ART surviving to the next year; and
- percent of children on both ART and cotrimoxazole surviving to the next year.

We estimated the default values for these percentages as those values that will give same survival by age 10 as in the schedules that were presented. They turn out to be:

- cotrimoxazole: 0.91;
- ART: 0.90;
- both: 0.942.

While this approach does not have all the detail available in the N&L model it does have the advantage that it is easy to understand the inputs and change them.

The population needing treatment is defined as follows:

- Cotrimoxazole: all children born to HIV+ mothers up to age 18 months, plus all HIV+ children 18 months to 14 years old.
- ART: all children with moderate-to-severe disease. Since the rates of progression to death are similar in the N&L model and Spectrum already, and progression to MSD occurs about 2 years before death in the N&L model, we have kept the current Spectrum progression curve and estimate that treatment is needed two years before death.

In summary this version is based on the data in Newell et al. (2004) but does not implement all the age detail available in that paper. We can do this in future versions but it seemed premature to do it now. For both cotrimoxazole and ART the inputs are specified as the percent of those in need who get treatment.

This model shows similar behaviour to the adult ART model in that deaths tend to catch up with the no treatment case once the percent on treatment stops increasing. This is puzzling since this does not appear to be seen in the mortality data from the US and Europe; it may be due to how we are defining treatment coverage in the model. We specify that a certain percentage of those needing treatment get it. As coverage increases more and more people are continuing on coverage. As a result a large and larger percentage of those needing treatment are those already on treatment. If we say that 50% of those needing treatment get it, then in a mature programme where most people needing treatment are already on treatment, the 50% coverage figure means that many who are currently on treatment will not get it next year. So some people are forced to stop treatment and hence die quickly. This would not happen if we defined coverage as the percent *newly* needing treatment that get it. In that case we would not be stopping treatment for anyone who is continuing successfully on it. This is not how the 3x5 target was developed, but it may make more sense for projections.

References

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Appendix: List of Participants

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