INTERNATIONAL PARTNERSHIP *for* MICROBICIDES

Identifying optimal strategies for microbicide distribution in India and South Africa:

Modelling and cost-effectiveness analyses

A policy paper prepared by IPM with the HIVTools Research Group at the London School of Hygiene and Tropical Medicine

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Executive Summary

Introduction

Substantial investments have been made to find effective HIV prevention tools for women. Microbicides are investigational products that women could apply vaginally to impede the sexual transmission of HIV. If clinical development provides evidence that microbicides have a preventive effect, their potential will only be realized if they can be successfully and appropriately introduced into HIV prevention programs and used effectively by women and their partners. Over 97% of people living with HIV reside in low-income countries, 68% of whom live in sub-Saharan Africa. Women account for half of all people living with HIV/AIDS worldwide and nearly 60 percent of HIV infections in sub-Saharan Africa. Reaching these women and enabling them to access the potential benefit of microbicides requires early planning and timely mobilisation of a network of partners and resources. A range of important questions must be addressed in order to ensure future product approval and a successful introduction. What scale of impact might be achieved if an effective microbicide were added to current preventative measures in a particular setting? If supplies or resources are limited, should a product be widely available, or focus on reaching specific, vulnerable groups? What is the likely potential public health impact of a product in a specific setting? Will it be cost-effective, in comparison to other areas of health investment?

Mathematical modelling and economic analysis have been widely used to help inform such complex policy questions. This report presents the findings from a study that uses epidemiological modelling and economic analyses to explore the potential impact and cost-effectiveness of different microbicide introduction strategies in Southern India and South Africa. Specifically, the project aimed to:

- estimate the impact of microbicide introduction on the HIV epidemic in two contrasting settings (Southern India and urban South Africa)
- explore how impact is related to product efficacy and use; microbicide introduction strategy; uptake, speed of approval, and potential restrictions on product delivery
- build on previous cost estimate exercises and cost studies to estimate the total costs of each of the different microbicide introduction strategies in each setting, explore which strategy is most cost-effective, and assess whether the delivery scenarios with the highest impact are also the most cost-effective.

Methods

In India and South Africa, country workshops were set up to discuss likely strategies for future product introduction. Reviews of current evidence about the rate of introduction of new health technologies were used to inform the likely rate of product introduction. Population-based data from each country were analysed to produce estimates of the extent to which women accessed different services in each setting. This was used to develop potential introduction scenarios with low and high uptake assumptions. 120 and 156 different scenario combinations were considered in India and South Africa respectively.

An existing epidemiological model was adapted in order to assess the impact of each of the introduction strategies on HIV transmission, taking into account temporal changes in product use. The modelling analysis considered two contrasting settings - Mysore District, Karnataka, in Southern India, and Gauteng Province, South Africa. Matching dynamic HIV models were parameterised to each setting, and fitted to setting-specific data on the levels of HIV and other sexually transmitted infections.

Mysore District has a population at a reproductive age of around 1.6 million, with approximately 810,000 females and 839,000 males. In Mysore the HIV epidemic is largely concentrated among the most vulnerable groups; HIV prevalence in the general

population is around 1%, as opposed to 26% among female sex workers (FSWs). The model closely replicates the prevalence of HIV and other STI among both sex workers and clients.

Gauteng Province has a population of reproductive age of about 5.7 million, with around 2.7 million females and 2.9 million males. In Gauteng the HIV epidemic is generalised, with a general population HIV prevalence of around 10.8%, with 8.2% of males and 13.3% of females infected; 10.3% of the 15 - 25 year olds are HIV infected and 15.6% of the over 25 year old age group. Estimates of the HIV prevalence in FSWs varied considerably, depending on the study location and year, this work uses prevalences in the range of 40 - 67%. Again, the model replicates the distribution of HIV and other STI in this setting, including the differences in infection by age and sex.

A parallel economic analysis estimated the costs of delivering a microbicide, for each of the distribution strategies modelled. A range of estimates for the potential unit cost for a range of products were developed in consultation with experts in the field. As a base-case for the analysis, we considered a microbicide product that is used daily, and priced at $0.10. The sensitivity of the findings to different cost and use assumptions was also explored, including low and high cost assumptions for daily use of $0.05 and $1.00 and low and high cost scenarios for a monthly use product, of $1 and $5 respectively, were also considered.

In addition to product costs, the costing also estimated the costs of services to deliver the product. For this, the intervention was conceptualised as an addition to existing services. Drawing on other costing studies, cost projections included the potential costs required to deliver a product, such as training, provider time, the provision of voluntary counselling, HIV testing, and product promotion. As is standard in economic analysis, a discount rate of 3% was used to convert future costs and benefits to their present value. The costs of product distribution in the different scenarios were estimated using a spread-sheet model that linked the model projections of the annual number of women reached from the different populations (where relevant) to cost estimates. The cost per HIV infection averted over 15 years was then estimated using the model projections of HIV infections averted.

To consider whether a particular distribution strategy is 'cost-effective' or not, it is necessary to compare it with other possible interventions. The 1993 World Bank Development Report provides generic cost-effectiveness cut-off values. Adjusted to 2008 figures, the cost-effectiveness cut off is $1,425 per HIV infection averted in India, and $3,005 per HIV infection averted in South Africa. Interventions averting HIV infections for less than these figures are thereby seen as 'cost-effective'. These values were then used to assess the cost-effectiveness of each distribution scenario.

Results

Key findings from country workshops and expert consultative meeting

There were both similarities and differences in the issues raised in South Africa and India. In both settings, sexually active or married women were identified as a key group to consider for targeting, although there was debate about the extent to which women may feel at risk of HIV. Youth were also identified as a vulnerable group in both settings, with discussion focusing on all sexually active youth in South Africa, and on newly married men and non-sterilised women in India. There was also discussion about the extent to which it may or may not be desirable to target sex workers. The issue was most debated in India, where there are relatively low population levels of HIV infection. It was recognised that microbicides may provide additional protection both in commercial or non-commercial sexual

relationships, although there were some fears about the impact of potential reductions in condom use following microbicide introduction. In all settings, the efficacy of a microbicide was identified as a central issue affecting product acceptability and its potential market, although issues of cost (especially whether a product would be free at the point of delivery or not), pleasure, accessibility, and contraceptive efficacy were also discussed. Discussions about the likely rate of uptake, and examples of successful product introduction varied between settings.

Consultative meetings with a range of international experts in the field of microbicides also helped inform the development of scenarios for product distribution. They highlighted that it may take some time for a product to be approved through local regulatory mechanisms and that, even once approved, the potential speed and likelihood of a product graduating from provision through prescription by health care workers to broader methods of distribution should be considered.

Scenarios considered

Based upon the reviews and workshop recommendations, agreements were reached about levels for the efficacy and consistency of microbicides, potential approaches to targeting and likely strategies and timeframes for introduction, as illustrated in the following tables.

Microbicide efficacy and consistency:
(Agreed combinations to be used for the scenarios)

HIV- efficacy per sex act	Percentage of sex acts protected (Consistency)
Low - 35%	Moderate - 50%
Low - 35%	High - 80%
Medium - 60%	Moderate - 50%
Medium - 60%	High - 80%
High - 85%	Moderate - 50%
High - 85%	High - 80%

The analysis only considered a microbicide that provides protection to women who are not infected with HIV. For a range of targeting approaches and introduction strategies, six combinations of low, medium and high per sex act efficacy, and moderate and high consistency strategies were compared in each setting.

Introduction strategies modelled in India and South Africa

In Southern India, population level distribution versus more focused provision to sex workers through sex worker programmes were compared. In urban South Africa, three distribution scenarios were compared: population distribution only, population distribution with enhanced youth provision; and population distribution with enhanced sex worker provision.

Urban Southern India

1. Population-level distribution to all sexually active women
2. Focused provision to female sex workers (FSWs) through sex worker programmes

Urban South Africa

1. Population distribution to all sexually active women
2. Population distribution with enhanced provision to youth 3 years post-approval
3. Population distribution with enhanced provision to FSWs through sex worker programmes

Phases of product introduction

It was recognised that a product would not immediately be provided widely; and that instead product introduction would go through several phases. While a product awaited regulatory approval it was assumed that it would be provided on a limited scale to trial participants. Two potential speeds of authorisation were compared - a slow scenario of three years, and a fast scenario of one year.

The next phase of product introduction was conceptualised as being a time of restricted delivery, where provision would be to HIV-negative women upon prescription, through public health facilities. Coverage would depend on the extent to which women could access these services. In the longer term (three years for the purpose of the analysis), it was envisaged that some products could potentially become more widely available through other outlets.

This led to 120 and 156 different scenario combinations being considered for India and South Africa respectively.

Microbicide impact results, India

Of the 120 different distribution scenarios modelled in the India analysis, the highest impact ('top') scenario was a high efficacy product (85%), that cleared regulatory approval quickly (1 year) and then was distributed with focused provision to FSWs, with a relatively fast transition from a restricted to an unrestricted microbicide introduction program (3 years post-approval), progressing to a high level of uptake (80% after 10 years post-approval) and consistency of usage (80%).

Parameterisation of stages of product introduction in Urban India and South Africa

Stage	India	South Africa
Regulatory approval & market authorisation: product provided on a limited scale to trial participants	Up to 1% of FSWs have access to microbicides Slow – 3 yrs Fast – 1 year	Up to 0.1% of females in general population have access to *microbicides* Slow – 3 yrs Fast – 1 year
Restricted delivery for 3 years: product only available on prescription, through public health facilities	34% of the general population have access to public health facilities 68% of FSWs have access to public health facilities	50% of the general population have access to public health facilities 70% youth (3 yrs post approval) have access to public health facilities 70% FSWs (3 yrs post approval) have access to public health facilities
Potentially unrestricted delivery e.g. supermarkets, shops, social marketing, GPs, pharmacies	Coverage 10 years post approval: Gen population Low – 3% Med – 15% High – 30% FSW: Low – 30% High – 80%	Coverage 10 years post-approval Gen pop / youth Low – 3% Med – 15% High – 30% FSW: Low – 30% High – 80%
Achievable market saturation	Levels of distribution plateau	

The model projected that approximately 91,000 HIV infections would occur over 15 years if no microbicide or other new intervention was introduced. In the highest impact scenario, the model predicted that 17,390 (range 6,638 – 28,672) HIV infections would be averted over 15 years. Nine of the top ten scenarios involved the targeted provision of microbicides to sex workers and their clients. Indeed, this targeting is so important, that even in the top general distribution scenario, many of the infections averted were among clients and FSWs (69% of averted male infections were among clients and 38% of averted female infections were among FSWs). After the top impact scenario, the next four impact scenarios closely correspond to the top impact scenario, with only one other aspect being less than ideal. For the top scenario, a drop from a high per sex act efficacy of 85% to a low per sex act efficacy of 35% reduces the projected impact to 39% of the impact of the top scenario.

This overall impact reflects what may be realistic to expect from a gradual increase in product distribution. For all of the top ten scenarios the impact in the final year is on average about 2.4 times the average number of HIV infections averted per year over the 15 years of the intervention. After 15 years, the best model fit predicts a relative reduction in incidence per susceptible of 49% over all the population and 70% among FSWs alone.

Top 10 impact scenarios in India analysis using model best-fit

Distribution scenario	Infections averted	Infections averted / 100,000 population	Relative percentage of top scenario
FSW Top - all high / fast / good	17,390	1,054	100%
FSW Top, but restricted always	12,560	762	72%
FSW Top, but slow approval	12,095	733	70%
FSW Top, but medium efficacy	12,015	728	69%
FSW Top, but moderate consistency	10,564	641	61%
FSW Top, but restricted always AND slow approval	8,965	544	52%
FSW Top, but restricted always AND medium efficacy	8,701	528	50%
FSW Top, but slow approval AND medium efficacy	8,368	507	48%
FSW Top, but restricted always AND moderate consistency	7,661	464	44%
Gen pop Top - all high / fast / good	7,415	450	43%

Microbicide impact results, South Africa

Of the 156 different distribution scenarios modelled in the South Africa analysis, the highest impact ('top') scenario came from clearing regulatory approval quickly (1 year) and then distributing microbicides to the general population and FSWs. The model projected that almost 2.5 million HIV infections would occur over 15 years if no microbicides or other new interventions were introduced. In the highest impact scenario 167,223 (143,255 – 193,381) HIV

infections would be averted over 15 years, equivalent to 2,930 HIV infections averted per 100,000 people[1]. This overall impact reflects what might be expected from a gradual increase in product distribution. After 15 years, for all of the top ten scenarios, the number of HIV infections averted per 100,000 population is on average about twice as high as the average number of HIV infections averted per year over the 15 year period. The most effective scenario reduces incidence per susceptible by 15% after 15 years.

Although the enhanced provision to sex workers does improve impact, the model also suggests that a population-only distribution strategy could still achieve substantial impact. Among the scenarios with general distribution and enhanced distribution to youth (in which it was assumed delivery always remained restricted), the highest impact scenario ranked 11 out of 156 scenarios considered.

It is interesting to contrast this with the India analysis. In South Africa, the impact of microbicides on the number of HIV infections averted per 100,000 population was projected to be higher than in India, but the percentage reduction in HIV incidence was lower. These findings are consistent with modelled projections of the impact of other HIV prevention interventions in different epidemiological settings.

Cost-effectiveness results for India

All of the targeted strategies would be considered cost-effective, assuming a base case of a microbicide product used daily and priced at $0.10 with a cut off of $1,425 per HIV infection averted, and using the undiscounted values of cost-effectiveness. Using the 3% discounted values, the top five scenarios are cost-effective, while the remaining five are close to cost-effective. When compared to accepted thresholds, the population distribution scenario was cost-ineffective.

Exploration of how the costs and cost-effectiveness of the top scenario may vary with the price of the microbicide, or if the product can be used monthly,

Top 10 impact strategies in South Africa analysis using model best-fit

Distribution scenario	Infections averted	Infections averted / 100,000 population	Relative percentage of top scenario
Gen pop + FSW Top - all high / fast / good	167,223	2,930	100%
Gen pop Top - all high / fast / good	130,444	2,286	78%
Gen pop + FSW Top, but slow approval	124,333	2,179	74%
Gen pop + FSW Top, but medium efficacy	115,392	2,022	69%
Gen pop + FSW Top, but moderate consistency	101,544	1,779	61%
Gen pop + FSW Top, but restricted always	98,110	1,719	59%
Gen pop Top, but slow approval	97,887	1,715	59%
Gen pop Top, but medium efficacy	90,973	1,594	54%
Gen pop + FSW Top, but slow approval AND medium efficacy	86,089	1,508	51%
Gen pop Top, but moderate consistency	80,281	1,407	48%

1. Confidence bounds were estimated by predicting the impact for all the model fits and reporting the range spanned by 95% of the fits.

found that as expected, a monthly product priced relatively cheaply would be the most cost-effective, whilst a higher unit cost for a microbicide substantially reduces the cost-effectiveness of product delivery.

Cost-effectiveness results for South Africa

Of the 156 scenarios modelled, 40 were found to be cost effective using a cut off of $3005 per HIV infection averted. Of these, 24 were combined population and FSW interventions, 10 were general population only scenarios, including non-health facility delivery, two were combined population and youth interventions and four were facility-based general population scenarios.

Halving the microbicide price would lead to a 19% reduction in the cost per HIV infection averted. An increase to $1.00 would severely jeopardise the cost-effectiveness of a microbicide, estimated here as $6,563 per HIV infection averted, well above the current threshold values. The use of a monthly product, priced at $0.10, would lead to a 36% reduction in the cost per HIV infection averted. Even at a price of $1.00, costs would still be lower for a monthly product, with a 25% improved cost per infection averted. At a price of $5.00 per month, for our top scenario, using a 3% discount rate, a monthly product would be cost-effective.

Discussion

Following extensive consultation, the analysis considered a range of potential introduction scenarios in urban Southern India, and urban South Africa, to try to identify optimal strategies for product introduction. The results indicated that different approaches and speeds of delivery may lead to differing levels of impact - ranging from disappointing to impressive. Our findings illustrate the extent to which a product's impact is influenced not only by the characteristics of the product, but also by the speed with which it can be introduced, and the restrictions placed on its distribution. In practise, the overall coverage of a product is fundamentally determined by the target population's access to the distribution mechanisms. Whilst population-based strategies that extend beyond health service delivery may be considered ideal, in practise these strategies may take years to achieve – with initial introduction likely restricted to prescription-only provision, especially in the case of ARV-based products.

Considered alone, the modelling projections give insights into the methods of distribution that may have the greatest impact on HIV transmission. In both settings, they illustrate the potential importance of a microbicide, and the urgency of distributing safe and effective products as rapidly and widely as possible. They also re-confirm the importance of ensuring that microbicides are used by those who are most vulnerable to HIV infection in both concentrated and generalised HIV epidemic settings, as well as the importance of enabling sex workers to access microbicides. The challenge associated with this, however, is ensuring that the product does not then become stigmatised, which may limit its potential use in non-commercial sexual relationships, including relationships between sex workers and their non-commercial sexual partners. The complementary cost-effectiveness analyses illustrate that there is a range of plausible scenarios where microbicide distribution could be highly cost-effective in both settings.

Overall, our findings illustrate that microbicides are likely to be an important addition to our current portfolio of prevention options in both established and generalised epidemic settings. Success and the efficient use of resources depend upon rapid and informed decisions about distribution. The coverage figures for contraceptive delivery should serve as minimum benchmarks for what is achievable.

We must not lose sight of the epidemic reality in different settings, and what this means in terms of prioritising the introduction of microbicides. Expectations must be realistic in terms of probable challenges and barriers, but also sufficiently visionary to ensure the bar is not set too low. Ultimately,

success in the microbicide field depends not only on the identification of an effective product, but also on the ability to have the systems, financing and political constituencies in place, to promote its rapid approval and effective introduction.

Conclusion

From the epidemiological modelling we conclude that depending on the specific epidemiological setting, microbicides could lead to significant and cost-effective reductions of new HIV infections, and are likely to be an important addition to our current combination prevention portfolio. To fully utilize the protective potential of microbicides it will be important to ensure that microbicides are accessible and used by those who are most vulnerable to HIV infection, both in concentrated and generalised epidemics, including sex workers.

In all settings, the likely HIV efficacy of a microbicide was identified as a central issue affecting product acceptability and its potential market, although issues of cost (especially of whether a product would be free at the point of delivery or not), pleasure, accessibility, and contraceptive efficacy are also of importance.

Beyond the preventive efficacy of the microbicide and its ease of use by women, distribution strategies and the pace of product introduction and uptake will determine the impact of this potential new prevention technology on the HIV epidemic.

This analysis helps understanding the interrelationship of the various parameters of product characteristics, access and use, and can inform optimisation of product introduction strategies by identifying scenarios where preventive impact and cost-effectiveness are achieved. Microbicides potential preventive impact on the HIV-epidemic supports the investment in this new prevention approach and alerts to the future need for careful and forward-looking product implementation planning.

Introduction

Over the past 25 years, HIV/AIDS has taken an immense toll. Almost 60 million men, women and children have been infected, and nearly 25 million people have died [1]. The burden of HIV still largely falls on sub-Saharan Africa, although the epidemic is also taking its toll across Asia, in some regions of Latin America, as well as in Europe and North America.

However, these figures mask important achievements. Hundreds of millions of dollars in global resources have been mobilised to tackle the HIV epidemic. Effective antiretroviral drug (ARV) treatment has been developed, that can rapidly reduce HIV morbidity, and dramatically improve life expectancy. Ambitious targets to provide AIDS treatment to 3 million people have been met, countering fears about the feasibility of scaling up treatment in the developing world. Prevention has been implemented on a scale that has led to sizable reductions in the population spread of HIV in countries such as Thailand and Uganda. Inexpensive and simple drugs now reduce the chance of a pregnant woman passing HIV on to her child.

Yet there are still many gaps in the global response to HIV/AIDS. A disproportionate number of HIV infections occur among women, yet most options for HIV prevention remain in the control of men, including male circumcision and male condom use. Gender and power inequalities may often limit the extent to which girls and women can negotiate safer sex strategies with their partners. Although the female condom is an important addition, to date its use has been limited.

In response to this vulnerability, there has been a substantial investment to find an effective HIV prevention for women, including microbicides. Microbicides are investigational products that woman can apply vaginally to impede sexual transmission of HIV. They are currently being formulated in a variety of forms, including gels, films, vaginal tablets, and intravaginal rings [2]. Various early-generation microbicides have been tested, or are currently being tested, in phase III clinical trials. These early-generation products are non-specific compounds that work by electrostatically binding the virus and preventing it from interacting with its target cells in the vagina (i.e., entry inhibitors, such as polyanions).[3] All of these compounds have been formulated in clear gels and are intended to be applied vaginally just prior to sex (i.e. they are coitally dependent). To date, none of the early generation of products has been shown to be effective[2].

Now in development is a new generation of microbicides that consists primarily of products based on antiretroviral (ARV) drugs, which specifically target HIV, be it outside or within the cells it infects. These include reverse transcriptase inhibitors, entry inhibitors, and chemokine receptor blockers. [4] Current testing of these candidates includes dosing regimens that are not coitally dependant.

It is important to note that microbicides are not designed to replace other prevention strategies, but rather to add to existing options and to increase overall HIV prevention effectiveness, as well as addressing some existing prevention gaps. For example, abstinence is not a viable option for married women, women who wish to become pregnant, or women involved in coercive sex. Additionally, being faithful in a monogamous relationship does not protect women with unfaithful partners from exposure to HIV. In fact, in many countries, being a married and monogamous woman is one of the highest risk factors for HIV infection. [5] Although the consistent use of male or female condoms is highly effective in preventing infection [6-8] , women in

2. At the time of completion of this report two trials with early generation candidates (PRO2000 resp. Buffergel) are ongoing. Trial finalisation and reporting are awaited in 2009.

many developing countries are not able to insist that their partner use a condom [9]. The ability of a woman to bear children is also often critical to her status within her marriage and within society, [10] making neither abstinence nor condoms a practical option.

If clinical development proves that microbicides have a preventive effect, they must be successfully and appropriately introduced into HIV prevention programs and used effectively by women and their partners in order to realize their potential. Over 97% of people living with HIV residing in low-income countries, 68% of those live in sub-Saharan Africa. Women account for half of all people living with HIV/AIDS worldwide and nearly 60 percent of HIV infections in sub-Saharan Africa [11]. Reaching these women will require early planning and timely mobilisation of a network of partners and resources. Microbicides will need to be available in sufficient quantities to meet demand, geographically accessible at appropriate distribution points, acceptable to women (and to policymakers and health professionals), and affordable (for both end users and those financing their use). As a point of comparison, it is estimated that only 20% of people living in developing countries currently have access to existing HIV prevention services [12].

Important questions about future product approval and introduction include; What scale of impact might be achieved if an effective microbicide is added to the current prevention mix in a particular setting? If supplies or resources are limited, should a product should be made widely available? Whether programmes should focus on reaching specific, vulnerable groups. Questions about the potential public health impact of a product in a specific setting? Affordability and cost-effectiveness in comparison to other potential areas of health investment? Epidemiological and economic models can help answer such complex policy questions.

Mathematical epidemiological modelling has been widely used to predict future epidemic trajectories of infectious diseases, and to estimate the impact of interventions. In the field of HIV, mathematical models examined the effect of different forms of intervention, including the scale up of male circumcision [13-18]; the widespread provision of ARVs [19, 20]; and the effect of different forms of behaviour change [21, 22]. This modelling has considered the implementation of specific interventions in a particular setting, as well as multiple types of concurrent intervention in many countries simultaneously [28].

Mathematical modelling has also been used to explore the potential impact of different new HIV prevention technologies, including rapid STI diagnostics, AIDS vaccines, herpes treatment, and microbicides [23-27]. Microbicide modelling has explored the potential impact of a microbicide with different properties, and to identify potential thresholds for the levels of condom migration that could occur following microbicide introduction without increasing HIV risk [23-27]. Epidemiological modelling has been used both to consider the impact of similar products used in different epidemiological settings, as well as the overall impact of widespread microbicide introduction in many countries simultaneously.

Similarly, economic analyses are increasingly used to inform health investments. Within the field of HIV, several reviews have sought to classify different forms of HIV prevention according to their cost-effectiveness in different settings, and to compare the cost-effectiveness of different intervention options [21, 22, 31-33]. These reviews commonly find that the cost effectiveness of any intervention approach is highly dependent on the epidemiological context, with targeted prevention being more cost-effective in concentrated epidemic settings [34].

Although there has been a long history of using mathematical modelling and economic analysis to

inform policy decisions and debates about new HIV prevention technologies, there is still room to improve on previous work. Only a few models looking at product introduction have explicitly included a gradual increase in intervention coverage over time [13-15], an essential feature for any realistic estimation. Since previous modelling has not been not always been clearly parameterised to a particular setting, the context in which the conclusions apply may not be clear. Some estimates of costs focus primarily on the unit costs of technologies, and do not include the costs of other inputs that will be needed to ensure the effective delivery of a particular technology. In addition, within microbicide modelling most previous models assume that microbicides offer the same protection to males as to females [23-27], yet this may not be an appropriate assumption. Phase III microbicide trials are designed to measure the impact of microbicide use on HIV negative women's risk of HIV acquisition, and so a more appropriate assumption may be that a microbicide will only protect females directly.

Thus, while epidemiological modelling and economic analysis are both powerful tools, it is important that such research tries, as much as is practical, to consider realistic policy options and scenarios, and is parameterised to reflect specific epidemiological situations.

Project aims

This report presents the findings from a study that uses epidemiological and economic analyses to explore the potential impact and cost-effectiveness of different microbicide introduction strategies in Southern India and South Africa. Specifically, the project aims to:

1. Estimate the impact of the introduction of a preventative microbicide on HIV incidence and prevalence in two contrasting settings (Southern India and urban South Africa).
2. Explore how impact is related to:
   - product efficacy
   - speed of approval
   - potential restrictions on product delivery
   - microbicide introduction strategy (i.e. through public health facilities, or private sector outlets)
   - uptake
   - consistency of use
3. Building on previous cost estimate exercises and cost studies, estimate the total costs of each of the different microbicide introduction strategies in each setting, explore which strategy is most cost-effective, and assess whether the delivery scenarios with highest impact are also the most cost-effective.

The project has several complementary and parallel components, which feed into the final modelling and economic analysis (Figure 1.1).

In India and South Africa, country workshops were set up to discuss the likely strategies for future product introduction, including potential target groups if resources are constrained; the likely strategies for microbicide introduction, key settings, specific opportunities and constraints, and to identify examples of successful product introductions.

Reviews of current evidence relating to the rate of introduction[3] of new health technologies have been conducted. Population-based data from urban and rural areas in each country were analysed to produce estimates of the extent to which, in each setting, women of reproductive age were accessing different

3. This term is used interchangeably with 'uptake' throughout this document.

Figure 1.1: Project activities

services. These figures, in combination with the information from the literature review, and the country workshops, were then used to develop potentially feasible introduction scenarios (with low and high uptake assumptions for each). These introduction scenarios included 120 scenario combinations in India and 156 scenarios in South Africa.

An existing epidemiological model was adapted to enable it to assess the impact of different microbicide introduction strategies on the HIV epidemic. Key new aspects of this model are the inclusion of an explicit age structure, and the potential for the model to change levels of microbicide coverage over time. This enabled the modelling analysis to consider age-specific targeting strategies, and to include projections concerning how a microbicide's impact may be affected by delays in product introduction, or slow rates of product uptake.

The mathematical model was parameterised to an urban setting in South Africa (Gauteng[4]) and an urban southern Indian setting (Mysore District, Karnataka), and fitted to setting-specific data on the prevalence of infection with HIV and other sexually transmitted infections (STI). In each setting, the model was then used to simulate the potential impact of the different microbicide introduction scenarios, and to identify which scenarios achieve the greatest impact.

Parallel economic analyses estimated the costs associated with each scenario. The costs of different potential distribution strategies were modelled using a range of assumptions about the potential unit costs of microbicide introduction, and drawing upon existing evidence about the costs of different activities that may be associated with product delivery. Thus, these projections not only included the costs of the product itself, but also the costs of provider training, staff time for interpersonal communication about product use, Voluntary Counselling and Testing (VCT) costs to ensure that users are HIV-negative, and mass media campaigns to sensitise communities to the availability of a new prevention technology. These were then used, in combination with the modelled HIV impact projections, to estimate the potential costs and cost-effectiveness of different distribution strategies.

This report summarises the key findings and policy implications of this research. Section one presents the main issues emerging from country and international consultative workshops held in India and South Africa[5], and the findings from a detailed review of the lessons about the likely rate of uptake and coverage following the introduction of other reproductive health technologies.

The findings were used to develop a range of plausible scenarios about:

- Microbicide product characteristics.
- Speed of regulatory approval and product introduction.
- Focus of product distribution.
- Potential long-term coverage achieved.

Section two presents the methods and findings of the modelling analysis, which estimated the HIV impact of each scenario in India and South Africa. Section three describes the methods and findings from the complementary cost and cost-effectiveness analysis. The implications for future microbicide introduction strategies are then discussed in Section four. In each case, further methodological detail is provided in the online appendices.

4. Gauteng is the most urban of the 11 South African provinces and contains both Johannesburg and Pretoria.

5. This project initially included Tanzania. However insufficient data was found to complete the modelling analysis in Dar Es Salaam. Results from the consultative meeting and other preliminary analyses will not be presented in this report.

"Microbicides' potential preventive impact on the HIV-epidemic supports the investment in this new prevention approach"

Section 1

Insights from country workshops and reviews of the experience from the introduction of other health technologies

Key findings from country workshops and expert consultative meeting

An important component of the project was the use of national level consultations to agree on the introduction strategies to be modelled in each setting. In each country, workshops brought together researchers familiar with microbicides and HIV, practitioners with experience with the delivery of various health services, and experts in social marketing. In South Africa, there were also representatives familiar with local regulatory procedures. After providing information about microbicides and national level experiences with products, likely distribution scenarios were discussed, as well as whether there are particular groups who should be prioritised, the potential role of the public and private sector, and the expected opportunities and constraints to future product distribution. Examples of successful and less successful product introduction were also identified and discussed.

There were similarities and differences in the issues raised in South Africa and India. In both settings, sexually active women (married or unmarried) were cited as an important group to consider for targeting, although there was debate about the extent to which they may or may not feel at risk of HIV. Youth were also identified as a vulnerable group in both settings – with discussion focusing on all sexually active youth in South Africa, and on newly married men and non-sterilised women in India. The importance of a non-contraceptive microbicide for sero-discordant couples trying to conceive was raised in South Africa. There was also discussion about the extent to which it may or may not be desirable to target a microbicide to sex workers; this issue was especially important in India, where the HIV epidemic is concentrated in this high prevalence group. It was recognised that a microbicide may provide an additional means of protection both in commercial or non-commercial sexual relationships, although there were some concerns raised about risk-disinhibition, e.g. the potential reductions in condom use, resulting from microbicide introduction.

In all settings, the HIV preventative efficacy of a microbicide was identified as a central issue affecting product acceptability and potential markets, although issues of cost (especially of whether a product would be free at the point of delivery or not), pleasure, accessibility, and contraceptive efficacy were also discussed. There was also discussion in South Africa about whether microbicides would always be provided together with condoms (as in trials), and the cost implications of this.

A common issue raised in each setting was the importance of not stigmatising microbicides. Participants in India were concerned that a microbicide should not be too directly linked to sex and that if a distribution strategy of targeting to sex workers was used, this would impact negatively on its potential for wider use. Instead they supported promotion strategies that stressed issues such as vaginal cleanliness or hygiene.

In each country there was discussion about the potential role of the government, private and public sector. In general, in each setting it was agreed that product introduction and distribution would need government support, while recognising that the role of government in provision may vary. In South Africa, where the majority of condoms are provided by government services, public sector provision of

microbicides was recognised as being very important, although other forms of distribution may also help improve access. Indeed, recent market research suggested that women were particularly interested in accessing microbicides from clinics and pharmacies, or places where they could be assured of some privacy [35]. In India, the role of the private sector was particularly stressed, with key providers potentially being clinics or other facilities where women can go without being stigmatised, rather than locations such as pharmacists, which women access less frequently.

Discussions about the likely rate of uptake, and examples of successful product introduction varied between settings. In South Africa, successful examples included injectable contraceptives and mobile phones. Products with a lower rate of uptake included the female condom and social marketing of the male condom. In India, marketing microbicides as a female hygiene product rather than an HIV prevention product was felt to be very important. Workshop participants highlighted the success of sanitary napkins in this light, and also discussed the failure of products such as tampons and diaphragms (Table 1.1).

In each setting, discussions about opportunities and constraints for microbicide delivery identified a range of key stake-holders who could strongly influence the process, including politicians, journalists, teaching institutions, faith-based organisations, and traditional healers. The constraints that were identified related to weak health infrastructures, logistical challenges and potential price constraints. Potential issues included whether microbicide use could somehow lead to higher levels of sexual activity, for example, by enhancing sexual pleasure. Likewise, there was some concern about promoting microbicides to women who were able to use condoms with high levels of consistency, in case it led to reductions in condom use. Generally however, workshop participants were very enthusiastic about the future potential for microbicides, and there was widespread recognition of the need for microbicides to help fill current gaps in HIV prevention options. The benefits of bringing together researchers familiar with microbicides, policy makers and practitioners in each setting also emerged from the workshop.

Table 1.1: Illustrative examples of low and high product uptake in India and South Africa

Country	Low Uptake	High Uptake
India	*Tampons* Less than 10% market penetration in urban areas	*Sanitary Napkins* Since 1997, rapid growth in sales, annual growth rates of 6%. Estimated coverage rates of 20-25% achieved after 10 years in urban areas.
South Africa	*Socially Marketed Condoms* Less than 10% market penetration	*Injectable contraceptives* More than 50% coverage achieved within 20 years

Expert consultative meetings also provided us with the opportunity to present the proposed methods and progress-to-date to a range of international experts in the field of microbicides. Participants stressed the need to recognise that it may take some time for a product to be approved through local regulatory mechanisms and, even once it is approved, it would not be appropriate to assume that widespread distribution was imminent. Participants described the probable steps of product introduction – initially, products would likely be distributed in the trial communities. Following regulatory approval, products would be distributed more widely, but still on a limited scale, to ensure that follow-up research and monitoring could be conducted. It was expected that the next step – over-the-counter product distribution – would take some time. It was felt that the potential speed and likelihood of a product graduating from provision through prescription by health care workers to broader methods of distribution was likely to depend upon the characteristics of the microbicide itself, and in particular, whether there were concerns about the development of drug-resistance. Ultimately, the experts highlighted that this would be a decision for local regulatory bodies, and that for the purposes of this project, we should estimate the impact of a microbicide if provision remains restricted, but also consider what may potentially be the gains if, after a few years, the product was made more widely available. Experts with substantial experience in the distribution of contraceptives and other health commodities also confirmed the need to be realistic about length of time that it may take, and the coverage that could be achieved.

Evidence about the rate of introduction of different health technologies in low and middle income countries (LMICs), and factors influencing this

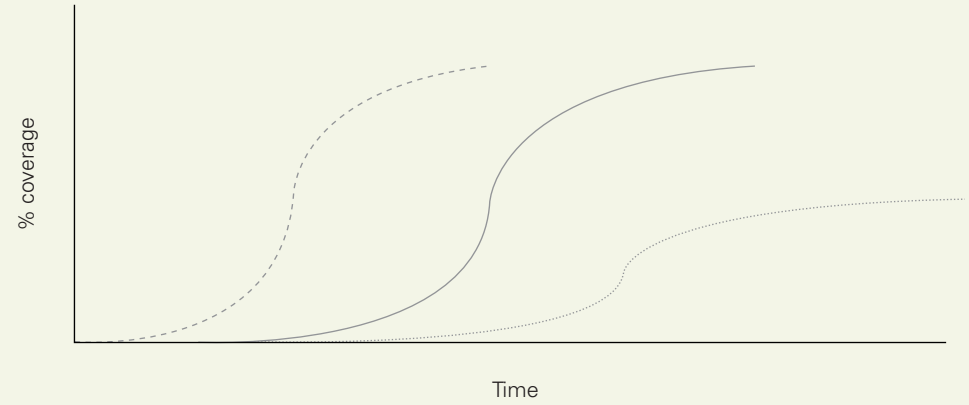
To complement these workshops, a detailed literature review was used to compile international experience with the introduction of new products (especially contraceptives). National experience with the introduction of new products, including male and female condoms and contraceptives, was also reviewed.

The theoretical literature on product introduction suggests a backwards bending S trajectory curve, with a relatively low rate of uptake initially, followed by a take-off phase, and then a maturation phase where the rate of uptake continues to increase at a decreasing rate. It also highlights that there are several key issues when thinking about likely trajectories for the introduction of microbicides, including the time until the product enters the take-off phase, the level of coverage or sales achieved at the different phases, and the amount of time needed for the maturation of the market.

The empirical findings highlight:

- The large variation in uptake by product and setting. This variation appears to be affected by a large range of factors including price and distribution channels (vending machines, over the counter, use of wholesalers, marketing and targeting of advertising, ability of staff to be discrete in health facilities).
- The upper range for the rates of coverage are approximately 70% (e.g. condoms for married couples in Japan), however this is exceptional. The successful introduction of tampons in the United States had gradual uptake, with only 25% of women using them 10 years after market introduction.

Figure 1.2: The classic diffusion model [36]



- The take-off phase generally takes at least five years (e.g. over a 6 year period, male condom use increased from 1% to 16% in Uganda).
- The maturation phase can also vary, but is likely to be about 10-15 years (e.g. in Thailand, oral contraceptives increased from 26% to 45% of the market share over an 18 year period)

Evidence from South Africa and India on the extent to which women of reproductive age have contact with different health services

When considering optimal strategies for the distribution of microbicides, a key consideration is the extent to which women have access to different potential providers of microbicides in different settings. As discussed above, potential target groups for the delivery of microbicides identified in the country workshops included youth (identified in all countries), sero-discordant couples (South Africa), women of reproductive age (all countries), and sex worker populations (India and South Africa).

To gain insights into this issue, we analysed population data collected from women of reproductive age as part of national demographic and health surveys (DHS). Although these surveys were not designed specifically for this purpose, they could be used to obtain population-based estimates of the extent to which women in each setting have contact with different services. DHS data sets were obtained for India (2005/6) and South Africa (2003).

In Gauteng, 50% of sexually active[6] women aged between 15 and 49 used a modern method of contraception[7]. Contraceptive use was highest in the 15 to 24 age group (59%) and lowest in the 35 to 49 age group (41%). Injectable contraceptives were the most popular, representing 46% of all the contraceptives used, followed by the pill (21%). Condoms were most popular in the youngest age group (26%, versus 8% and 10% in the older

6. Defined as sexually active within the past year. Please note this differs from the more conservative definition of sexually active as women who have had sex in the last 4 weeks. Among this group contraceptive use is 63%.

7. This excludes sterilisation, because these numbers are used to proxy regular access to health services. Including sterilisation, 59% of women use modern contraception.

age groups). This high use of contraceptives also illustrates high levels of access to health care. The most popular health facilities were government clinics (21%) and private doctors (17.2%). However, private hospital/clinics, community health centres, and chemist/pharmacist together contributed another 20%, with approximately equal shares. There was also evidence of relatively high levels of uptake of VCT: 47.4% of women were tested. This was higher than in rural areas, where only 25.6% reported having been tested for HIV.

In India, between one-third (urban Karnataka) and 44% (Delhi) of women reported having visited a health facility or camp in the past 3 months. Few, however, reported having accessed family planning or ante / post natal care. The proportion of women using a modern method of contraception was high in both urban and rural settings (40% in Delhi, 44% in urban Karnataka and 51% in rural Karnataka), with contraceptive use increasing by age in all 3 sites. The largest increase was between the 15-24 and the 25-34 age groups. However, the most common method of modern contraception was female sterilisation: 55% of women aged 25 to 49 were sterilised in urban Karnataka, 72% in rural Karnataka and 26% in Delhi. This suggests that in practise, these relatively high levels of contraceptive use are not associated with a regular attendance at a health service[8]. Very few women reported having sought advice or treatment for STIs in the past 3 months.

When reviewing the current levels of coverage and discussing potential distribution options with country workshop participants, it was clear that high levels of coverage are unlikely to be achieved by focusing on contraceptive delivery mechanisms alone. For example, ignoring additional supply side constraints and excluding women who are sterilised, the potential integration of a microbicide into contraceptive delivery would reach at most 6% of women in urban Karnataka, and up to 21% in Delhi. There may be even greater potential coverage in South Africa, where a greater proportion of both urban and rural women use modern methods of contraception, ensuring regular contact with some sort of family planning provider.

Although our project initially focused on using modelling to inform future distribution strategies, the process illustrated that important insights can be gained from this intermediate step, in which the potential coverage of existing services are explored. This is an activity that could be more widely supported, with the findings being used to inform microbicide access discussions.

Based upon our discussions with our collaborators in India and South Africa, it was agreed that female sex workers (FSWs) had a higher level of access to HIV prevention services than other women, due to their recognised vulnerability to HIV, and the extent of ongoing HIV service provision in each setting. In these consultations, it was estimated that approximately 70% of sex workers in each setting had access to HIV prevention interventions.

Summary and discussion: development of introduction scenarios

Based upon the reviews and workshop recommendations, the following illustrative scenarios about the efficacy and consistency of microbicides, potential approaches to targeting, and likely strategies and timeframes for introduction were agreed upon.

It was agreed that the analysis would consider three possible levels of HIV efficacy per sex act (35%, 60% and 85%), with two potential values being used to represent the proportion of sex acts in which the

8. Results on coverage of services in India show data for male and female sterilisation. However, virtually all the cases involved female sterilisation. The reported number of male sterilisations were 5 out of 791 in urban Karnataka; 3 out of 1638 in rural Karnataka and 22 out of 583 in Delhi.

Table 1.2: Selected scenarios for microbicide efficacy and coverage

HIV-efficacy per sex act	Percentage of sex acts protected
Low - 35%	Moderate - 50%
Low - 35%	High - 80%
Medium - 60%	Moderate - 50%
Medium - 60%	High - 80%
High – 85%	Moderate - 50%
High – 85%	High - 80%

microbicide provides protection i.e. the microbicide is used (moderate of 50% and high of 80%) (Table 1.2). In addition, it was agreed that the analysis would only consider a microbicide that provides protection to HIV uninfected women, and that we would not consider any protective effect associated with an HIV positive woman using a microbicide with an uninfected partner. It was also agreed that the analysis would focus on estimating the impact of a microbicide effective only against HIV; although there has been some debate about whether some gel-based products may protect against other STIs, we would not include this in the analysis. Since it was recognised that there may be some potential for reductions in condom use following microbicide introduction, the analysis assumes a theoretical 5% reduction in condom use.

Participants suggested that we compare a range of contrasting introduction strategies in each setting: comparing population level distribution versus more focused provision to sex workers through sex worker programmes in Southern India, and population distribution only, population distribution with enhanced youth provision; and population provision with enhanced sex worker provision in urban South Africa (Table 1.3).

In addition, a range of scenarios about the process of product introduction in each setting would be considered (Table 1.4). It was proposed that we should consider two potential scenarios related

Table 1.3: Selected introduction strategies to model in India and South Africa

Urban Southern India
1. Population-level distribution to all sexually active women 2. Focused provision to female sex workers (FSWs) through sex worker programmes
Urban South Africa
1. Population-level distribution to all sexually active women 2. Population distribution with enhanced provision to youth 3 yrs post-approval 3. Population distribution with enhanced provision to FSWs through sex worker outreach programmes

to the speed of regulatory approval and market authorisation, during which time a product would be provided on a limited scale to trial participants. Although it was recognised that there could be wide variation in the time that this may take, for the purposes of the analysis it was suggested that a slow scenario of 3 years and a fast scenario of one year would be reasonable.

The next phase of product introduction was conceptualised as a time of restricted delivery for a product, with an assumption that this phase may last for three years. Over this period, it was suggested that we consider the provision of a microbicide to HIV negative women upon prescription, through public health facilities.

The final stage to consider was then where a product may become more widely available through other outlets, with the levels of coverage achievable being determined by the existing levels of contact that different populations have with services, and with the assumption that the coverage levels would eventually plateau to a saturation level of distribution.

For each setting, the coverage levels associated with each stage was parameterised using site-specific data, in combination with evidence about the successes of other technologies (Table 1.4).

These different factors led to the consideration of 120 different scenario combinations in India and 156 different scenarios in South Africa. To illustrate how this worked, Figure 1.3 gives an example of the high uptake trajectories considered for microbicide provision to female sex workers in the India analysis. Similarly, Figure 1.4 shows the high uptake scenarios considered in South Africa.

Table 1.4: Parameterisation of stages of product introduction in Urban India and South Africa

Stage	India	South Africa
Regulatory approval & market authorisation: product provided on a limited scale to trial participants	Up to 1% of FSWs have access to microbicides Slow – 3 yrs Fast – 1 year	Up to 0.1% of females in general population have access to microbicides Slow – 3 yrs Fast – 1 year
Restricted delivery for 3 years: product only available on prescription, through public health facilities	34% of the general population have access to public health facilities 68% of FSWs have access to public health facilities	50% of the general population have access to public health facilities 70% youth (3 yrs post approval) have access to public health facilities 70% FSWs (3 yrs post approval) have access to public health facilities
Potentially unrestricted delivery e.g. supermarkets, shops, social marketing, GPs, pharmacies	Coverage 10yrs post approval: Gen population Low – 3% Med – 15% High – 30% FSW: Low – 30% High – 80%	Coverage 10 years post-approval Gen pop / youth FSWs Low – 3% Med – 15% High – 30% FSW: Low – 30% High – 80%
Achievable market saturation	Levels of distribution plateau	

Figure 1.3: Example of high uptake trajectories modelled in India analysis

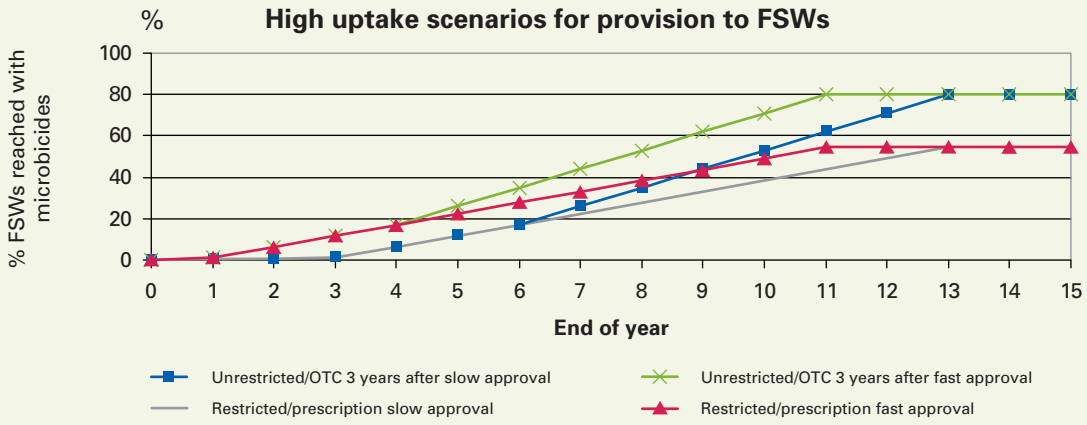
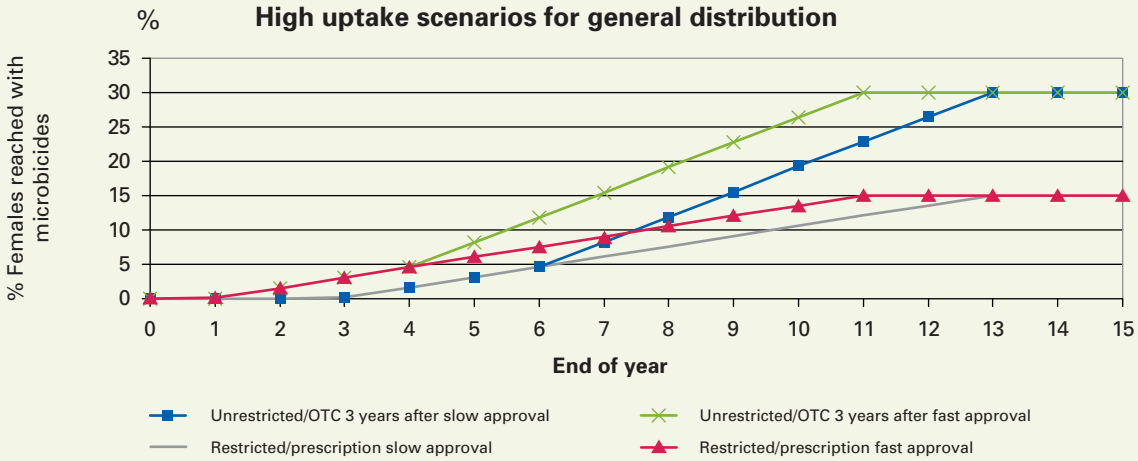


Figure 1.4: Example of high uptake trajectories modelled in South Africa analysis



- The grey line shows the assumptions about the proportion of female sex workers using microbicides every year, assuming slow approval (3 years), and that product provision remains restricted to the private sector.
- The red line shows the same introduction scenario, but assumes a faster approval (1 year).
- The blue line shows the coverage achieved assuming slow approval, with the product becoming available over the counter three years following product introduction.
- The green line represents the highest coverage achieved, with an optimal introduction scenario of fast approval, and that the product quickly becomes available over the counter.

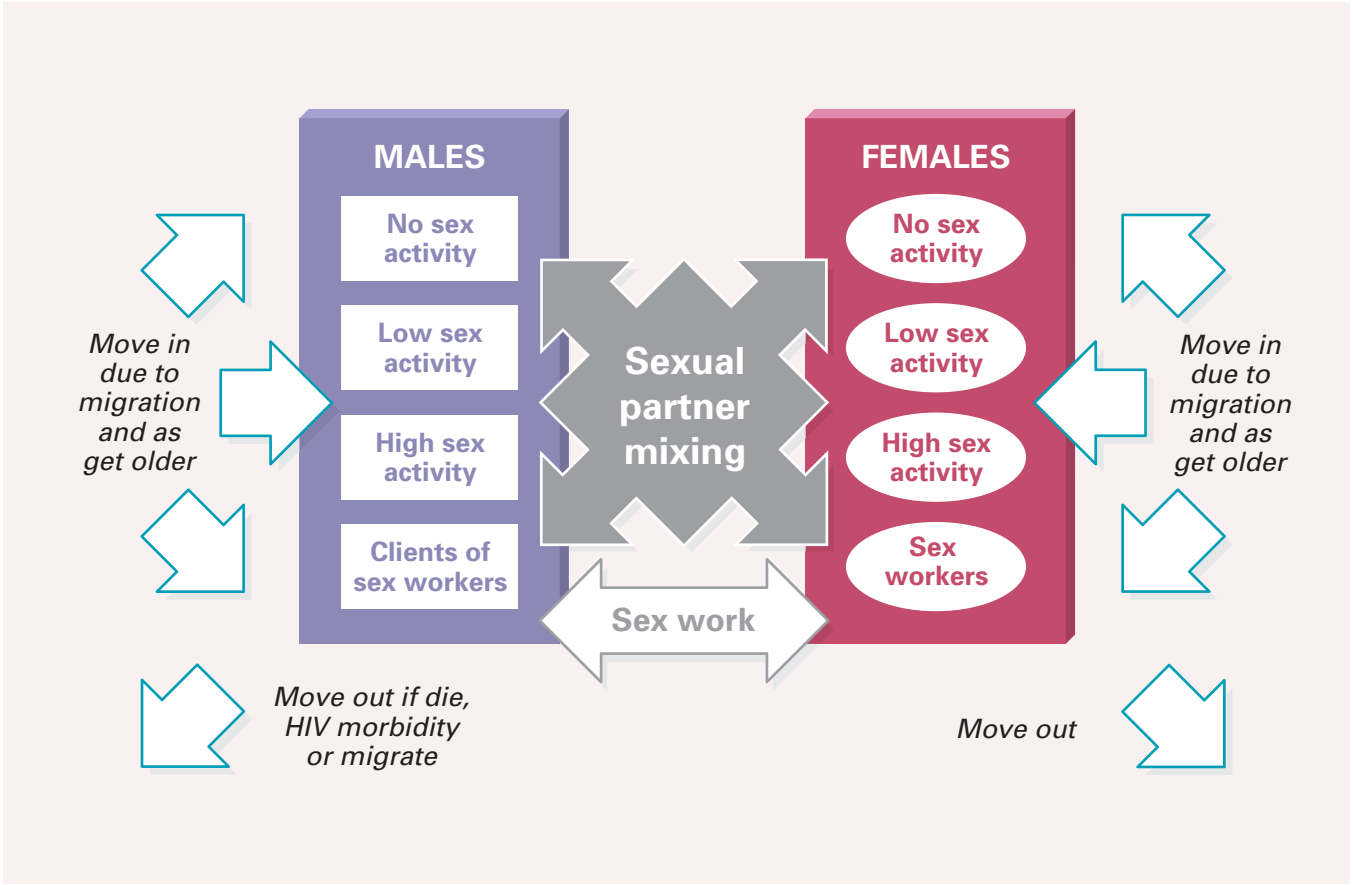
Section 2

Modelling of community level impact of microbicide introduction in Karnataka, Southern India and Gauteng, South Africa

This section describes the methods used to estimate the public health impact of the different microbicide products for the different targeting and introduction strategies described above. In addition, this section shows how the model fits the two settings considered and presents the model impact projections.

For this analysis, two matched community level deterministic HIV transmission models were developed. The models divide the population into sub-groups, with stratifications by level of sexual behaviour and HIV/STI status, and by age for the South Africa model. The models simulate the transmission of HIV resulting from heterosexual contact between these sub-groups within the male and female population. The heterosexual transmission of herpes simplex virus type-2 (HSV-2), syphilis and a third sexually transmitted infection between these sub-groups are also simulated. The models incorporate the facilitating effect of STIs on HIV transmission and the higher HIV infectivity associated with primary and late-stage HIV infection. Modelled 'individuals' of different levels of sexual activity form different types of sexual partnerships with defined durations, frequencies of sex and levels of condom and microbicide use (Figure 2.1).The model was parameterised using detailed site-specific

Figure 2.1: Basic structure of HIV models



and scientific data, and in close consultation with organisations that have a detailed knowledge and experience of each location. In collaboration with Karnataka Health Promotion Trust (KSAPS / University of Manitoba), the model was parameterised for Mysore, Karnataka, using detailed baseline behavioural and epidemiological data collected as part of the monitoring and evaluation of the Avahan HIV prevention programme[9]. In South Africa, in collaboration with the Reproductive Health and Research Unit at the University of Witwatersrand, a detailed population model was parameterised to represent Gauteng, the urban province housing the capital city. In both cases, the detailed parameter values are provided in Appendix 2.

For this modelling analysis we assumed that a microbicide will protect only females directly. In addition, rather than assuming that saturation levels of microbicide use will occur instantaneously following microbicide introduction, the model was refined to enable changing levels of microbicide use to be considered. This revision is a substantial improvement, as it enables us to simulate a gradual increase in microbicide use over time, with the shape of the uptake trajectories being informed by the above review of the rates of uptake of other health technologies. As described above, in the modelling analysis, the uptake curve was composed of four stages, to mimic the different stages in product uptake.

The models were formulated in Borland C++ and run within the Microsoft Windows environment. Each setting-specific model consists of the same set of deterministic ordinary differential equations that describe the movement of individuals between discrete sub-groups (and with additional age stratification in South Africa). The models use established mathematical techniques to estimate how HIV and other STI spread between the sub-groups over time[10] [37-39]. The basic model prior to the modifications made for this IPM project is detailed in Williams et al. (2006) [40] (Figure 2.1). The mathematical description of the model is provided in Appendix 4.

Due to the complexity of the model, during development it was necessary to implement an extensive cross-checking procedure. The model was constructed using a staging process, whereby at key stages in the model development, the newly revised model outputs were compared with the model outputs from the previous stage. Each section of model code was also thoroughly cross-checked by two experienced mathematical modellers/programmers.

In order to reflect the uncertainty contained in the supporting behavioural, demographic and epidemiological data, the model was constructed to allow a specified level of uncertainty associated with the approximately 68 model input parameters. Different combinations of these parameters were run through the model. Any combination that provided a model projection which matched the data on HIV and STI prevalence for each sub-group for that setting was retained as one possible 'fit' to the data. Each of these different 'fits' were then used in the simulations of microbicide introduction, with the range of projections produced used to reflect the uncertainty in the final outcomes.

9. The India AIDS Initiative is funded by Bill & Melinda Gates Foundation.

10. References for model parameters can be found online at www.ipm-microbicides.org and click on "Publications."

Overview of settings considered and model fits

Mysore District, Karnataka

The modelling analysis considered two contrasting settings. In India, the analysis considered Mysore District, in Southern India. Mysore District has a population at a reproductive age of around 1.6 million, with approximately 810,000 females and 839,000 males. The first round of behavioural surveys suggest that there are around 7,000 female sex workers (FSWs), and 51,000 clients. Condoms are used in about half of commercial sex acts (51%) and less than 7% of non-commercial sex acts.

In Mysore the HIV epidemic is largely concentrated among the most vulnerable groups i.e. the HIV prevalence in FSWs is about 26%, whereas the prevalence in the general population of Mysore is around 1%. Other prevalent sexually transmitted infections were HSV-2, with a prevalence of 64% in female sex workers (FSW) and 11-13% in the general population. Trichomonas vaginalis and active syphilis were present, with prevalences of around 33% and 25% respectively in FSW. The prevalences of syphilis, chlamydia and gonorrhoea in the general population were all reported to be below 2%.

The best model fits to this epidemiological data are shown in Table 2.1. As can be seen, the model fits closely to the prevalence of HIV and other STI among both sex workers and clients.

The HIV incidence per year was projected by the model to be 13% for FSWs, 4% for clients, 0.2% for females in the general population and 0.3% for males in the general population.

Overview of data and model best-fit from Gauteng, South Africa

In South Africa, the model simulated HIV transmission in Gauteng province. Gauteng has a population, aged between 15 – 45 years of age, of about 5.7 million, with around 2.8 million females and 2.9 million males. Behavioural surveys suggest that there are around 55,000 FSWs and 408,000 clients, and that condoms are used in most commercial sex acts (60-90%), and less than half of non-commercial sex acts.

In Gauteng the HIV epidemic is generalised, with the general population HIV prevalence of around

Table 2.1: Model fit to local data from Mysore District, Karnataka, India

STI	Risk Group	Prevalence Data*		Model best fit
		Range used in fitting	Source**	
HIV	FSW Clients	22 – 33% < 24%	[80] [80]	26% 12%
Trichomonas vaginalis	FSW	28 – 37%	[76]	37%
Treponema pallidum	FSW Clients	21 – 29% < 16%	[76] [79]	26% 14%
HSV-2	FSW Clients	60– 69% < 40%	[76] [80]	64% 40%

*Data from 1st round (pre-intervention) **Refer to Appendix 3 for citation listing

10.8%, with 8.2% and 13.3% of males and females HIV infected respectively. There were also large differences in age, with 10.3% of 15 - 25 year olds being HIV infected and 15.6% of over 25 year olds. Estimates of the prevalence of HIV in female sex workers varied considerably, depending on the study location and year. For this work HIV prevalence in the range of 40 - 67% was used for FSW.

Other prevalent sexually transmitted infections (other than HIV) were HSV-2 with a prevalence of 84% in FSW. Trichomonas vaginalis and active syphilis were present with prevalence in FSW of around 41% and 26% respectively. The prevalence of syphilis, chlamydia and gonorrhoea in the general population were all largely reported to be below 10%.

Table 2.2. shows the best model fits for Gauteng. Again, the model fits replicate the distribution of HIV and other STI in this setting, including the differences in infection by age and sex. Using this fit, the HIV incidence per year was projected by the model to be 8% for clients, 5% for females in the general population and 2% for males in the general population.

Microbicide impact results, India

In the India analysis, 120 different distribution scenarios were modelled. Table 2.3 shows the ten scenarios with the highest projected HIV impact (the full set of impact projections are provided in Appendix 5). As expected, the highest impact ('top') scenario in this setting was a high efficacy product (85%), that cleared regulatory approval quickly (1 year) and then was distributed using focused provision to FSWs, with a quick transition from a restricted to an unrestricted microbicide introduction program (3 years

Table 2.2: Best model fit to epidemiological data from Gauteng, South Africa

STI	Risk Group	Prevalence Data*		Model best fit
		Range used in fitting	Source	
HIV	All males (15 – 25)	0.03 – 0.07	[74]	0.04
	All males (>25-49)	0.11 – 0.192	[74]	0.128
	All females (15 – 25)	0.13 – 0.185	[74]	0.177
	All females (>25-49)	0.185 – 0.23	[74]	0.23
	FSW	0.4 – 0.67	[69][81]	0.66
	Clients	<0.425	[82]	0.41
Trichomonas vaginalis	FSW	0.17 – 0.55	[83]	0.54
Treponema pallidum	FSW	0.1 – 0.35	[69]	0.33
	Clients	<0.45		0.2
HSV2	FSW	0.66 – 0.87	[81][84]	0.83
	Clients	<0.6	[85]	0.58

*Data from 1st round (pre-intervention); refer to Appendix 3 for citation listing

post-approval), and ensuring a high level of uptake (80% after 10 years post-approval) and consistency of usage (80%). This level of impact occurs when all of the most desirable levels are considered for each of the model inputs, and microbicide distribution is focused on vulnerable sections of the population.

The model projected that approximately 91,000 HIV infections would occur over 15 years if no microbicide or other new intervention was introduced. In the highest impact scenario, the model predicted that 17,390 (6,638 – 28,672[11]) HIV infections would be averted over 15 years.

among clients and 38% of averted female infections were among FSWs).

What this table also illustrates is that after the top impact scenario, the next four scenarios closely correspond in situation to the top impact scenario, with only one other aspect being less than ideal. For example, the model projects that 762 infections per 100,000 population could be averted, if the efficacy and consistency of usage were high, approval was fast, uptake was high, but the product distribution always remained restricted. In other words, in order to achieve over

Table 2.3: Summary of top 10 impact scenarios in India analysis using model best-fit

Distribution scenario	Infections averted	Infections averted / 100,000 population	Relative percentage of top scenario
FSW Top - all high / fast / good	17,390	1,054	100%
FSW Top, but restricted always	12,560	762	72%
FSW Top, but slow approval	12,095	733	70%
FSW Top, but medium efficacy	12,015	728	69%
FSW Top, but moderate consistency	10,564	641	61%
FSW Top, but restricted always AND slow approval	8,965	544	52%
FSW Top, but restricted always AND medium efficacy	8,701	528	50%
FSW Top, but slow approval AND medium efficacy	8,368	507	48%
FSW Top, but restricted always AND moderate consistency	7,661	464	44%
Gen pop Top - all high / fast / good	7,415	450	43%

What is important to note in this setting is the central importance of targeting microbicide provision to FSW, with nine of the top ten scenarios involving the targeted provision of microbicides to sex workers and their clients. Indeed, so important is this targeting, that even in the top general distribution scenario, many of the infections averted were among clients and FSWs (69% of averted male infections were

640 infections averted per 100,000 population, one dimension can slip from the ideal so long as all the other dimensions remain high / fast / good. Similarly, the next grouping of scenarios relate to when two factors have deviated from the top scenario – and avert between 464 and 544 HIV infections per 100,000 population.

The one exception to this related to the

11. Confidence bounds were estimated by predicting the impact for all the model fits and reporting the range spanned by 95% of the fits.

assumptions about product uptake: in all the top 10 scenarios the uptake needed to be high. In part, this result arose from the ways in which the scenarios were parameterised – the difference between the high and low uptake was relatively large. In the FSWs distribution scenarios (from 80% to 30% 10 years post-approval), the model predicts only 6,310 (2,349 – 10,118) infections would be averted (383 per 100,000 population) following such a reduction in uptake. This is just 36% of the impact of the top scenario (rank 14 of 120 scenarios) (See Appendix 5).

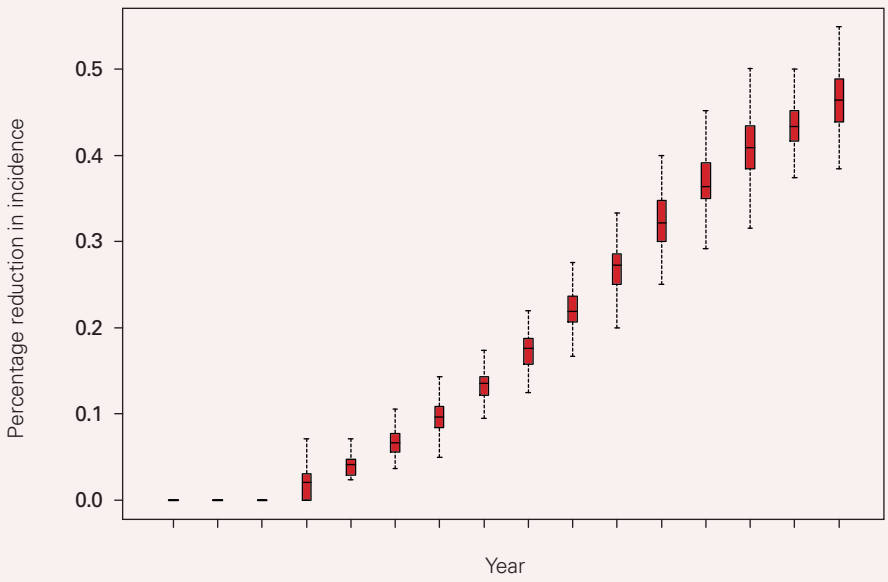
Similarly, a drop from a high per sex act efficacy of 85% to a low per sex act efficacy of 35% reduces impact to 39% of the impact of the top scenario, bringing the predicted number of infections averted down to 6,818 (2,539 – 10,948), assuming the microbicide is distributed to FSWs and all other factors are high / fast / good (rank 13 of 120 scenarios).

HIV impact in year 15 in India

The previous projections provide an overall estimate of the impact of the gradual introduction of a microbicide over fifteen years. To gain an insight into the likely long term potential of a microbicide for each of the distribution strategies, it is also useful to consider how it may impact on patterns of HIV incidence over time, and what the impact may be in year fifteen, when levels of distribution are becoming saturated.

Figure 2.2 shows the temporal trends in the reduction in HIV incidence for the most effective scenario, illustrating how the yearly infections averted are continuing to increase over time. Interestingly, the reduction in incidence is continuing on an increasing trend when the modelled intervention has ended in year 15. This suggests that further reductions in incidence might be expected to occur after the fifteen year period, even though the saturation coverage

Figure 2.2: Percentage reduction in HIV incidence in urban Southern India setting in most effective scenario[12]



12. The box plot show the range of model outputs for percentage reduction in incidence for the India setting for each year of the intervention. The mean values are shown by the black bar within red the box, the extent of the red box indicates the area in which 50% of the model projections lie and the whiskers indicate the area in which 95% of the model projections lie. The extent of the box and whiskers indicate the degree of uncertainty about the mean value.

Table 2.4: Summary of impact achieved in year 15 in urban Southern India setting using model best fit

Distribution scenario	Scenario Number	Reduction in incidence achieved by year 15 – general population (%)	Reduction in Incidence achieved by year 15 – FSW (%)	Mean infections averted per 100,000 population per year over 15 years	Infections averted per 100,000 population in year 15
FSW Top - all high / fast / good	118	48.8	69.6	70	163
FSW Top, but restricted always	94	32.6	51.5	51	110
FSW Top, but slow approval	106	41.9	65.9	49	141
FSW Top, but medium efficacy	119	32.6	52.4	49	112
FSW Top, but moderate consistency	117	30.2	47.2	43	98
FSW Top, but restricted always AND slow approval	82	27.9	48.2	36	96
FSW Top, but restricted always AND medium efficacy	95	23.3	37.7	35	75
FSW Top, but slow approval AND medium efficacy	107	27.9	49.0	34	97
FSW Top, but restricted always AND moderate consistency	93	20.9	33.7	31	66
Gen pop Top - all high / fast / good	70	20.9	29.2	30	67

of the population has been reached. The continued reduction in incidence beyond this time results from future 'chains of infection' being averted.

Table 2.4 shows the mean yearly infections averted per 100,000 population and the infections averted per 100,000 population achieved in the final year of the modelled intervention. For all of the top ten scenarios the impact in year 15 is on average about 2.4 times the mean impact over the 15 years of the intervention. After 15 years, the model best-fit predicts a relative reduction in incidence per susceptible of 49% over all the population and 70% among FSWs alone. When comparing the impact projections across scenarios, our findings illustrate how factors such as delays in product approval and/or a failure to ensure that microbicides are used by those most vulnerable to HIV infection may undermine impact. For example, one possibility is that a product is found to have high HIV-efficacy and this leads to a high uptake and high consistency of usage [41]. However, regulatory approval and market authorisation are slow, and afterwards the product remains always restricted to delivery through public health facilities. Policy makers choose a population approach to product distribution, and so only a relatively small proportion of commercial sex acts acquire additional HIV protection. As the HIV epidemic in India is highly concentrated among vulnerable groups such as FSW, our modelling suggests that this would only result in 2,284 (943 – 3,788) HIV infections being averted over 15 years (138 per 100,000 population). This is in contrast to the projected 12,560 HIV infections (762 per 100,000) that would have been averted if the same product had been rapidly introduced through sex worker projects, even if it remained having restricted delivery.

Impact results for South Africa

In the South Africa analysis, 156 different distribution scenarios were modelled. Table 2.5 shows the ten scenarios with the highest-projected HIV impact (the full set of impact projections are provided in Appendix 6). In this case, the highest impact ('top') scenario for this setting of South Africa came from clearing regulatory approval quickly (1 year) and then distributing microbicides to the general population, in combination with enhanced provision to FSWs (though sex worker programmes) of a microbicide with high preventive HIV-efficacy (85%), through an unrestricted microbicide introduction program (3 years post-approval). This scenario assumes a high level of uptake (80% for FSWs and 30% for the general population, after 10 years post-approval) and consistency of protection (80%) were achieved.

averted over 15 years in this highest impact scenario. Using the best model fit, this is equivalent to 2,930 HIV infections per 100,000 infections averted.

It is interesting to contrast this with the India analysis. In South Africa, we project that microbicides could have a higher impact on the number of HIV infections averted per 100,000 population, but a lower percentage reduction in HIV incidence in this setting. These findings are consistent with modelled projections of the impact of other HIV prevention interventions in different epidemiological settings. There is a lower percentage reduction in HIV incidence because the HIV epidemic is highly generalised in these settings, making it more difficult to remain HIV-uninfected for long periods of time, as any occurrence of unsafe sexual behaviour may be associated with substantial HIV risk.

Table 2.5: Summary of top ten impact strategies in South Africa analysis using model best-fit

Distribution scenario	Infections averted	Infections averted / 100,000 population	Relative percentage of top scenario
Gen pop + FSW Top - all high / fast / good	167,223	2,930	100%
Gen pop Top - all high / fast / good	130,444	2,286	78%
Gen pop + FSW Top, but slow approval	124,333	2,179	74%
Gen pop + FSW Top, but medium efficacy	115,392	2,022	69%
Gen pop + FSW Top, but moderate consistency	101,544	1,779	61%
Gen pop + FSW Top, but restricted always	98,110	1,719	59%
Gen pop Top, but slow approval	97,887	1,715	59%
Gen pop Top, but medium efficacy	90,973	1,594	54%
Gen pop + FSW Top, but slow approval AND medium efficacy	86,089	1,508	51%
Gen pop Top, but moderate consistency	80,281	1,407	48%

The model projected that almost 2.5 million HIV infections would occur over 15 years if no microbicide or other new intervention was introduced, and that 167,223 (143,255 – 193,381[13]) HIV infections would be

We project that over 2,022 infections per 100,000 population could be averted if there is a general distribution of microbicides with enhanced provision of microbicides through FSW programmes if either,

13 . Confidence bounds were estimated by predicting the impact for all the model fits and reporting the range spanned by 95% of the fits.

regulatory approval and market authorisation is slow but microbicide efficacy and consistency of protection are high; or microbicide efficacy is medium, but consistency and uptake is high, and the product becomes unrestricted 3 years post-approval.

Similarly, the modelling suggests that a high impact can be achieved with a product of medium HIV-efficacy if consistency of usage is high, uptake is high, approval is fast, and the product's delivery eventually becomes unrestricted.

Although the enhanced provision to sex workers does improve impact, the model also suggests that a population-only distribution strategy could achieve substantial impact. Over 2,286 infections per 100,000 population would be averted through the general distribution of microbicides, without the enhanced provision of microbicides through FSW programmes, so long as efficacy and consistency of usage are high, uptake is high, approval is fast and the product is unrestricted (3 years post-approval). In this case also, our projections suggest that a disproportionate number of infections averted were among clients and FSWs (37% of male infections averted were among clients and 15% of female infections averted were among FSWs). However, these percentages are much less than in the Indian analysis, due to the different epidemics in these two settings.

As in the India analysis, the uptake needs to be high in the top 10 scenarios, since the relative drop to low uptake is so great (from 80% to 30% among FSWs and from 30% to 3% among the general population, 10 years post-approval). This means that the model predicts only 29,902 (25,988 – 35,348) infections would be averted if there is low uptake (524 per 100,000 population), 18% of the impact of the top scenario (ranking 58 out of 156 scenarios). For the general distribution scenarios (without enhanced provision to FSWs), the model predicts that a medium uptake scenario (15% coverage 10 years post-approval) would avert 64,044 (52,936 – 79,581) infections, i.e. 1,122 per 100,000 population, (ranking 19 out of all 156 scenarios, and 7 out of the 72 general distribution scenarios only).

A drop from a high efficacy of 85% to a low efficacy of 35% reduces the projected impact to 39% of the impact of the top scenario, bringing the predicted number of infections averted down to 65,837 (56,621 – 77,075), 1,154 per 100,000 population, assuming the microbicide is distributed to FSWs and all other factors are high / fast / good (rank 18 out of 156 scenarios).

Among the scenarios with general distribution and enhanced distribution to youth (in which delivery was assumed to always remain restricted), the highest impact scenario ranked 11 out of all 156 scenarios. In this scenario, the model predicts that 79,977 (66,064 – 99,794) infections would be averted over 15 years (1,401 per 100,000 population).

HIV impact in year 15 in Gauteng, South Africa

Again, it is interesting to consider the temporal trends in reduction in HIV incidence over time. Figure 2.3 shows the yearly reduction in incidence achieved for the most effective scenario. The yearly reduction in incidence increases rapidly from year three to year 12. After year twelve the reduction continues to increase although at a more gradual rate. This coincides with uptake reaching its maximum levels by year twelve (in this scenario). The continued increase is again due to the effect of preventing chains of future infection, with the trend shown in this plot suggesting that further modest reductions in incidence might be expected after the 15-year period considered. The most effective scenario reduces incidence per susceptible by 15% after 15 years.

Figure 2.3: Percentage reduction in HIV incidence in urban South African setting in most effective scenario[14]

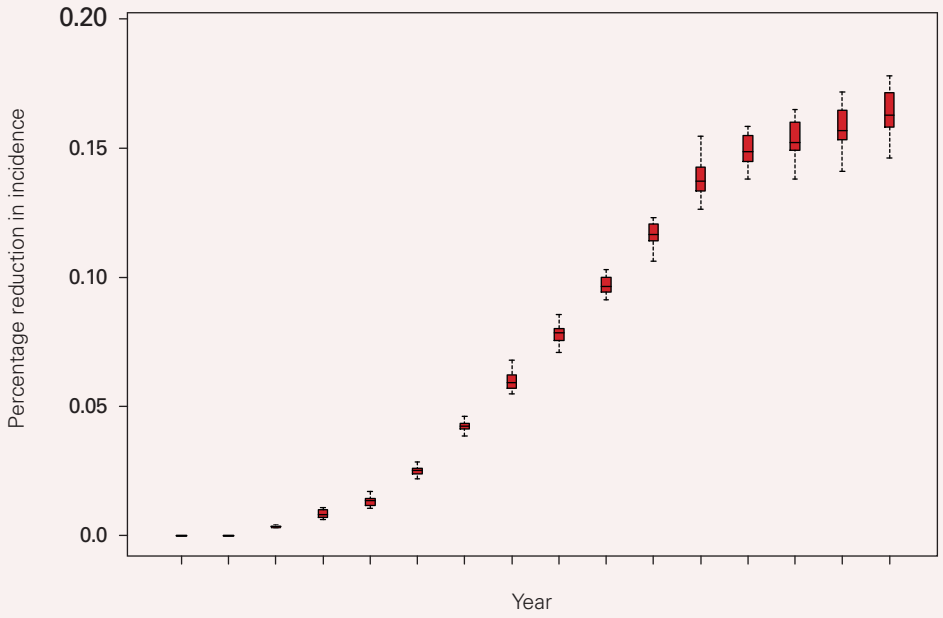


Table 2.6: Summary of impact achieved in year 15 in urban South African setting using model best fit

Distribution scenario	Scenario Number	Reduction in incidence achieved by year 15 – general population (%)	Reduction in Incidence achieved by year 15 – FSW (%)	Mean infections averted per 100,000 population per year over 15 years	Infections averted per 100,000 population in year 15
Gen pop+FSW Top - all high / fast / good	154	14.6	26.3	195	373
Gen pop Top - all high / fast / good	70	6.6	7.4	152	293
Gen pop+FSW Top, but slow approval	142	13.7	25.4	145	359
Gen pop+FSW Top, but medium efficacy	155	10.1	18.7	135	254
Gen pop+FSW Top, but moderate consistency	153	9.0	16.6	119	223
Gen pop+FSW Top, but restricted always	130	6.3	7.0	115	283
Gen pop Top, but slow approval	52	8.1	17.8	114	205
Gen pop Top, but medium efficacy	71	4.6	5.2	106	203
Gen pop+FSW Top, but slow approval AND medium efficacy	143	9.6	18.0	101	246
Gen pop Top, but moderate consistency	69	4.0	4.6	94	179

14 . The box plot show the range of model outputs for percentage reduction in incidence for the South African setting for each year of the intervention. The mean values are shown by the black bar within red the box, the extent of the red box indicates the area in which 50% of the model projections lie and the whiskers indicate the area in which 95% of the model projections lie. The extent of the box and whiskers indicate the degree of uncertainty about the mean value.

Table 2.6 shows the mean yearly infections averted per 100,000 population and the infections averted per 100,000 population achieved in year 15. For all of the top ten scenarios the impact in the final year is on average two times the mean impact over the 15 years of the intervention.

Although we have considered a range of combinations of scenarios that combine different permutations of variables, in practise, several may be related. For example, there may be a greater demand and use of high efficacy products than lower efficacy options. The following example illustrates how these factors may act in combination. If we consider a product with high HIV-efficacy, high uptake and high consistency of usage [41]. Even if regulatory approval and market authorisation are slow, and the product is solely provided through population distribution channels, without enhanced provision to youth or FSWs, and the delivery of the product through public health facilities remains restricted, the model nevertheless predicts that 54,213 (44,668 – 66,751) HIV infections would be averted over 15 years (950 per 100,000 population). In contrast, if a product has medium HIV-efficacy (50%), and this leads to a low uptake and moderate consistency of usage [5], even if regulatory approval and market authorisation are fast and the product becomes unrestricted 3 years post-approval, and the microbicide is distributed to the general population, with enhanced provision to FSWs, the model predicts that we would achieve less than a third of the impact of the high efficacy high use scenario. This illustrates the importance in product development of considering not only what formulations may have high efficacy, but also what may be most effective in ensuring a high consistency of protection, and that in the long term, could potentially be delivered with no or limited health sector input.

"A disproportionate number of HIV infections occur among women, yet most options for HIV prevention remain in the control of men"

Section 3

Economic analysis of microbicide distribution strategies

This section presents the methods used and results from the economic analysis of microbicide distribution. The aims of this analysis were three-fold:

- To estimate the costs of introducing microbicides based on the different distribution scenarios considered in each setting.
- To estimate the average cost and cost-effectiveness of different distribution scenarios.
- To assess whether the delivery scenarios with highest impact are also the most cost-effective.

Methods to estimate costs of microbicide delivery

The costing of the different distribution scenarios considered used established methods for costing HIV prevention interventions [42]. The analysis uses ***economic*** costs, which includes the value of all items used in implementing services, even if not paid for or donated to fully count all resources needed for implementation. This is in contrast to financial costs, which only include expenditures which are actually paid but ignores donated or subsidised items. Costs included are from the ***provider's*** perspective which accounts for all costs incurred by the provider of the intervention, but excludes costs to others. For example, costs borne by women using the services, such as travel time to collect the product, are not included.

For the analysis, the intervention is conceptualised as being added onto existing services, rather than being a new vertical service. In such instances the ***incremental*** costs and effectiveness will serve to answer the question if it is worthwhile to add microbicides onto existing programmes. Costs included in incremental analysis are limited to those extra costs incurred with the new product, rather than the full costs of establishing a new facility, which would include infrastructure and higher level programmatic costs.

The incremental costs included are the costs of the microbicide product, annual HIV testing, product distribution, interpersonal communications, mass media communications and training costs. In South Africa, the latter two are modelled as fixed costs per programme or per health facility, respectively, while the others are modelled based on the number of women reached, generated by the epidemiological model. In India, the average cost of training in facilities was obtained and used.

As is standard for cost-effectiveness analysis ***discounting*** is used to convert future costs and benefits to their present value. For the purposes of the analysis, both undiscounted values and the discounted values, using a 3% discount rate is used.

Estimates of the potential unit cost ranges of different forms of products were chosen in discussion with IPM. As a base-case for the analysis, we considered a microbicide product that is used daily, and is priced at $0.10. We then explored the sensitivity of the findings to different cost and use assumptions (Table 3.1). The low and high cost assumptions for daily use where 5 cents and $1.00. Low and high cost scenarios for a monthly use product, of $1 and $5 respectively, were also considered.

Estimates of the volume of microbicides required were modelled based on the annual number of women reached, the consistency of product protection, and the assumed required frequency of

Table 3.1: Assumptions about unit costs of products (US$ 2008)

Scenario	Price ($)
Daily use	
Medium (Base case)	0.10
Low	0.05
High	1.00
Monthly use	
Low	1.00
High	5.00

product use (daily or monthly use). It is common to model in some level of wastage. For this analysis we assumed a 10% loss of product due to product non-use or expiration.

The costing also modelled the other costs required to deliver a product. For this, the unit costs for different forms of inputs were compiled from different projects from the relevant countries. In India, the costing drew in particular from an ongoing costing of the Avahan intervention [43]. In South Africa, the costing drew upon other costing studies that the team have conducted, as well as the broader costing literature.

As we are considering a scenario where microbicides are provided to HIV-negative women, as well as the product costs, in all scenarios, we assumed that VCT is provided annually to all women reached, to ensure product is only provided to HIV-negative women.

For facility-based distribution, it was assumed that staff received training in how to introduce the product to clients, and to teach clients about how to use the products effectively. This training was assumed to be rolled out to all facilities over the three year restricted access period. Thereafter, it was assumed that staff received a brief refresher training (at one-third the intensity of the initial training), every 3 years.

For non-facility based distribution, it was envisaged that the product is distributed through non-health facility outlets after the restricted phase. That is from year 4 onwards if regulatory approval is fast and from year 7 if it is slow. For this non-facility based distribution, we assumed that the reliance on mass media communications is greater, with 30% higher costs per programme. Women are still required to have VCT annually. Providers are not given any special training to dispense product (note all clinic staff were trained during the initial restricted period, but not given refresher courses).

To support the population-based provision of a microbicide, it was assumed that for 5 years after the 3 years of restricted access, mass media communications are used to inform and promote the product to the general population, with this media activity tapering off over time.

In South Africa, the costs of enhanced provision to the youth, over and above the general population facility-based distribution strategy above, was modelled as including an additional mass media campaign, and the costs of supporting peer educators. Similarly, the strategy for the enhanced provision to FSWs include the costs of peer educators to educate FSWs and encourage them to go to the clinic to collect product was included. The unit costs used for this analysis are summarised in Appendix 10.

Assessment of cost-effectiveness

The costs of product distribution through the different scenarios were estimated using a spread-sheet model to link the model projections of the annual number of women reached from the different populations (where relevant) into cost estimates. The cost per HIV infection averted was estimated by dividing these cost estimates by the epidemiological model projections of the cumulative number of HIV infections averted (Section 2).

To consider whether a particular distribution strategy is 'cost-effective' or not, it is necessary to compare this with other possible interventions. Two outcomes can be used to compare cost-effectiveness among

health interventions: HIV infections averted and Disability Adjusted Life Years (DALYs)[15] saved. Use of HIV infections averted allows for comparison of the cost-effectiveness of other HIV prevention interventions, while DALYs saved allow for comparison with broader health interventions. In cost-effectiveness analysis, DALYs are setting specific, as they use a figure for the average age at infection, duration of illness and age at death. In India, it is estimated that there are on average 27 DALYs saved per HIV infection averted. In South Africa, it is estimated that averting an HIV infection translated to approximately 25 DALYs.

In the 1993 World Bank Development Report [44] some generic cost-effectiveness cut-offs were suggested. For middle income countries, such as India and South Africa, this was $100 per DALY in 1993 US Dollars. Adjusted to 2008, this becomes $173 dollars per DALY. This then translates into a cost-effectiveness cut off in India of $1,425 per HIV infection averted and in South Africa of $3,005 per HIV infection averted, with interventions achieving a cost-effectiveness of less than these figures being seen to be 'cost-effective'. In South Africa the cost of the prevention of mother to child transmission of HIV ranges from $2,029-$4,728 per HIV infection averted ($81-$189 per DALY), and STI treatment for FSW around $2,574 per HIV infection averted ($103 per DALY saved).

Cost-effectiveness results for India

Assuming a base case of a microbicide product being used daily, priced at $0.10, Table 3.2 shows the top ten distribution scenarios in terms of cost-effectiveness, with both the discounted and undiscounted figures given. The full findings are given in Appendix 8. All of these strategies are associated with targeted distribution to female sex workers, and include a mix of facility and non-facility based delivery strategies. Reviewing the undiscounted values of cost-effectiveness, using a cut off of $1,425 per HIV infection averted, all of the targeted strategies would be considered cost-effective. Using the discounted values, the top five scenarios are cost-effective, with the remaining five being close to cost-effective.

Comparing the ranking by cost-effectiveness with the ranking by impact, in general the findings were very similar, with the top nine impact strategies also being the top nine cost-effectiveness strategies, although the ordering did differ slightly. The main difference related to the population level distribution strategies. Whilst the impact projections ranked the population distribution of an efficacious product used with high consistency tenth, when compared to accepted thresholds, this would be considered cost-ineffective. This is because the general population distribution strategies have significantly higher costs, associated with reaching and providing a microbicide to large numbers of people. Given the low levels of HIV in the general population, this is a relatively inefficient approach, which does not result in many HIV infections being averted.

The profile of the cost components associated with each of the above scenarios, in each case the largest component of costs is the cost of the microbicide (60%-73%), reflecting that we are considering the incremental nature of the cost analysis. After this, the costs were interpersonal communication and promotion (11%-18%), training (6%-11%), VCT (5%-9%) and delivery (1%-12%). What was interesting to see when comparing the cost profiles across strategies was that the higher

15 . Disability Adjusted Life Years (DALYs) were first used by the World Bank in the 1993 World Development Report: Investing in Health. The measure represents a discounted and weighed sum of values estimated to represent the years of different levels of morbidity and years of life gained by averting or treating a specific health problem. For HIV, the measure includes estimates of the duration of HIV related morbility, and the average number of life years gained from averting an HIV infection.

consistency of protection scenarios were associated with a greater use of microbicides, and hence a greater proportion of costs for the product.

Table 3.3 shows the total and average distribution costs. For the FSW strategies, the total projected undiscounted costs over the 15 years range from $9.6 million to $10.2 million, averaging between $213 and $378 per woman reached per year. For the top population based strategies the total cost is far greater – approximately $48 million over the 15 years – averaging $42 per woman reached per year. Table 3.4 shows how the assessments of costs and cost-effectiveness of the top scenario vary if the price of the microbicide, or if the product can

Table 3.2: Top ten cost-effectiveness scenarios for microbicide distribution in Mysore District, India (US$ 2008)

		Discounted		Undiscounted	
Rank	**Distribution focus and attributes**	**HIV infections averted**	**C-E***	**HIV infections averted**	**C-E**
1	FSW, Non-facility, fast approval, high uptake, high efficacy, high consistency	10,696	788	17,.390	585
2	FSW, Facility, fast approval, high uptake, high efficacy, high consistency	7,879	1,048	12,560	790
3	FSW, Non-Facility, fast approval, high uptake, medium efficacy, high consistency	7,408	1,138	12,015	846
4	FSW, Non-Facility, slow approval, high uptake, high efficacy, high consistency	6,984	1,154	12,015	803
5	FSW, Non-Facility, fast approval, high uptake, high efficacy, low consistency	6,520	1,236	10,564	915
6	FSW, Facility, slow approval, high uptake, high efficacy, high consistency	5,313	1,499	8,965	1,067
7	FSW, Facility, fast approval, high uptake, high efficacy, high consistency	5,473	1,509	8,701	1,141
8	FSW, Facility, fast approval, high uptake, medium efficacy, high consistency	4,823	1,656	7,661	1,249
9	FSW, Non-facility, slow approval, high uptake, medium efficacy, high consistency	4,846	1,664	8,368	1,161
10	FSW, Non-Facility, fast approval, high uptake, medium efficacy, low consistency	4,534	1,777	7,327	1,320
Most Cost-effective General Population Strategy					
44	General, Non-facility, fast approval, high uptake, high efficacy, high consistency	4,584	7,959	7,415	6,470

* C-E = Cost-effectiveness (cost per HIV infection averted), FSW = female sex workers

be used monthly. As would be expected, a monthly product priced relatively inexpensively would be the most cost-effective, whilst a higher unit cost for a microbicide substantially reduces the cost-effectiveness of product delivery.

Cost-effectiveness results for South Africa

Of the 156 scenarios modelled, 37 were found to be cost effective using the World Bank cut off of $3005 per HIV infection averted. Of these cost-effective scenarios, 23 were combined population and FSW interventions, nine were general population only scenarios reached through non-health facility

Table 3.3: Average distribution costs per microbicide distributed and per woman year reached in Mysore District, Karnataka, India

Distribution focus: Target group deliver, divergence from all best	Total Costs undis-counted($)	Microbicides distributed	Women reached	Cost per microbicide distributed ($)	Cost per women reached ($)
FSW, Non-facility, fast approval, high uptake, high efficacy, high consistency	10,165,997	13,258,414	45,406	0.77	224
FSW, Facility, fast approval, high uptake, high efficacy, high consistency	9,926,236	9,586,198	32,829	1.04	302
FSW, Non-Facility, fast approval, high uptake, medium efficacy, high consistency	10,165,997	13,258,414	45,406	0.77	224
FSW, Non-Facility, slow approval, high uptake, high efficacy, high consistency	9,712,097	10,004,020	34,260	0.97	283
FSW, Non-Facility, fast approval, high uptake, high efficacy, low consistency	9,668,806	8,286,509	45,406	1.17	213
FSW, Facility, slow approval, high uptake, high efficacy, high consistency	9,562,562	7,379,759	25,273	1.30	378
FSW, Facility, fast approval, high uptake, high efficacy, high consistency	9,926,236	9,586,198	32,829	1.04	302
FSW, Facility, fast approval, high uptake, medium efficacy, high consistency	9,566,754	5,991,374	32,829	1.60	291
FSW, Non-facility, slow approval, high uptake, medium efficacy, high consistency	9,712,097	10,004,020	34,260	0.97	283
FSW, Non-Facility, fast approval, high uptake, medium efficacy, low consistency	9,668,806	8,286,509	45,406	1.17	213
General, Non-facility, fast approval, high uptake, high efficacy, high consistency	47,977,279	336,715,319	1,153,135	0.14	42

Table 3.4: Sensitivity analysis of the effect of microbicide price and use frequency for India findings

Distribution focus:		Cost per microbicide distributed ($)*	Cost per women reached ($)	Cost per HIV infect averted ($)	% Change in $ per infection averted relative to base case
Top CE scenario: **FSW, Facility, fast approval, high uptake, high efficacy, high consistency**	**Price ($)**				
Daily use (base case)	0.10	0.77	224	585	
Low	0.05	0.72	209	546	-7%
High	1.00	1.67	487	1,271	+217%
Monthly use					
Low	1.00	0.70	204	533	-9%
High	5.00	0.63	243	634	+108

* Undiscounted costs are presented

delivery, one was combined population and youth interventions, and four were facility-based general population scenarios (see Appendix 8).

Table 3.5 presents the discounted and undiscounted cost per HIV infections averted for the top four population scenario, as well as the top population only and youth distribution scenario. What is interesting to note is that the most cost effective scenario, with a discounted cost per HIV infection averted of $1,678, is not a scenario where everything is provided optimally, but is instead is a scenario where a highly efficacious microbicide is provided to the general population through health facility based provision, in combination with facility based FSW provision, and assuming a low product uptake. Further investigation of these unexpected results

Table 3.5: The cost-effectiveness of microbicide distribution scenarios in South Africa

			Discounted (3%)		Undiscounted	
Rank	**Scenario**	**Distribution scenario: divergence from all top**	**HIV infections averted**	**C-E**	**HIV infections averted**	**C-E**
1	124	Pop + FSW facility based, low uptake	13,977	1,678	19,262	1,570
2	148	Pop + FSW not facility based, low uptake	21,585	1,786	29,902	1,716
3	112	Pop + FSW facility based, slow reg app & low uptake	10,289	1,881	14,540	1,790
4	136	Pop + FSW not facility based, slow reg app & low uptake	15,694	1,930	22,306	1,870
9	70	Pop, not facility based, all best	94,574	2,182	130,444	2,150
27	34	Pop facility based, all best	51,559	2,738	70,142	2,695
35	106	Pop + Youth, all best	58,583	2,948	79,977	2,887

showed that this strategy had the highest ratio of infections averted per woman reached (0.05)[16]. However this has limited scale of impact – averting a total of 13,977 discounted HIV infections[17] – as the coverage of the strategy is constrained by the focus on facility-based provision. The much larger scale intervention which targets to FSWs through an outreach programme in addition to the general population intervention is still cost-effective, but ranks lower, as proportionally, the resources required to achieve the population level distribution are much larger. However, the ranking of the larger programmes would potentially improve if some economies of scale were achieved.

In this setting, when we compare what proportion of costs are used for different forms of project input, there is a lot of variation in the cost profiles between the scenarios (Appendix 8). The unit costs of the microbicides were again generally the largest cost driver, averaging 46% across all of the scenarios considered, but ranging from 19% to 74% across the scenarios considered. The proportion of total costs that were for mass media averaged 18%, but ranged from 3% to 53% across strategies. The relative costs of VCT and product delivery were relatively consistent (averaging 17% and 15% respectively), and the proportional costs of training and interpersonal communication were relatively small across scenarios. Table 3.6 shows the total and average distribution costs for the top strategies. For the four top FSW strategies, the total projected undiscounted costs over the 15 years range from $26 million to $51 million, averaging between $76 and $87 per woman reached per year.

The small strategies have relatively large unit costs per microbicide distributed and per women year reached, as the fixed programme costs are spread over relative small variable costs. However, from above we can also see that some of these small strategies are still highly cost-effective due to the high numbers of HIV infections averted per woman reached.

Table 3.6 Average distribution costs per microbicide distributed and per woman year reached in Gauteng, South Africa

Scenario	Distribution focus: Target group, divergence from all best	Total Costs undiscounted ($)	Micro-bicides distributed	Women years reached	Cost per micro-bicide distributed ($)	Cost per women year reached ($)
124	Pop + FSW facility based, low uptake	30,238,917	108,051,237	370,038	0.28	81.72
148	Pop + FSW not facility based, low uptake	51,302,590	195,677,600	670,129	0.26	76.56
112	Pop + FSW facility based, & low uptake slow reg app	26,025,145	86,896,902	297,592	0.30	87.45
136	Pop + FSW not facility based, slow reg app & low uptake	41,707,972	152,639,470	522,738	0.27	79.79
70	Gen pop, not facility based, all best	280,394,302	1,920,667,735	6,577,629	0.15	42.63
34	Gen pop facility based, all best	189,035,433	1,044,404,113	3,576,726	0.18	52.85
106	Youth, all best	230,877,744	1,166,325,060	3,994,264	0.20	57.80

16. Appendix 6 shows the number of infections averted per woman reached for all scenarios.

17. Women years refers to the fact that the annual number of women reached is modelled, then summed over 15 years. It could be the same women repeatedly or different women each year.

Table 3.7 Comparison of impact and cost-effectiveness rankings in Gauteng, South Africa

Scenario	Population and distribution, relative to all best	Impact Ranking (undiscounted)	CE rank (discounted)
124	FSW facility based, low uptake	79	1
148	FSW not facility based, low uptake	58	2
112	FSW facility based, slow reg app & low uptake	92	3
136	FSW not facility based, slow reg app & low uptake	71	4
154	FSW facility based, all best	1	5
130	FSW, restricted	6	6
142	FSW, unrestricted, slow reg app	3	7
118	FSW, restricted, slow reg app	13	8
70	Gen pop, all best	2	9
52	Gen bop, slow reg app	7	10

The comparison between impact rankings and cost-effectiveness rankings highlight the importance of women's risk profiles in the cost-effectiveness (Table 3.7). Although the top 3 scenarios for cost effectiveness are low in impact, they are the top three when ranked by infections averted per woman reached. However, the top 3 impact scenarios do still appear in the top 10 cost-effective scenarios.

In the analysis above, the microbicide was modelled as a daily use product priced at $0.10 per application. A halving of the price would lead to a 20% reduction in the cost per HIV infection averted, while an increase in the price to $1 would sincerely jeopardise microbicides cost-effectiveness, estimated here as $7,123 per HIV infection averted (Table 3.8).
A monthly use product would lead to a 38% reduction in the cost per HIV infection averted. Even at a price of $1, costs would still be lower, with a 26% improved cost per infection averted. A monthly microbicide with a price of $3.01 would have the same cost-effectiveness as a daily product with a price of $0.10.

Table 3.8 Sensitivity analysis of microbicide price and use frequency

Based on most cost effective scenario (Distribution focus: FSW facility based, low uptake (scenario 124)) and undiscounted cost-effectiveness.

Price	Cost per ($)	Divergence from central estimate	Cost per ($)	Divergence from central estimate
Cost per microbicide distributed ($)*				
Use frequency	**Daily**	**Monthly**		
$0.05	0.11	*-60%*	0.09	*-69%*
$0.1	0.28	*0%*	0.17	*-38%*
$1.00	12.70	*4438%*	2.06	*636%*
$5.00	283.49	*101199%*	17.53	*6165*
Cost per women reached ($)				
Use frequency	**Daily**	**Monthly**		
$0.05	65.66	*-20%*	50.13	*-39%*
$0.1	81.72	*0%*	50.65	*-38%*
$1.00	370.80	*354%*	60.16	*-26%*
$5.00	1,656	*1926%*	102.40	*25%*
Cost per HIV infect averted ($)				
Use frequency	**Daily**	**Monthly**		
$0.05	1,261	*-20%*	963	*-39%*
$0.1	1,570	*0%*	973	*-38%*
$1.00	7,123	*354%*	1156	*-26%*
$5.00	31,806	*1926%*	1967	*25%*

* Undiscounted costs are presented

"There has been a substantial investment to find an effective HIV prevention for women, including microbicides"

Section 4

Discussion

Following extensive consultation, we have simulated a range of potential introduction scenarios in urban Southern India, and urban South Africa, to try to identify optimal strategies for product introduction. What we find is that different approaches and speeds of delivery may lead to differing levels of impact - ranging from the disappointing to the impressive. In particular, our findings illustrate the extent to which a product's impact will be influenced not only by the characteristics of the product, but also the speed to which it can be introduced, and the extent to which it distribution remains restricted or not. In practise, the overall coverage of a product will fundamentally be determined by the extent to which the target populations targeted have access to the proposed distribution mechanisms. Whilst population-based strategies that extend beyond health service delivery may be most ideal, in practise these may not be able to be utilised for many years – with initial introduction being likely to be restricted to prescription only provision of products.

Considered alone, the modelling impact projections point to what may be the methods of distribution that may have greatest public health impact. In both settings, they illustrate the potential importance of a microbicide, and the urgency of distributing safe and effective products as rapidly and widely as possible. They also re-confirm the importance of ensuring that microbicides are used by those who are most vulnerable to HIV infection – and in both concentrated and generalised HIV epidemic settings, the importance of sex workers being able to access microbicides. The challenge associated with this, however, is ensuring that the product does not then become stigmatised, which may limit the potential for it to be used in non-commercial sexual relationships, including by sex workers with their non-commercial sexual partners.

The complementary cost-effectiveness analyses illustrate that, in both settings considered, there are a range of plausible scenarios where microbicide distribution is likely to be highly cost-effective. What also emerges is that bigger may not always be better. In India, only distribution strategies to sex workers are cost-effective. In South Africa, as well as some large scale distribution programmes being cost-effective, more focused strategies which may not result in a large absolute HIV impact may nevertheless also be highly cost-effective, and so merit investment.

Overall, our findings illustrate that microbicides are likely to be an important addition to the current portfolio of combination prevention, and in particular, help provide more comprehensive prevention options for women. There is an important role for microbicides in both established and generalised epidemic settings, and the rapid and informed distribution of an effective product will make an important difference. However, there is also the potential for bureaucratic delays, and inefficient and slow distribution. The coverage figures in contraceptive delivery should serve as minimum benchmarks for what is achievable. We must not lose site of the epidemic reality in different settings, and what this means for where introduction should be prioritised. Expectations need to be realistic enough to recognise these likely challenges and barriers, but also sufficiently visionary so as to not set the bar too low. For ultimately, success in the microbicide field will come not only by identifying an effective product, but also by ensuring that once a product is found, there are the systems, financing and political constituencies in place to promote its rapid approval and effective introduction.

Conclusion

From the epidemiological modelling we conclude that depending on the specific epidemiological setting, microbicides could lead to significant and cost-effective reductions of new HIV infections, and are likely to be an important addition to our current combination prevention portfolio. To fully utilize the protective potential of microbicides it will be important to ensure that microbicides are accessible and used by those who are most vulnerable to HIV infection, both in concentrated and generalised epidemics, including sex workers.

In all settings, the likely HIV efficacy of a microbicide was identified as a central issue affecting product acceptability and its potential market, although issues of cost (especially of whether a product would be free at the point of delivery or not), pleasure, accessibility, and contraceptive efficacy are also of importance.

Beyond the preventive efficacy of the microbicide and its ease of use by women, distribution strategies and the pace of product introduction and uptake will determine the impact of this potential new prevention technology on the HIV epidemic. This analysis helps understanding the interrelationship of the various parameters of product characteristics, access and use, and can inform optimisation of product introduction strategies by identifying scenarios where preventive impact and cost-effectiveness are achieved.

Microbicides potential preventive impact on the HIV-epidemic supports the investment in this new prevention approach and alerts to the future need for careful and forward-looking product implementation planning.

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