HIV prevention policy and programme planning: What can mathematical modelling contribute?

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Chapter 18

General discussion

This thesis addresses the topic of policy making and programme planning with respect to novel HIV prevention tools and hypothesises that mathematical modelling can contribute to evidence-informed decision-making by assessing the likely epidemic impact and cost of introducing additional HIV prevention modalities into combination HIV prevention. The thesis began with an article that described changes in the state of the global HIV epidemic (Chapter 2)(1), followed by two articles that defined combination HIV prevention, both in its broad meaning of combining biomedical, behavioural, and structural HIV prevention components (Chapter 3)(2) and in the more narrow concept of combining components of biomedical HIV prevention (Chapter 4)(3).

Part 2 presented the example of male circumcision (MC) for HIV prevention as a new technology, albeit the oldest surgical procedure in the world, undertaken heretofore primarily for cultural, social, or religious reasons. It covered some of the inputs to policy making on MC scale-up, including the scientific evidence (Chapters 5 and 7)(4)(5), the sociolegal barriers (Chapter 6)(6), male circumcision and HIV risk for women (Chapter 8)(7), and factors influencing country adoption and scale-up of voluntary medical male circumcision (VMMC) (Chapter 9)(8). These set the stage for the discussion in Part 3 of the contribution of mathematical modelling and costing to decision making on VMMC for HIV prevention, including the result of practical application of the Decision Makers Programme Planning Tool in 13 priority countries and the challenge of costing demand creation activities (Chapters 10-13)(9)(10)(11)(12).

Part 4 outlined the promise of PrEP (Chapter 14)(13) and presented a systematic review of oral PrEP cost-effectiveness studies that revealed that prioritising key populations at highest risk of HIV acquisition would be the most cost-effective strategy (Chapter 15)(14). The potential population impact of an HIV vaccine regimen similar to that of the RV144 regimen, which had shown moderate effectiveness in a community-based trial in Thailand, was explored by 5 modelling teams in Part 5 (Chapter 16)(15). The impact on HIV incidence of increasing coverage of NSP, OST, and ART among people who inject drugs in Odessa (Ukraine), Karachi (Pakistan), and Nairobi (Kenya) and alleviating key structural barriers to uptake of risk reduction measures was explored through mathematical modelling in Part 6 (Chapter 17)(16).

What lessons can be drawn from this body of work about the potential contribution of mathematical modelling to the policy formulation process and to programme decision-making on novel HIV prevention tools? As this thesis sets out to demonstrate, the most salient example to date of mathematical modelling influencing policy and programme planning is the VMMC modelling and its practical application in a useful planning tool(9). The systematic review of PrEP modelling has sent a signal that factors such as context, adherence, and coverage clearly influence cost-effectiveness, suggesting that this is an HIV prevention tool that should be tailored to those most likely to benefit(14). The HIV vaccine

modelling served to provide a measure of encouragement to a field that, on the one hand, finally had a first proof of concept result and, on the other hand, had a result of low efficacy with wide confidence bounds(15). The modelling work undertaken for the Lancet series on injecting drug use in 2010 broke new ground in its effort to link structural determinants and HIV risk through non-provision or inadequate provision of key HIV prevention services or modifiable environmental influences on HIV risk(16).

Mathematical modelling clearly can contribute to decision-making on HIV prevention policy and programming, however several concerns have been raised about modelling in the HIV prevention field and these tend to undermine its potential to provide insights. Following a description of the evolution in thinking and practice of mathematical modelling in relation to novel HIV prevention tools, some lessons learned and their potential implications are discussed, using examples from the preceding articles. The thesis concludes with some practical questions that HIV prevention policy makers and programme planners can ask about mathematical models when modelling results are presented to them.

The potential contribution of mathematical modelling to policy formulation on HIV prevention

Establishing the point of departure: the need for good incidence data

Mathematical models have been used for decades to provide insights into the dynamics of the HIV epidemic and inform national HIV programming by estimating HIV incidence, HIV prevalence, numbers of people dying of HIV-related illnesses, and numbers of children orphaned by AIDS. In the HIV prevention world, mathematical models can only be useful if they are populated with accurate information concerning the epidemic setting in which a novel HIV prevention tool could be introduced. Since not every person's HIV status is known, nor is everyone part of a cohort study documenting HIV seroconversion, extrapolations must be made to estimate HIV prevalence and HIV incidence. Trends in HIV prevalence can be helpful but, as indicated in Chapter 2, they require careful interpretation since increases may indicate improved survival rather than increasing incidence(1). In the same manner, declines in HIV prevalence may reflect the natural evolution of an epidemic(17) rather than a strong, effective prevention programme, as was seen for example in Thailand(18)(19).

HIV incidence, or more specifically, trends over time in HIV incidence, is the best metric for determining where HIV prevention programmes are most needed. Further, it is the gold standard for measuring whether programmes are having intended effects. However, knowledge of transmission patterns is not easy to obtain. Improved incidence assays that could measure a well-characterised biomarker for the recentness of infection would have immediate practical

application(20). For example, validated, reliable assays could be used to estimate HIV incidence in surveillance programmes, contribute to impact evaluations, and could assist in community HIV prevention trial planning. In the absence of these, a broad-brush picture is painted by surveillance strategies such as antenatal care (ANC) HIV testing to give an approximation of HIV prevalence in the general population. Data from national Demographic and Health Surveys with non-nominal HIV screening (DHS+) help to calibrate the ANC surveillance data from generalised epidemic settings(21). These provide inputs to the UNAIDS Estimates and Projection Package (EPP), an epidemiological model that UNAIDS has used since 2001 to model HIV incidence, with updates and revisions(22). EPP is now combined with Spectrum, a programme that takes EPP outputs and generates programme-related outputs(23).

Triangulation of information can permit more precision in country- and even province- or district-level estimates, depending on the amount and quality of surveillance data available. When improved modelling methodologies and better data* informed a critical downward adjustment of UNAIDS global HIV estimates, published in the Global AIDS Epidemic Report of June 2004(24), UNAIDS faced a knowledge translation challenge of explaining this change to the media, development partners, national governments, advocates, activists, and others. Explaining the concept of imprecision in the estimates, by introducing, for the first time, ranges around the estimates to convey the extent of uncertainty, was generally well received, in part because it implied increased transparency. Furthermore, adjusting all the biannual estimates retrospectively revealed that the numbers of people living with HIV had continued to grow from the adjusted 2001 baseline against which country progress is marked for the United Nations General Assembly Declaration of Commitment on HIV/AIDS(25). Partners understood that the epidemic curve remained the same globally but at a slightly lower level than previously represented.

Governments renewed their commitments to reducing and eventually eliminating HIV infection in 2006(26) and again in 2011(27). Tracking country progress in terms of reductions in HIV incidence, i.e. fewer people becoming newly infected with HIV, is a key monitoring and evaluation indicator. UN member states have set goals of a 50% reduction in both sexual HIV transmission and in HIV transmission among people who inject drugs, a 50% reduction in tuberculosis deaths among people living with HIV, reaching 15 million eligible people with ART, and ensuring that no children are born with HIV, while reducing AIDS-related maternal deaths by half, all

* The assumption that HIV prevalence among pregnant women approximates the prevalence among both men and women in surrounding communities may not be valid in all countries. Data from antenatal clinics do not fully represent remote rural populations and adjusting for this bias is hampered by a lack of data. In household surveys, people who refuse to participate, and those who are not at home when the survey team passes, may well have higher levels of HIV infection. Contrasting and using both sources of information can provide more realistic inputs to national estimates.

to be achieved by 2015. 'Getting to zero' is the vision: zero new HIV infections, zero discrimination, and zero AIDS-related deaths(28).

It is against this backdrop that the potential contribution of novel HIV prevention tools must be assessed. Time is short and policy makers want to see limited funds used most effectively, ideally for visible results 'on their watch' rather then further into the future. With HIV testing recognised everywhere as the doorway to prevention, treatment, support, and care, progress in increasing HIV testing coverage from the current suboptimal levels is being closely tracked. HIV testing behaviour and knowledge of HIV status is assessed using the indicator for generalised epidemics of % men and women aged 15 years and older who have been tested in the past 12 months and know their result. For concentrated and low-level epidemics the corresponding indicator is % of key populations such as sex workers, people who inject drugs (PWID), and men who have sex with men (MSM) who have been tested in the past 12 months and know their result. Some countries are going well beyond simply comparing HIV testing statistics to surveillance information in order to assess epidemic trends and are actively promoting HIV testing in both care settings and in the community. Since the advent of WHO guidance on provider-initiated HIV testing and counselling in 2007(29), HIV testing uptake in health care settings in which HIV testing is routinely proposed to patients has increased(30)(31) although poor linkages to care(32) and losses along the care cascade persist(33). South Africa is a striking example of a successful community-based testing campaign, with an estimated 20 million people reached during a year-long testing campaign in 2010(34).

Among the proxy measures that have been used by many countries to estimate HIV incidence are HIV prevalence among young women attending antenatal clinics, HIV prevalence among 15- to 24-year old participants in national DHS+ surveys, and modelled incidence estimates for adults aged 15-49 years(35). Trends in HIV prevalence among 15- to 24-year old young people are considered a proxy for HIV incidence since sexual debut during this period presents the first opportunities for sexual exposure to HIV and other sexually transmitted infections. But for national HIV prevention planning purposes, a more extensive understanding of spatial and temporal variations in HIV transmission patterns and associated risk behaviours is needed to define where and how the epidemic is moving locally for effective programme planning. Previous numerical proxy threshold approaches that simply defined HIV epidemics by HIV prevalence levels as low-level (less than 5% in any sub-population), concentrated (greater than 5% in any key population but less than 1% among pregnant women), and generalised (greater than 1% among pregnant women) have been discarded because of their perceived rigidity and because they were a source of confusion to policy-makers, although the terminology remains in use(36).

Second generation HIV surveillance focuses on multiple information sources at country level, with UNAIDS/WHO recommending use of the Spectrum modelling

package(23)(37) to estimate the number of people (adults and children) currently living with HIV, number of new HIV infections, number of adults and children eligible for antiretroviral therapy, number of women in need of prophylaxis to prevent mother-to-child HIV transmission, and number of AIDS-related deaths. The Modes of Transmission (MOT) analysis introduced in 2007 estimates the distribution of new adult HIV infections by key modes of exposure(38) and has been recently revised(39) in light of some limitations(40)(41). Nonetheless, since 2007 more than 40 countries have conducted the country-owned, multistage process of 'Know your epidemic, Know your response', of which the MOT analysis is an integral component, to inform resource allocation decisions(39)(42). As attention has increasingly turned to synthesising and triangulating data, improving data quality, conducting uncertainty analyses, being transparent in communicating about model strengths and weaknesses, and, most of all, engaging multiple stakeholders in validating inputs and owning results, data gaps have been highlighted. MOT analyses have shone a spotlight on neglected key populations at the same time that mathematical modellers have been encouraged through these country-led processes to become more attuned to the sociolegal and political environments in which resource allocation decisions are made(43).

Mathematical Modelling of Novel HIV Prevention Tools

In the world of biomedical HIV prevention, mathematical modellers tackled a wide range of topics, such as the potential impact of HIV vaccines and microbicides, even before any randomised controlled trial (RCT) results were available. Their objective was to predict whether the addition of a vaccine or a microbicide could bring the reproductive rate, i.e. that average number of secondary cases generated by a single infectious person in a totally susceptible population, down below the threshold of 1(44). This modelling also provided estimates to basic scientists and product developers, among others, of the level of vaccine efficacy or microbicide effectiveness that would be required to accomplish this. For example, a variety of hypothetical effectiveness scenarios (often erroneously referred to as 'efficacy scenarios') was used in models of the potential impact of microbicides(45)(46)(47), including those looking at whether a microbicide that was active against other sexually transmitted infections (STIs) would contribute to its HIV effectiveness(48). The big breakthrough for modellers (and potentially also for women) came with the modest CAPRISA 004 1% tenofovir gel RCT results(49). Despite wide confidence bounds, these results were used to parameterise a model estimating epidemiological impact, with the model results(50) being presented in exactly the same session at which the RCT results were met with a standing ovation during the 18th International AIDS Society Conference in Vienna in 2010. Overall, modellers no longer have to invent possible trial effectiveness results for VMMC, oral PrEP, and an HIV vaccine candidate regimen, as they have been provided with the results of large randomised controlled trials.

Modelling the Impact and Cost of Voluntary Medical Male Circumcision

Five years prior to the results of the 1% tenofovir vaginal gel trial, the first male circumcision trial results in 2005 had been compelling, catalysing a process of reflection about the potential population-level impact of introducing and scaling up safe VMMC. When the first mathematical modelling meeting on male circumcision was convened in Geneva in 2005(51), although only the results of the first trial were known(52), it was judged timely to predict the impact of rolling out male circumcision services at population level. The likelihood that the two on-going trials might produce equally convincing efficacy evidence was strong. Interest was high in applying different types of models in different geographic settings to identify priority populations in which VMMC might have the greatest impact on HIV transmission. It was understood that modellers would need to take into account heterogeneity of sexual activity and the structure of sexual networks; to vary modes of service delivery by provider (doctors, nurses, clinical officers, counsellors), including costs of training, supervision, and monitoring, and by circumcision procedure and number of follow-up visits; and to model different rates of scaling up. They agreed to assess potential synergies with other services, such as STI treatment, HIV testing and counselling, condom promotion and provision, sensitisation and socialisation programmes for young men concerning gender relations and violence against women, behavioural counselling, and peer support. Available data were to be used for answering the main modelling questions and these would be formulated to identify costs to individuals, families, communities, and governments, differentiating between total resources required and cost-effectiveness analyses, and where possible, anticipating marginal costs with increasing coverage.

The additional input that was introduced in the VMMC modelling process was facility-based costing. The first presentation that incorporated facility-based testing data took place at the PEPFAR Implementers Meeting in 2007(53) and compared the costs of investing in VMMC services against HIV treatment costs averted in Zambia(54). By the time that the second VMMC modelling meeting was held at the South African Centre for Epidemiological Modelling and Analysis (SACEMA) in Stellenbosch, South Africa(55), the modelling results of three teams had been accepted for publication or published(56)(57)(58). In addition to reviewing progress in modelling the potential impact of male circumcision on HIV prevention and approaches to costing and cost-effectiveness, the meeting assessed a UNAIDS/Futures Institute programme planning spreadsheet tool for decision-makers and discussed the implications of the revised UNAIDS/WHO HIV survival estimate parameters for male circumcision modelling and costing. The spreadsheet tool was designed to calculate the costs of various programming choices for male circumcision, provide budgeting information in appropriate formats for funding proposals, calculate cost per HIV infection averted by programming option (age at circumcision, provider, coverage, speed of scale up) and show the time frame for impact on a country's epidemic. Modellers were

challenged to justify parameter values and assumptions about sexual behaviour, HIV testing frequency, speed of scale-up, and other factors. They were encouraged to refine their models, adjusting parameter inputs to reflect new data of which they had been unaware.

When the modelling teams were convened 4 months later in London(9), costing information was available from the three RCT along with data from costing studies in Lesotho(59) and Swaziland(60), in addition to the Zambian data(54). The eight key questions mentioned in Chapter One that have implications for policy and programmatic decision-making had been formulated and they underpinned the discussions at the meeting. Focus turned to the six modelling studies by members of what became known as the *UNAIDS/WHO/SACEMA Expert Group on Modelling the Impact and Cost of Male Circumcision for HIV Prevention* that had now been published(61)(56)(57)(62)(63) or were under review(64). Two modelling studies(65)(66) published after the meeting by modellers who had not played a role in the meeting's consensus process were included in the comparison of dynamic HIV transmission models and results published by the Expert Group(9). In interrogating the models for answers to the key policy questions, not all models were relevant to every question and quantitative model outputs could not always be compared because of the differing contexts to which each one referred and the alternative underlying assumptions that were employed. Nonetheless, the fact that these groups had worked independently using diverse modelling approaches strengthened the broad, qualitative consensus that emerged as the modelling group applied their models to the key questions.
The Expert Group found large benefits for heterosexual men in low MC prevalence, high HIV prevalence settings: one HIV infection averted for every 5 to 15 MC performed and costs to avert one HIV infection ranging from USD 150 to USD 900 using a 10-year time horizon. Two major concerns of policy makers, early resumption of sexual activity before wound healing and behavioural risk compensation(67), were predicted to have only small population-level effects on the anticipated HIV incidence impact of male circumcision. Benefits for women were indirect, but not insubstantial, as the probability of encountering a male sexual partner living with HIV fell over time. Synergies could be had to further reduce disease burden if male circumcision scale-up was accompanied by other HIV prevention strategies.

Perhaps most importantly, the London consensus meeting results further refined and validated the spreadsheet tool that became known as the Decision Makers Programme Planning Tool (DMPPT). It helps analysts and decision-makers to understand the potential costs and impacts of differing policy options for scaling up male circumcision services. In effect, this user-friendly pragmatic tool permits decision-makers to indirectly access the main findings from academic modelling studies. Using recent country-specific epidemiology figures and locally derived information about staff time and salaries, supplies, equipment, and shared facility and staff costs, the DMPPT calculates the cost of VMMC services by delivery

mode based on clinical guidelines and estimates the impact of VMMC scale-up on the HIV epidemic. Coverage levels and speed of scale-up can be varied to examine potential cost and impact under different scenarios. The DMPPT incorporates sensitivity analysis for key inputs, including the impact of male circumcision on women. It estimates HIV incidence, HIV prevalence, AIDS deaths, overall costs, and net cost per HIV infection averted as a function of the number of male circumcisions performed.

The potential of the DMPPT was revealed when UNAIDS and USAID through the Health Policy Initiative and Futures Institute funded facility-based costing studies in a number of priority countries and entered costing findings into the tool, along with epidemiologic and demographic data relevant for each priority country: Botswana, Lesotho, Malawi, Mozambique, Namibia, Rwanda, South Africa, Swaziland, Tanzania, Uganda, Zambia, Zimbabwe and Nyanza province in Kenya. For the 13-country exercise, data from the Zimbabwe costing study formed the basis for the unit cost because it had adopted the WHO MOVE model(68) to make efficient use of facility space and staff time, while bundling commodities required for VMMC. Supply chain costs and waste management costs that had not been included were added to the DMPPT. Inadequate information on demand creation costs resulted in these not being included, although a seven-step methodology to estimate demand creation costs was proposed, given the importance of tailoring strategies to specific country contexts(12). The unit costs were adjusted using after tax median monthly disposable salary to account for significant variations in labour costs across countries.

When the results were presented at the International Conference on AIDS and STIs in Africa in Addis Ababa in December 2011, on the very day that a series of PLoS Medicine articles on the cost, impact, and challenges of accelerated scaling up of VMMC was published(10), international leaders called for accelerated access to voluntary medical male circumcision in eastern and southern Africa(69). An investment of $1.5 billion US between 2011 and 2015 to achieve 80% coverage in the 13 priority countries, with an additional $500 million US to maintain 80% coverage out to 2025, would result in net savings of $16.5 billion. The base case parameter values and the assumptions used in sensitivity analyses were transparently laid out(11), along with each country's progress to date, emphasising the cumulative number and percentage of HIV infections that would be averted by 2025 through accelerated scale-up. South Africa, with 3% achievement towards its coverage target stood to avert more than a million HIV infections, while Zimbabwe with 1% of its coverage target attained would avert the highest percentage of new infections of any of the priority countries (41.7%)(10). An analysis undertaken to identify key barriers and facilitators influencing the speed of scale-up using the 'diffusion of innovation' conceptual framework(70)(71) classified countries as innovators (Kenya), early adopters (South Africa, Zambia, and Swaziland), early majority (Botswana, Zimbabwe, Tanzania, Namibia, and Mozambique), late majority (Uganda and Rwanda), and laggards (Malawi and Lesotho). Country

ownership, explicit political leadership, stakeholder engagement, and community mobilisation were the key drivers for early adoption and sustained scale-up(8).

What had started in 2005 as a small meeting to stimulate modellers to think about and undertake VMMC modelling in light of the Orange Farm male circumcision trial results, had led, through a process of open peer review and constructive criticism, to the development of a network of modellers keen to look at novel HIV prevention modalities. By 2011, their modelling work and the DMPPT refined by their modelling had informed resource mobilisation targets and scale-up objectives for VMMC in 13 priority high HIV prevalence countries. Among the wide ranging set of tools developed by UNAIDS, WHO, and partners was operational guidance(72), a surgical manual(73), human rights guidance(74), and a legal and regulatory self-assessment tool(75). All resources, including country progress reports and the WHO framework for evaluation of VMMC devices(76), are readily accessible, along with the DMPPT, on the website created by WHO, UNAIDS, FHI 360, and AVAC - www.malecircumcision.org.

Modelling the Impact and Cost of Pre-Exposure Prophylaxis

A similar process was undertaken to examine the potential impact that pre-exposure prophylaxis with antiretroviral drugs, both systemically through tablets and topically through gels, could have in different populations. A first PrEP Modelling Meeting convened by UNAIDS and WHO in Geneva in March 2010(77), brought together experts in mathematical modelling to compare current models and discuss the various modelling approaches that could be used, although no RCT effectiveness trial data were yet available. This consultation helped inform work by a number of modelling teams, including region-specific modelling conducted by Imperial College with inputs from the Bill and Melinda Gates Foundation-funded PrEP Delivery Working Group (WHO, UNAIDS, Georgetown University, Imperial College, London School of Hygiene and Tropical Medicine). The modelling results were presented first at the Georgetown-led regional consultation in Dakar in June 2010 and at the UNAIDS-led Nairobi regional consultation in September 2010. They were followed by presentations of region-specific modelling in Johannesburg, Brasilia, and Bangkok, stimulating discussions among the broad range of stakeholders at each regional meeting about the potential of PrEP as an additional HIV prevention tool.

When mathematical modellers, trial statisticians, and public health professionals met again in March 2011 at the invitation of UNAIDS and WHO, two PrEP trials had reported results – CAPRISA 004 (1% tenofovir gel)(49) and iPrEX (TDF/FTC in MSM and transgender women)(78). Having already developed their models, the modelling teams were in a position to indicate to leading PrEP trialists what additional data would be useful to inform their models while the PrEP trialists were able to comment on the assumptions used by the modelling teams. Among the data needs identified by the modellers were: within-person variability in pill-taking

behaviour over time; oral and topical pharmacokinetic/pharmacodynamic (PK/PD) biological data; potential delivery scenarios, including task shifting, task sharing, method and frequency of monitoring HIV breakthrough and resistance, drug and testing costs, and delivery venues; life course estimations of patterns of use; and estimates of risk compensation, including scenarios in both directions, type of risk compensation, and break even points for crossing cost-effectiveness lines(79).

Knowledge Translation Considerations

Acknowledging that policymakers are the key audience for modelling results that present country-specific information on the potential impact and cost of introducing a novel biomedical HIV prevention tool, questions were raised by the PrEP modellers at the Montreux meeting about how best to communicate with them. The question of which metrics would speak most persuasively remained unresolved but the following were discussed: number of cases averted, cost per infection averted, cost per life years gained, cost per DALY (disability adjusted life year), cost per QALY (quality adjusted life year), number needed to treat, cases postponed, and ratio of infections averted to drug resistance created. Understanding that politicians need to be able to explain to others why they have chosen to do certain things, modellers expressed a need to better understand the language of policymakers, including on topics such as productivity, youth employment, security of the State, welfare of communities, and the well-being of citizens.

These processes of convening modellers to stimulate interest in addressing pertinent public health issues through modelling the potential impact of VMMC or PrEP had concrete effects on decision-making. In the case of VMMC, the UNAIDS/WHO/SACEMA modelling consensus(9) helped refine the decision-makers programme planning tool (DMPPT) that UNAIDS and Futures Institute, funded by the USAID Health Policy Initiative, had begun developing. It produced analyses that informed scale-up strategies in a number of countries(80).

In the case of PrEP, a systematic review of cost-effectiveness explored prioritisation strategies, adherence, behaviour change, toxicity and drug resistance(14). It identified 13 studies that modelled different populations (heterosexual couples, MSM, and PWID) in generalised and concentrated epidemics from southern Africa, the Ukraine, the USA, and Peru. Assumptions concerning cost, epidemic context, programme coverage, prioritisation strategies, and individual-level adherence determined the potential impact of PrEP. It became evident that the five key considerations in assessing cost-effectiveness analyses of PrEP as a novel HIV prevention tool were cost, epidemic context, individual adherence levels, PrEP programme coverage, and prioritisation strategy. The most cost-effective strategy was delivery of PrEP to key populations at highest risk of HIV exposure. Thus, this systematic review of 13 studies made explicit to decision-makers that a crucial challenge in PrEP programme planning is that of reaching

populations that in many countries are stigmatised, marginalised, and underground due to illicit activities that increase HIV risk.

Mathematical Modelling Using Vaccine Trial Results

Following the results of the RV144 vaccine trial in Thailand, a consultation was convened by WHO, UNAIDS, the Global HIV Vaccine Enterprise, the Thai Ministry of Public Health, and the US Military Research Program to address the utility of the trial results. Aspects addressed were public health and future access; ethical, regulatory, and community issues; science and vaccine development; and clinical trial design and statistics. Among the recommendations was one encouraging modelling teams to estimate the cost and impact on the HIV epidemic of vaccine regimens with varying efficacy and durability, including a 31% efficacious general population vaccine with a 1-year duration of protection(81). Modellers capable of evaluating the potential impact of RV144-like vaccines were invited to investigate a common scenario with variations for a number of countries and to present their findings at a satellite symposium at the 2010 AIDS Vaccine conference held in Atlanta, Georgia entitled 'Preparing for the Availability of a Partially Effective HIV Vaccine'(82).

Because the reported efficacy of 31.2% at 42 months was an average over the entire life of the trial, modellers were provided with cumulative and interval–specific vaccine efficacies so that they would make similar assumptions about the exponential function for vaccine efficacy. They were asked to estimate fractions of HIV infections that could be averted over a 10-year follow-up period by mass vaccinations of 30% and 60% of sexually active adults. Although studies are now underway to determine if vaccinees respond immunologically to vaccine booster doses(83), at the time of the modelling it was the temporal decay of vaccine efficacy that they had learned of that led some of the teams to explore hypothetical booster vaccinations at 1- to 5-year intervals. The consistency of the modelled findings in demonstrating the tangible population-wide benefits of a vaccine that is modestly efficacious in a low-risk heterosexual population, when combined with the scale up of other HIV prevention approaches, was encouraging. RV144-like vaccines could avert 5-15% of infections over 10-year periods, particularly in countries with high HIV incidence. Even if efficacy might be lower in key populations at higher risk of HIV exposure than that observed in the trial, the models addressing this aspect found that prioritising such populations was more efficient. As more information becomes available from the ongoing trials in infants(84), MSM in Thailand and the USA, and in South Africa where the clade inserts are being modified to match locally circulating clades(85), modellers will be able to further refine their models.

Modelling HIV prevention for people who inject drugs

Modellers interested in estimating the impact of various HIV prevention strategies among people who inject drugs have assessed various strategies. Although there has been considerable discussion about the risk environment within which injecting drug use takes place(86)(87)(88)(89)(90), modelling exercises to date have focused mainly on topics such as the cost-effectiveness of harm reduction including methadone maintenance therapy as HIV prevention(91)(92), syringe distribution(93), combinations for hepatitis C prevention(94), and the impact of supervised injecting facilities(95). Modellers have even addressed the question of whether introduction and use of low dead-space syringes would have the effect to reduce HIV incidence among people who inject drugs(96). Low dead-space syringes retain no fluid in the syringe itself when the plunger is fully supressed, only in the needle. They are therefore less likely to transmit HIV when others use the equipment of injectors who have very high viral loads in the acute phase of HIV. However, no one had attempted to model the potential impact of structural interventions that could reduce the likelihood that people who use drugs would transition to injecting drugs or remove barriers for people who inject drugs to accessing HIV prevention modalities such as needle syringe programmes (NSP) and opioid substitution treatment (OST), as well as of ART for those already HIV-positive. The challenge in assessing the potential impact of structural interventions on risk behaviour and subsequent HIV incidence is that this truly is a data-free zone in which assumptions have to be made about the impact of changes in the risk environment on drug use behaviours or uptake of services.

First, the impact of reducing unmet need for NSP, OST, and ART was modelled for three cities chosen because they had important epidemics among people who inject drugs and enough data to be able to model impact with some confidence. Reducing unmet need by 60% during the period 2010 to 2015 could prevent 41% of incident infections in Odessa, Ukraine, 43% in Karachi, Pakistan, and 30% in Nairobi, Kenya(16). The structural changes considered were different by city. Reducing the transition from non-injecting drug use to injecting drug use by 8-12% in Karachi was estimated to have the potential to prevent 65-98% of incident infections. Eliminating police beatings in Odessa could avert 4-19% of new infections among people who inject drugs. Removing laws prohibiting opioid substitution in Nairobi and scaling up OST coverage to 80% could prevent 14% of incident infections there. The challenges to this type of modelling include difficulties in estimating the population size, the unreliability of self-reporting of a behaviour that is highly stigmatised, and the dearth of information on network typology(97) for people who inject drugs, as in many settings. Furthermore, structural determinants of risk act through both direct and indirect causal pathways, making it impossible to generate precise quantitative estimates without additional data. This seminal paper drew attention to the importance of understanding the risk environment and shifting the focus for change from individuals to the social and political contexts that heighten their risk.

Modelling population-level prevention benefits of antiretroviral therapy

In 2011, after the last PrEP modelling meeting, the Bill and Melinda Gates Foundation decided to fund an HIV Modelling Consortium(98), with a secretariat at Imperial College, London. It met for the first time in November 2011 to discuss the potential impact of expanding ART in sub-Saharan Africa. The result was a series of articles in a special collection(99) published in time for the International AIDS Society meeting in Washington in July 2012(100). These addressed the potential impact of antiretroviral treatment for HIV prevention from different perspectives, in light of the 'game-changing' results of the HIV Prevention Trials Network (HPTN) 052 trial that documented a 96% reduction in genotypically-related HIV transmissions within serodiscordant couples(101). This trial result confirmed observational data from other studies(102) and was consistent with data previously published as far back as the year 2000 on viral load and HIV transmission (103)(104)(105). Acknowledging that decisions about the optimal use of ART would be framed by epidemiology, economics, demography, statistics, biology and mathematical modelling, the series included a systematic comparison of mathematical models of the potential impact of antiretroviral therapy on HIV incidence in South Africa(106), similar in intent to the VMMC modelling comparisons. Interestingly, it found that although the mathematical models varied substantially in structure, complexity, and parameter choices, they all suggested that high levels of access to ART combined with high adherence would have the potential to substantially reduce new HIV infections in the short-term. There was more divergence in the predicted epidemiologic impact of ambitious treatment scale-up over the longer term and in the efficiency with which treatment can reduce new infections.

There had been some previous efforts to use mathematical modelling to look at the prevention benefits of ART scale-up, with diverse results. One modelling team reported in 2006 that even with the most optimistic scenario of widespread testing and treatment initiation, new infections would remain stable, ART would not eliminate HIV regardless of the degree of coverage, and effective prevention strategies were essential for impact in high prevalence settings(107). In 2009, a second team published modelling results assuming that ART coverage would reach 90% by 2016, all adults would accept annual testing, and all those found to be HIV-positive would accept to start immediately on ART. They concluded that immediate ART regardless of CD4 count actually was a strategy for elimination of HIV (108). These divergent results were potentially confusing for policy makers who were not in a position to interrogate and/or understand the contents of the 'black box'. More recently, modelling of both ART and PrEP in the South African context estimates that the combination will prevent more infections than either strategy alone, but with a higher prevalence of drug resistance, contributed mainly by ART(109). Similar modelling findings on the relative contributions of ART and PrEP to drug resistance are now reported for Africa overall(110).

Currently, in weighing the costs, benefits, and risks of ART and PrEP for HIV prevention, debate has become very heated among ethicists(111)(112)(113)(114). There has been confusion about terminology, with the term 'treatment as prevention' meaning different things to different people, with consequent muddying of the arguments. One way forward is to distinguish between the concept of *early treatment for prevention* (early T4P) before CD4+ cells fall to eligibility criteria [350-500/uL, depending on national guidelines] and the concept of *treatment as prevention* (TasP) meaning the population-level benefits of lower community viral load as ART is scaled up according to national eligibility criteria. The strategy of *test and treat* in which ART is offered to all those who test HIV-positive regardless of CD4 count, which is intended to avoid loss to follow-up and draw people into treatment, then can be understood as a strategy of early treatment that has the potential to have prevention benefits that result in lower community viral load. Antiretroviral prophylaxis to reduce the risk of HIV acquisition, *pre-exposure prophylaxis,* involves the use of antiretroviral drugs for HIV-negative persons. The concepts of both early T4P and PrEP are stimulating considerable controversy among ethicists.

The rule of rescue in ethics gives weight to rescuing people whose lives are imminently threatened even if so doing reduces the number of lives saved overall(115), while more utilitarian approaches argue that the strongest moral imperative is to use resources most efficiently to prevent disease and save the most lives(116). The issue of the trade-offs for antiretroviral drug use for treatment versus prevention in resource-poor settings will remain a hot button issue for policy makers, programme planners, advocates, activists, and ethicists well into the future, given the current global financial situation of constrained investment, a strong focus on efficiencies, and increasing devolution of funding responsibilities to national governments(117).

Looking Back to 2005: the Modelling Consensus Process

In 2005 when the first meeting of modellers was convened, the concept of sharing approaches and ideas seemed novel to virtually all of the modellers. They were working in isolation within their own teams and often in relation to only one randomised controlled trial (RCT). The principles and the process of convening modellers to address the impact of emerging biomedical HIV prevention findings that was initiated in 2005, eventually involved three VMMC modelling meetings that took place in Geneva in 2005(51), Stellenbosch in 2007(55), and London in 2008(9); two PrEP modelling meetings, convened in Geneva in March 2010(77) and in Montreux, Switzerland in March 2011(79); and an HIV vaccine modelling satellite held in Atlanta in 2010(82). Either at or following each face-to-face meeting, modellers spoke of how rewarding it had been to present their work to their peers and receive constructive criticism from researchers and public health practitioners, as well as a dose of reality about the parameter values that they had used in what

was at times a 'data-free' zone. Importantly, some modellers' assumptions about the timing of introduction, speed of scale-up, and maximum coverage levels achieved were challenged as overly optimistic(61)(108), although their somewhat controversial modelling results had clearly influenced thinking and stimulated debate more broadly in the HIV prevention field.

Increasingly, as data from RCT became available, as the amount of context-specific information increased concerning sexual practices (e.g. delayed sexual debut, numbers of partners, and condom use frequency), and as more valid estimates of country HIV prevalence and incidence were generated to populate the models, they were rendered more relevant for informed decision-making about HIV prevention policy.

The HIV Modelling Consortium, based at Imperial College, assumed the UNAIDS mantle in convening modellers in 2011 and has held a number of meetings addressing, among others, the potential impact of treatment on HIV incidence, the potential for PrEP to increase ARV resistance, and incidence estimation, and is embarking now on a validation exercise for models assessing community trials(98). Its funding from the Bill and Melinda Gates Foundation has recently been renewed for four years to 2017 and it will continue to constitute an important resource for modellers, policy makers, normative agencies, and others by co-coordinating a wide range of research activities in mathematical modelling of the HIV epidemic.

Practical questions that HIV prevention policy makers and programme planners can ask about mathematical modelling

HIV prevention policy makers and programme planners generally have different backgrounds, experiences, perspectives, time horizons, and urgencies in their respective mandates. What links them is the principle that public funds should be spent in the most cost-effective and culturally acceptable way to reduce HIV transmission. Their shared objective is to see the impact materialise in reductions in the need for HIV-related health care services, accompanied ideally by reductions in inequalities of access to public services for those who do need them. A higher concern may be that their country be portrayed as one that has demonstrated success and is recognised internationally for its concerted and fruitful action on HIV.

Given concerns about how much a programme will cost, what the impact will be, and how it should best be delivered for maximum effect, mathematical modelling can shed light on how different policy and programming options might play out in the short-, medium-, and long-term. However, modellers need to know how decision makers assess and value costs and potential savings at different time frames. Generally speaking, costs and benefits in the future are viewed differently than those in the present. Discounting is the process of converting future values, such as costs or health effects, to their present values, in order to reflect the belief

that, in general, society prefers to receive benefits sooner rather than later and pay costs later rather than sooner(118). Although there is some debate about whether health benefits and costs should be discounted at the same rate with some arguing that the value of health grows over time and therefore it should be discounted less(119), standard cost-effectiveness analysis for health policy purposes uses uniform discounting at 3%, with the discount percentage varied in sensitivity analyses(120).

Delva and colleagues argue cogently that there is a need for constructive dialogue between 'producers' and 'consumers' of modelling results about a model's assumptions and structure, the policy implications of the results, and what further empirical and modelling studies should be planned(121). They have developed a list of nine principles of good HIV epidemiology modelling, from both the model producer's viewpoint and the model consumer's viewpoint. These are: clear rationale, scope, and objectives; explicit model structure and key features; well-defined and justified model parameters; alignment of model output with data; clear presentation of results, including uncertainty in estimates; exploration of model limitations; contextualisation with other modelling studies; application of epidemiological modelling to health economic analyses; and clear language.

These principles are important for both those who conduct modelling research and those who use modelling results, however arguably among the most important questions that policy makers will have are whether the model is calibrated to locally collected data(122) and whether the modelling process is building local capacity, not just to understand models but also to use modelling to explore relevant local questions. Decision makers want to be reassured that input parameters have a strong empirical basis and that the modellers have conducted analyses of a broad array of scenarios to examine the impact of uncertainty in key parameters(123). But they also want to know what would happen in the absence of the intervention to contrast with what actually could happen, according to the model predictions. In impact evaluation circles, establishing the counterfactual means determining the difference that a project made compared to what would have happened without it(124). Counterfactuals play a central role throughout economics, providing genuine answers to genuine "What if…?" questions such as "What if the policy were put in place?"(125), a contrary-to-fact situation. Decision makers are also concerned with opportunity costs, i.e. the value of the road not taken. In economic terms, the opportunity cost of a choice is the value of the best alternative forgone, in a situation in which a choice needs to be made between several mutually exclusive alternatives given limited resources. Assuming the best choice is made, it is the "cost" incurred by not enjoying the benefit that would have been had by taking the second best choice available(126).

Programme planners are interested in models that do not assume that the addition of a novel HIV prevention tool takes place in isolation from the scale-up of other known cost-effective approaches. Are synergies likely and can these effects be

predicted? Should a new approach substitute for a less cost-effective modality or can the latter be made more efficient as a support to the new HIV prevention modality? For example, will the introduction of VMMC or PrEP actually increase correct and consistent condom use through increased access, counselling support, and changes in social and sexual norms? Are there spin-offs that can help justify initial financial outlays? For example, will scaling up medical male circumcision services strengthen supply chain management, enhance efficient use of facilities, create appropriate medical waste disposal systems, and train a cadre of health workers with minor surgical skills that can be deployed beyond the circumcision arena once the 'catch-up' phase begins to end? These are aspects that may not be captured in standard 'return on investment' analyses focused on costs averted, even if a health system perspective is used(127).

Decision makers can benefit from visual representations of the profiles of alternative policy options. A good example is found in a paper exploring optimisation of the impact of expanded HIV treatment programmes(128). Six prioritisation groups for ART expansion beyond the existing WHO guidelines are considered: expanding ART to those with CD4 cell count from 350 to 500 cells/uL, those with a viral load set point above 50,000 copies/ml, those with active tuberculosis disease, pregnant women, serodiscordant couples, and sex workers. For each of these options, a table presents the predicted impact on new HIV infections, impact on HIV-related morbidity and mortality, feasibility, and acceptability. With many different studies and trials now underway looking at the contribution of antiretroviral drugs to preventing HIV and preventing tuberculosis(129), it behoves researchers and modellers alike to anticipate the need to present the study inputs, assumptions, and findings in transparent, user-friendly accessible ways to policy makers. This is part of good participatory practice which begins in the design phase rather than being an add-on, after the fact, provision(130).

Furthermore, engaging decision-makers from the beginning can help ensure that modelling addresses relevant policy questions, can build model literacy(131), and can facilitate the identification of the most accurate and up-to-date information that can be used to parameterise models. Finally, it has been argued that involving other stakeholders early in the process, including the general public, concerning equity and autonomy issues, for example, will help modellers understand the broader social context (132).

The Future

Mathematical modelling in the field of HIV prevention has come into its own over the past 8 years, from being perceived as an intellectual exercise relying on limited data and much conjecture to being a key consideration in policy-making discussions. Models are focusing less on single interventions and examining combination prevention strategies in different settings. For example, a comprehensive portfolio of modestly-effective biomedical HIV prevention programmes, including male circumcision, vaginal microbicides, and oral PrEP, in

a context of expanded HIV testing and ART scale-up, could avert 62 % of new HIV infections and reduce HIV prevalence from a projected 14 % to 10 % after 10 years in South Africa and would likely be cost-effective(133). A model for a hyperendemic setting with relatively low levels of condom use, estimates that a combination of VMMC, early ART, and PrEP scaled up to ambitious coverage levels could produce dramatic declines in HIV incidence, but would not stop transmission completely(134). Another model of VMMC, ART, or early treatment in the South African context, estimates that the most cost-effective HIV prevention strategy is to expand VMMC coverage and then scale up ART; the most cost-effective HIV-mortality reduction strategy is to scale up VMMC and ART jointly. Early treatment was far less cost-effective than either VMMC or ART(135). A further model estimates that the full impact of the combination prevention initiatives accrues over 10-15 years, with significant synergy possible between programme components(136). The concept of joint effectiveness of prevention programmes that these modellers are examining highlights how some programs operate synergistically while others may create redundancies. The new frontier to be explored is whether combination HIV prevention programmes will perform with additive, multiplicative, or maximal effectiveness(137).

Modelling is also being used to inform and guide three large cluster randomised controlled trials of combination HIV prevention that have been commissioned by the US President's Emergency Plan for AIDS Relief (PEPFAR) and are planned or underway in Zambia and South Africa(138), Botswana(139), and Iringa, Tanzania(140). The scale-up of ART varies, with treatment initiation at different CD4 levels in Zambia and South Africa, prioritising those with highest viral loads in Botswana, and in combination with other interventions in Tanzania. HIV transmission dynamic modelling has been used at the formative stage of trial planning and will be used during trial conduct to monitor progress, and at the end of each trial to assist both in interpretation and in evaluation of short-term and long-term impact(141).Likewise, a fourth community trial, the South African TasP trial in Hlabisa, KwaZulu-Natal sponsored by the French Agence nationale de recherches sur le sida et les hépatites virales (ANRS)(142) is using modelling to inform trial design, track conduct, and evaluate results.

An example of the use of modelling during a community-based programme roll-out is from the 'Avahan' India HIV/AIDS Initiative's sex worker programme funded by the Bill and Melinda Gates Foundation and established in 2004. In an interim analysis, modellers set out to determine whether observed changes in HIV prevalence among sex workers could be solely due to natural disease dynamics rather than to a change related to introduction of the programme. They tested three hypotheses: the null hypothesis of stable condom use with no increase following the initiation of the Avahan intervention in 2004, an alternative hypothesis that condom use actually increased by as much as was reported in the programme survey of female sex workers, and a third hypothesis that there was a lower level of pre-intervention condom use and a sharper post-intervention increase, based on records of condom availability(143), than indicated in the survey data. They

concluded that increased condom use in Mysore following the start of the Avahan programme is likely to have played a role in curbing the epidemic.

Integrating modelling analysis into the design, conduct, and analysis of the large cluster randomised HIV combination prevention trials that are going forward now is intended to complement traditional statistical analyses and evaluation processes. Interim analyses, similar in timing to those undertaken in the Avahan initiative, will be used when interim incidence data are not available to indicate the possible need to modify or adapt a trial to reduce the likelihood of inconclusive outcomes(141). Pre-determined mid-course corrections(144), such as accelerated roll-out or modified trial duration, may be triggered as a result of interim modelling analyses conducted when interim HIV incidence measurements are unavailable. This clearly can constitute a valuable contribution given the size and expense of these large trials.

Modelling will increasingly be useful in biomedical prevention trial design, given the changing 'standard of prevention'(145) (146) being offered to all trial participants. In an HIV vaccine trial conducted in a high HIV prevalence setting, the prevention package was expanded by the researchers to include an offer of VMMC, even before national authorities had endorsed VMMC for HIV risk reduction(147). The first trial to grapple with the issue of oral PrEP following the iPrEx trial results(78) was the HIV Vaccine Trials Network (HVTN) study 505. After consultation with participants about their understanding and intentions(148), it was decided to provide information about PrEP and where it could be accessed(149). Evolving standard of prevention will mandate broad consultations to discuss the best way forward but it will also provide modellers with trial design challenges and the opportunity to look further into adaptive trial designs(150)(144)(151).

Decisions about the best use of resources are better informed when consideration of the policy options benefits from the strongest science(152) and when mathematical models that are rooted in robust empirical findings are valued as important inputs to decision making. Corroborating modelling predictions with empirical data, such as the rural South Africa ART scale-up's impact on life expectancy(153), employment(154), and HIV acquisition(155) in Hlabisa, is part of an iterative process of validation and refinement. Contrasting cost-effectiveness modelling results with each other in systematic reviews can make the findings more accessible to policy makers who lack the time to review each individual study.

The path that HIV modellers have taken since 2005 in the prevention arena, beginning with a small meeting of modellers, researchers, and public health specialists considering the results of one RCT of male circumcision has culminated in the formation of the HIV Modelling Consortium which has grants-awarding capacity to catalyse work and is active at the forefront of policy discussions. This process highlights the importance that modellers have placed on scientific respect, peer review, collaboration, consensus building where possible, and motivation to

influence policymaking and programme planning. Further work on knowledge translation and improved communication with those who are best situated to interpret and use the results of modelling exercises is highly desirable.

Modellers need to grow to appreciate that rational priority setting requires an understanding that allocation of scare resources should be 'fair and just', rather than either arbitrary or based simply on model outputs. For resource allocation decisions, policy makers and programme planners need to provide relevant reasons, supported by scientific evidence, which can include mathematical modelling results, and underpinned by ethical principles(156). Their rationale must be publically accessible and there must be opportunities for dispute resolution. Above all, the process for making decisions itself must be fair(157). Decision-makers are responsible for ensuring that all these conditions are met.

This thesis concludes that modellers can play an important role in evidence-informed policy making and programme planning processes. They can generate modelling results on questions of key importance that provide insights into the potential impact of competing HIV prevention scenarios in the context of constrained resources. In effect, they can paint pictures for policy makers of the paths that can lead to a future in which HIV transmission is increasingly rare.

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