

Mobilization for Microbicides

The Decisive Decade



The Microbicide Initiative

funded by

The Rockefeller Foundation

Mobilization for

The Decisive Decade

Two decades after the start of the HIV/AIDS pandemic:

- AIDS kills more people worldwide than any other infectious disease
- Nearly 6 out of every 10 new infections in sub-Saharan Africa occur in women
- More than 4,932 women are infected with HIV every day, nearly 90% of them in developing countries
- Women make up 55% of people living with HIV in sub-Saharan Africa
- 2.5 million children were at risk of HIV infection in 2001 through mother-to-child transmission
- More than 10 million children under the age of 15 have lost one or both parents to AIDS
- In the United States, 23% of all new AIDS cases are women and 31% of new HIV infections among adolescents and adults occur in women
- In the United States, 59% of new HIV cases among 14- to 19-year-olds occur in girls

Millions of women around the world need help now to prevent HIV infection and death from AIDS. The current HIV prevention strategies—monogamy, condom use, reduction in number of partners, and treatment of sexually transmitted infections—often are not feasible for them. Even when women have only one partner, they can be at risk of infection through that partner's other sexual relationships. Many simply do not have the power to insist that their husbands or partners use condoms. For some, multiple sexual partnerships often serve as their only source of economic and social security. Finally, in many parts of the world, diagnosis and treatment for sexually transmitted infections (STIs) are not available or are stigmatized, a problem that is complicated by the fact that many of these infections are asymptomatic in women.

For women at risk for HIV infection, the answer is clear and supported by good science: Microbicides could save millions of lives.

- People infected with HIV/AIDS since pandemic began: 60 million
- People who have died of AIDS: 20 million
- People who died of AIDS in 2001: 3 million
- People newly infected with HIV in 2001: 5 million
- Infections that could be averted by microbicide use: an estimated 2.5 million over three years

Microbicides



The world urgently needs both an HIV vaccine and a microbicide. A topical microbicide would act as the first barrier to HIV infection. It might also be able to interrupt the spread of other sexually transmitted infections that an HIV vaccine would be unlikely to affect. It is cost-effective when compared with the expense of treating people who are already infected. It would help prevent mother-to-child transmission of HIV at birth. In addition, a safe and effective microbicide, used rectally, might offer men and couples another means to interrupt the spread of HIV via anal intercourse.

Despite this enormous scientific and public health potential, however, microbicide research has been severely underfunded and politically marginalized.

What is a Microbicide?

A woman-controlled method applied before sex that could kill, neutralize, or block HIV and other sexually transmitted infections. With funding and commitment, an effective topical microbicide could be on the market by 2007.

The goal of developing a safe, effective microbicide depends on more than just good science: It requires political will and a ready willingness on the part of the public and private sectors to invest the necessary resources, coordinate efforts, ensure access, and mobilize to meet this urgent public health challenge.

These key points and others emerge from expert Working Group reports prepared for the Microbicide Initiative. The initiative was established to prioritize the key elements needed to bring microbicides to market in a timely manner. Out of the initiative came five fact-driven documents of critical importance to the field:

1. A scientific road map for understanding microbicides and accelerating their development
2. A pharmaco-economics study of the potential market size and expected return-on-investment for microbicide products in the long run
3. An assessment of the potential public health impact of microbicides and the millions of infections they could help avert
4. A framework to ensure consumer access to the products
5. An action plan for advocacy for microbicide research, development, and access

This publication synthesizes key points from these Working Group documents and makes the case for mobilization for microbicides now.

Accelerating the Development Pipeline



After more than a decade of research and development, the microbicides field looks increasingly bright: Almost sixty products or compounds are poised for further testing. Of these, one is slated for phase 3 clinical trials in 2002, four are in phase 2 clinical trials, and another six are in phase 1 trials.

An explosion of basic research and scientific understanding has created new insights into ways to interrupt the transmission of HIV and other sexually transmitted infections, and as the biology of the field has become better understood, new and interesting strategies have

emerged for microbicides that will be both safe and effective. However, despite dramatic progress in overall product development, the concept of a topical microbicide for preventing HIV has yet to be clinically proved. No major pharmaceutical firm has made a significant investment in developing a microbicide product, and public-sector support has fallen well short of providing the funding that is now required for optimal progress.

The time is ripe for acceleration of microbicide development. The first generation of microbicide products, now undergoing clinical testing, could

be on the market by 2007, given appropriate and sufficient attention and investment. Subsequent product generations will be more effective, and could be developed with a range of properties to provide additional appeal to consumers. A full-scale effort involving increased public and private investment, top-notch scientific inquiry, and international coordination for regulatory approval and manufacturing could make this “The Microbicide Decade.”

Stopping the HIV virus

Microbicide research involves understanding how the HIV virus crosses the mucous membranes of the female genital tract and how it can be stopped. Investigators are looking for ways to:

- kill or inactivate the HIV virus or pathogens;
- fortify normal vaginal defenses;
- prevent viral access, attachment, fusion, or entry to mucosal tissue; and
- prevent viral replication.

The precise sequence of events between exposure to HIV and the establishment of infection in the host has yet to be completely described. Even so, it is clear that the virus routinely comes into contact with a wide variety of tissues, each with

differing characteristics that are important to the eventual establishment of a host infection.

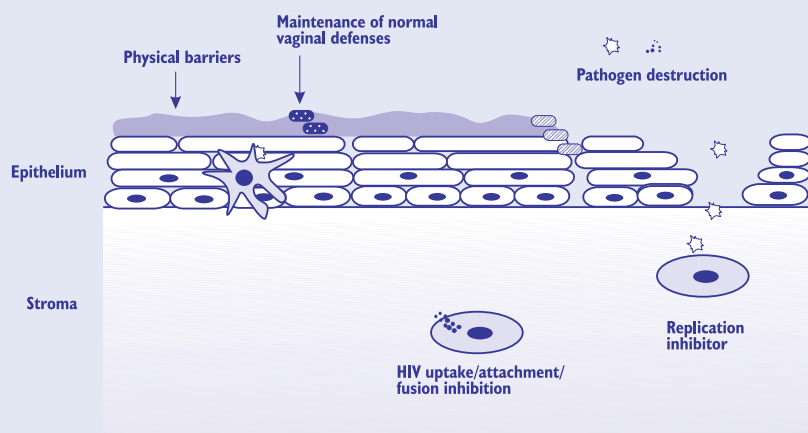
Figure 1 illustrates some of the points at which a microbicide product might effectively and specifically interrupt HIV and STI transmission or replication, and some of the mechanisms of action of products under consideration. The field is now well on its way to understanding the relative *in vitro* safety and efficacy profiles for products in each of these categories.

The roles of other sexually transmitted infections

The risk of HIV infection is greater when vaginal mucous membranes are inflamed or ulcerated by STIs, a critical public health problem by themselves. Many of the product leads under investigation could provide additional benefit since they are active against HIV and a range of other STI pathogens, both viral and bacterial.

Full protection against all potential STIs is likely to be achieved only by the combination of several microbicidal agents. Indeed, full protection against HIV alone may also require a combination microbicide.

Figure 1. Potential mechanisms of action for microbicides



1. Physical barriers — by using devices, gels or creams to keep HIV and other genital disease-causing pathogens from getting close to target cells

2. Maintenance or mobilization of normal vaginal defenses — by enhancing the vagina’s natural acidity, even in the presence of sperm, and by providing lactobacilli, the vagina’s natural protectors

3. Pathogen destruction — by detergent-like chemicals that strip infectious organisms of their outer surface shields

4. HIV uptake/attachment/fusion inhibition — by blocking HIV and several other pathogens from uptake or attachment to target cells, and preventing fusion between the outer envelope of HIV and its target cell

5. Replication inhibition — by preventing replication of the virus after its genetic material has entered the target cell

Viral pathogens:

- Herpes simplex virus (HSV): enters the body through a break or tear in a mucous membrane or area of skin, and is highly prevalent in sub-Saharan Africa
- Human papillomavirus (HPV): infects mucous membranes and has been associated with cervical cancer

Non-viral infections:

- Gonorrhea and chlamydia: can lead to pelvic inflammatory disease and infertility
- Syphilis: can cause cardiovascular and neurological damage
- Trichomonas: the single most common sexually transmitted infection

340 million new cases of STI infections each year worldwide:

- 170 million cases of trichomoniasis
- 89 million cases of chlamydia
- 62 million cases of gonorrhea
- 12 million cases of syphilis

Will a microbicide work? Proving the concept

For microbicides to be approved by regulators and accepted by consumers, they will have to be proved effective. “Proving the concept” for any prevention technology, including both vaccines and microbicides, is more complex than for a treatment technology—and thus more expensive. A treatment is administered to an ill patient, and the patient’s response can then be directly monitored; a preventative is given to a healthy person, who may then stay healthier—either because of the preventative or with no relationship to it whatsoever. As a result, microbicide trials (like those for vaccines) will require very large numbers of participants, who are followed for many months to years, to ensure that the results seen in the study will be likely to occur when women use the product outside of the trial.

Steps in this microbicide development path include:

- **Selection of the most promising compounds or leads for further investigation.** Lead selection is increasingly driven both by rapid testing and an improved understanding of the characteristics that would make a microbicide product successful. Such characteristics include an acceptable formulation (such as gel, cream, foam, film, impregnated sponge, or suppository); stability in warm climates; compatibility with physical barriers, such as condoms; and the potential to work against many different STIs.
- **Pre-clinical testing for safety and potential efficacy against a wide variety of in vitro and animal models.** These tests, which measure toxicity and carcinogenicity as well as absorption, metabolism, and irritation, are expensive: toxicology alone costs between US\$2.5 million and US\$5 million per product. In recent years, scientists have refined pre-clinical pathways for safety testing and developed criteria to assess optimal product characteristics. Product development is likely to proceed through a series of generations, as lead compounds are optimized for effectiveness and acceptability, and as combination products and formulations are advanced.
- **Clinical testing for safety and acceptability.** Phase 1 tests involve vaginal, penile, and rectal safety in small numbers of healthy, uninfected, and HIV-infected individuals. Phase 2 studies involve testing the product with larger numbers of participants, many of whom are representative of the population that will be studied in the large effectiveness trials.

Proof of concept for a microbicide requires:

- use of the microbicide by women not infected with HIV, to prevent infection; or by HIV-infected women to prevent transmission to an uninfected sexual partner; or both;

- large-scale phase 3 randomized, controlled, clinical trials to measure safety and effectiveness;
- demonstration of a statistically significant reduction in the number of new HIV infections. While prevention of HIV transmission is the primary objective, non-HIV pathogens should be included wherever possible;
- participation by many thousands of women, and thousands of woman-years of observation, often in areas of the world that currently lack the infrastructure to conduct large clinical trials; and
- identification/establishment/support of clinical trial sites in countries with sizable populations of women at substantial risk for

HIV infection; willing and able local scientific collaborators; and laboratory capacity to perform tens of thousands of HIV and STI tests. The trials must have national and local political support for microbicides research.

While microbicide testing has many issues in common with the development of new drugs for therapy or prevention, a number of features are unique to the prevention of HIV and complicate the design and conduct of such a trial.

The women who are potential study volunteers are likely to be already marginalized by the very characteristics that put them at risk for HIV infection. Such women may not have had access to education and health care, and may have

Figure 2. Products in clinical trials, as of February 2002

Product	Phase I	Phase 2	Phase 2/3	Contraceptive Efficacy	Phase 3
Acid buffers / enhancers of vaginal defenses					
Acidform™	GMP				
BufferGel™			HPTN ReProtect	NICHD ReProtect	
Invisible Condom™	Laval				
Lactin Vaginal Capsule		NIAID			
Surfactants					
Savvy (C31G)	GMP Biosyn			NICHD Biosyn	
Entry inhibitors					
Carraguard™ (PC 515)					Pop Council CDC
Cellulose Sulfate (CS)	GMP				
Emmelle™ Dextrin-2 Sulfate		MRC ITM			
Polystyrene Sulfonate	GMP				
PRO-2000			HPTN Interneuron		
Replication inhibitors					
Topical PMPA	HPTN Gilead				

GLOSSARY: Biosyn, Inc., CDC (Centers for Disease Control and Prevention), Gilead Sciences, Inc., GMP (Global Microbicide Project), HPTN (HIV Prevention Trials Network), ITM (Institute of Tropical Medicine), Interneuron Pharmaceutical, Inc., Laval (Laval University), MRC (Medical Research Council), NIAID (National Institute of Allergies and Infectious Diseases), NICHD (National Institute of Child Health and Human Development), Pop Council (Population Council), ReProtect LLC

Source: Alliance for Microbicide Development, Family Health International, and Global Microbicide Project

substantial language and cultural differences between them and the scientific investigators. Special attention must be given to ensuring protection for the thousands of women who will be enrolled in microbicide trials in the near future.

In addition, because the disease being prevented is both lethal and incurable, the ethical conduct of these clinical trials requires that condoms be provided, along with safer-sex counseling, as well as interventions to treat curable sexually-transmitted infections.

Figure 2 details the current status of the most advanced products and the companies or organizations conducting the studies. A pipeline database (accessible at www.microbicide.org) provides potential donors and investors with an up-to-date overview of the field.

The three products that are closest to phase 3 clinical trials in 2002 demonstrate the mechanisms of action of the “first generation” of microbicides.

- Carraguard™ a gel derived from seaweed, blocks attachment of pathogens to target cells; is effective against HIV, HSV-2, and gonorrhea *in vitro*; phase 3 trial in South Africa and Botswana. Developer: Population Council.
- PRO-2000, a naphthalene sulfonate polymer, blocks attachment of pathogens to target cells; is active against HIV-1 *in vitro* and against HIV-1 and HSV-2 *in vivo*. Developer: Interneuron Pharmaceutical, Inc.
- BufferGel™ an aqueous gel, employs an agent widely used in pharmaceuticals; helps maintain the vagina’s natural acidity in the presence of sperm. Developer: ReProtect LLC.

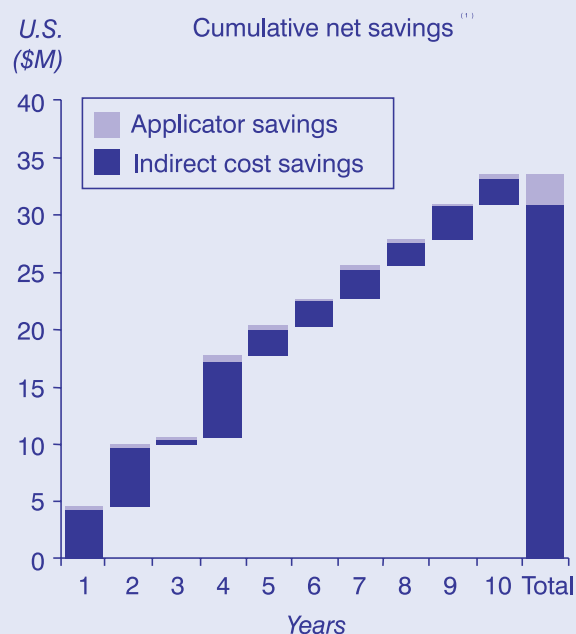
The BufferGel and PRO-2000 products are in a head-to-head phase 2/3 clinical trial. Several hundred women have been recruited in India, Malawi, Tanzania, South Africa, Zambia, and Zimbabwe. If the trial goes well from a safety standpoint, the trial design will proceed with a full-fledged recruitment of 8,000 women at a phase 3 level.

Saving costs through cooperation

In addition to the pre-clinical and clinical development challenges outlined above, microbicides face a number of parallel challenges in manufacturing, formulation, acceptability, and end use. The small companies and academic research organizations that are doing almost all of the work on microbicides lack capacity for testing, formulation, manufacturing, and packaging. Thus, they must rely on numerous contractors and subcontractors, which is particularly inefficient and risky for inexperienced and under-resourced developers undertaking these processes alone.

Opportunities exist, both in manufacturing and formulation, to coordinate investment in the field as a whole and ensure that an eventual product is as widely used as possible. Coordination could save considerable time and money. For example, bulk applicator purchasing, and agreement on a standard applicator design, could save

Figure 3. Net potential savings via coordination of direct and indirect costs





hundreds of thousands of dollars per developer, and indirect cost-sharing through a coordinated manufacturing approach offers potential savings of up to US\$30 million net over the next ten years.

Figure 3, left, shows potential cumulative net savings through collaboration over a ten-year period.

Coordination is not the only critical element for the microbicide field. The key to developing safe, effective, and accessible microbicides is sufficient investment. Increased funding will facilitate large-scale clinical effectiveness trials; provide greater support and coordination of formulation, manufacturing, and delivery of products; and sustain the development of microbicides through several product generations to allow the field eventually to become commercially self-sustaining.

The Case for Investment

Public and philanthropic funding have been critical to microbicide development thus far, but the field has reached the point where expanded investment will be vital for the rest of the decade in order to achieve proof of concept and bring the first generation of products to market. The data provided in the innovative modeling exercises suggest, however, that—in the long run—

microbicides will eventually attract enough of the market to be highly profitable to private investors.

To evaluate the market and profit potential of a microbicide, the Pharmaco-Economics Working Group estimated the likely evolution of the microbicides field over the next fifteen years.

Table 1 below illustrates the results of those efforts—three market scenarios, covering first-, second-, and third-generation microbicides, with varying formulations, indications for use, and effectiveness over time.

The modeling exercise assumes that in industrialized countries, a first-generation microbicide will be available only by prescription, but could be purchased over the counter (OTC) in its second and third generations. In developing countries, first-generation availability by prescription only could dramatically restrict access to the product. In the developing world, it will be imperative that microbicides be available over-the-counter from the outset.

While costs of a first-generation microbicide would have to be borne by public-sector funding, the economic analysis suggests that a second-generation product could get to market without a public-sector subsidy. Because of increased market size and decreased development costs,

a third generation of products offers the first potential for significant returns—estimated at up to US\$428 million.

Estimating the market potential

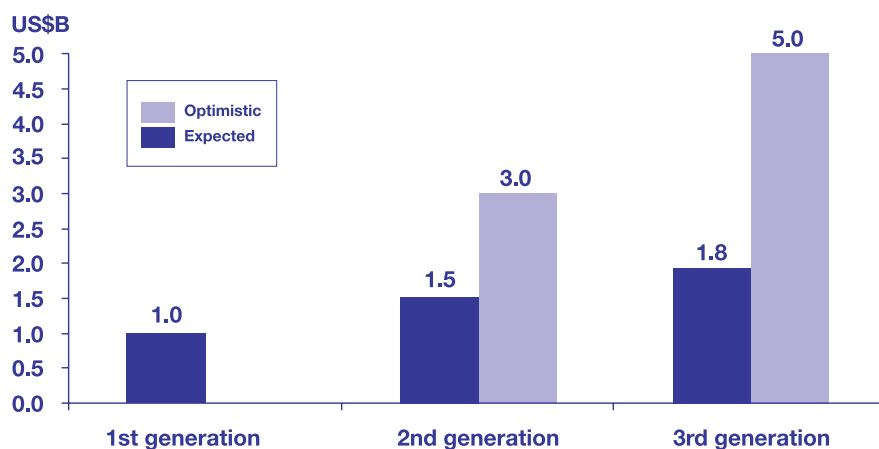
The most likely scenario suggests that a first-generation microbicide that meets the basic needs of women in both the industrialized and the developing world could have a global market size of US\$900 million by 2011, and a third-generation microbicide might have sales in excess of US\$1.8 billion by 2020.

This is a conservative estimate. The peak-market-size estimates assume that less than 10 percent of sexually active women everywhere will use the product. If, however, the products are able to meet a broader set of needs—including those for daily hygiene, vaginal health, and general protection against infection—there is potential to far exceed these forecasts, with an optimistic peak-market size as large as US\$5 billion.

Table 1. Summary of microbicide market evolution scenarios

	1 st generation	2 nd generation	3 rd generation
Expected launch	2007	2012	2017
Formulation	Vaginal only	Vaginal & rectal	Vaginal & rectal
Indications	HIV, possibly other STIs, possibly contraceptive	HIV, herpes, gonorrhea, HPV, chlamydia; choice of contraceptive or non-contraceptive	HIV, herpes, gonorrhea, HPV, chlamydia; choice of contraceptive or non-contraceptive
HIV effectiveness	50% to 60%	70% to 90%	85% to 97%
Contraceptive effectiveness	75% to 85%	80% to 90%	90% to 97%
Use instructions	W/condom or device	Stand alone	Stand alone
Sales channel:			
Industrialized countries	Prescription only	Over the counter	Over the counter
Developing countries	Over the counter	Over the counter	Over the counter

Figure 4. Expected and optimistic case scenarios of microbicide market potential



The exercise estimated that only 3% of women in developing countries and 7% of women in industrialized countries would be using the product at the outset, leaving plenty of room for greater market penetration. For example, the potential market in the United States could be 11.7 million women, or about 17% of those women 15 to 49 years old.

Closing the funding gap

There is still a large gap between required and available funding. It would take an estimated US\$775 million in direct product development expenses over the next five years to develop the existing portfolio of microbicide leads. This amount does not include the costs of basic research, discovery of additional leads, work on access and product introduction, organizational overhead, or advocacy efforts. With this investment there is a high likelihood of having several safe, effective microbicides by 2010. However, current estimates of public support for microbicide development are approximately only US\$230 million. The academics, small companies, and nonprofit organizations that are currently developing products are doing so with support from donors. Such support will continue to be critical through phase 3 trials and registration of the first generation of products.

While most of the current product leads exist because of prior investment by the National Institutes of Health (NIH) and the U.S. Agency for International Development (USAID), the current U.S. government budget for microbicide research is no longer sufficient for the expanding needs of the field. At present, the NIH invests less than 2 percent of its AIDS-

related research budget in microbicide research and development (US\$34.6 million in FY 2001); an additional US\$12 million for microbicide development was allocated by USAID, and \$2.6 million by the Centers for Disease Control and Prevention (CDC).

Increasingly, European governments, multilateral agencies, and foundations have shown great interest in the potential of microbicides, and are playing a more important role in funding product development. Academic researchers and small companies are pursuing microbicide development in a growing number of countries, including Australia, Belgium, Brazil, Canada, France, India, Italy, the United Kingdom, and the United States.

Nonetheless, public and private monies for microbicide research and development must expand dramatically—and quickly—if the promise of microbicides is to be realized. Such investment offers a realistic, manageable, and near-term chance to seize a powerful opportunity to promote the public good.

Averting Millions of Infections

The campaign to develop microbicides is all about saving lives around the world, but particularly in developing countries. In regions where the epidemic is still nascent or concentrated, there is substantial potential to avert infection. Just how many lives could be saved by microbicide use has always been an educated guess—until now. Researchers at the London School of Hygiene and Tropical Medicine have used epidemiological models to estimate the number of HIV infections that could be averted as a result of microbicide use—and the numbers are impressive.

Using conservative assumptions, the model examined the impact of introducing a microbicide in seventy-three lower-income countries. The model assumes that the product is used by 20% of individuals who can be reached through existing services, and that it is used in 50% of sex acts where condoms are not.

- A microbicide that is 60% efficacious against HIV and STIs could avert 2.5 million HIV infections in women, men, and children over three years
- At 30% coverage of those easily reached through existing services, 3.7 million infections could be averted

At 20% coverage, the model estimates that 31% of HIV infections averted would be in East Asia and the Pacific; 35% in South Asia; and 27% in sub-Saharan Africa. This distribution reflects

both the large differences in population sizes between regions and the relative stages of the HIV epidemic in each country. As the epidemic is emerging in many Asian countries, there is a large potential to avert substantial numbers of HIV infections.

Saving on health system costs and productivity

Averting HIV infection results in fewer people requiring HIV/AIDS-related hospitalization, home care and treatment for opportunistic infections. This is an added benefit of particular consequence to health care systems in resource-poor countries, where an estimated US\$2.7 billion would be saved by averting 2.5 million HIV infections through microbicide use between 2002 and 2005. These estimates do not include the costs of providing anti-retroviral drugs to HIV-infected individuals. Once anti-retrovirals become more widely available in developing countries, healthcare costs will increase—and so will the savings that could accrue from avoiding each infection.

Savings will also be gained by avoiding productivity losses, such as absences from the workplace due to illness, and the training of replacement workers. A conservative estimate of the productivity benefit associated with averting 2.5 million HIV infections between 2002 and 2005 is US\$1 billion (in 2002 dollars).

Microbicides make both public health and economic good sense.

The impact could be substantial:

- **Asia:** more than one million newly-infected people this year for the first time
- **India:** soon may have the largest number of people in a country living with HIV/AIDS
- **China:** by 2010 may have 20 million HIV-infected people
- **Eastern Europe:** infection rates rising faster than anywhere else in the world





Preparing for Microbicide Access and Use

If microbicides are to have an impact on the HIV/AIDS epidemic, they must be made accessible to women at highest risk—especially in the poorest regions of the world—as quickly as possible.

To date, the financial and intellectual investment in microbicides has appropriately focused on developing products to the point where they can be tested to find out if a microbicide can indeed block HIV and other STI pathogens in people. However, in addition to scientific research, it is essential to invest in efforts to accelerate access and use. These efforts are parallel and complementary; they must inform each other and move forward together.

While there has been widespread recognition and articulated commitment to the importance of ensuring access to microbicides, little attention has been given to identifying the special initiatives that will be needed to bring this about.

Experience demonstrates that new health technologies rarely become widely available in developing countries until more than a decade after their approval in the United States or Europe. Given that the need is greatest in developing countries, and that most large-scale clinical effectiveness testing will take place in developing-country sites, waiting for microbicide technology to “trickle down” is unacceptable.

Acceptability of microbicides to users

Microbicides will be user-controlled products that women and couples will have to use consistently and correctly over a long period of time. Therefore, a product’s appeal and ease of application will be critical factors in determining the effectiveness of microbicide use in everyday life. For a product to be employed consistently, the user must understand its benefits, the elements of correct use, and potential side effects.

It is clear from research that users desire both contraceptive and non-contraceptive forms of

An acceptable microbicide should:

- be safe, especially for long-term use
- be available over the counter
- be affordable
- allow application from several hours to immediately before intercourse, and last for up to eight hours
- be easy to apply
- have no odor
- not be messy
- not interfere with sexual pleasure

microbicides. Some women—especially in developing countries—have a need for products that will protect them from infection but still allow conception. Other women prefer a dual-acting product that can protect against unwanted pregnancy and infection at the same time.

Formulation preference studies also suggest that no one formulation or delivery device will meet the needs and preferences of all women. Some prefer gel applied with an applicator; others may opt for film, suppository, or sponge. Research suggests that perceived safety and effectiveness are more important than most product attributes in defining a woman’s willingness to use a microbicide. Ultimately, a constellation of products with a range of qualities, formulation, packaging, and indications will be able to meet the needs of a wide range of users.

The largest potential market segment for microbicides is married women at risk because they or their partners have other partners. Other potential user groups should be specifically considered because of the impact of their special needs and preferences on product development: minorities, adolescents, men and women engaging in anal sex, sex workers, menopausal women, and women who live in regions where “dry sex” is preferred by men and excess lubrication might be problematic.

Social science research conducted during the development process can shed light on the characteristics most likely to support or undermine women’s willingness and ability to use a microbicide, as well as the cultural and individual preferences that influence them. Research also can determine men’s attitudes toward the concept of a microbicide, and whether it is important for a woman to be able to use the product with or without her partner’s knowledge.

Product positioning

Microbicides could potentially be introduced as an HIV preventive, a contraceptive, a means of promoting reproductive or vaginal health, or a product to enhance sexual pleasure. The product’s introduction and marketing strategy set a social norm for acceptance and use. If initial promotion efforts are aimed at “high-risk” individuals, such as commercial sex workers, microbicides could be stigmatized and rejected by other groups. One challenge will be to determine whether to explicitly market the product to women, men, or both—and how openly and publicly to promote a product that some women may want to use without a partner’s knowledge.

Careful marketing of microbicides must make it clear that these products may be only partially effective. Realistic expectations should counteract the tendency to “oversell” the product or to mislead women or policymakers into thinking it will provide more protection than it does. At the same time, even a partially effective product could have a major impact on HIV transmission for individuals and communities, especially where condom use is low.

Like condoms, and in contrast to vaccines, microbicides will need to be produced, distributed, and used over a long period of time, so continuous supply must be efficient and guaranteed. Finally, in challenging traditions of power, autonomy, and sexuality, microbicides encompass complex social and political issues related to the unequal balance of power between men and women that limit women’s access to a range of products and services.

These gender-related constraints make it critical to address access to microbicides from a user perspective. For a woman or girl to use a microbicide, it must be acceptable to her; she must know how to use it properly and where to obtain it. Microbicides should be introduced into a political and social environment that actively promotes and incorporates these products into policies and programs.

Making microbicides accessible

Ensuring that microbicides, once approved, are widely available throughout the world is an enormous and complex undertaking. A microbicide must be readily and reliably available at convenient and easily accessible locations, in good condition, and priced so that consumers can afford it.

Distribution of microbicides should be through as many traditional channels as possible, offering great potential for making microbicides widely accessible:

- Government health and family-planning clinics
- Nongovernmental (NGO), religious, private, and workplace health and family-planning clinics
- Pharmacies
- Community-based distributors and village health workers
- Local shops, beauty parlors, taxi stands, markets, convenience stores, cinemas, etc.
- Organizations targeting particular populations: youth and women’s groups and sex workers

Reducing product and distribution costs

Cost should not be a barrier to microbicide use. Products should be provided free to people who cannot afford to purchase them. Affordability must be considered and addressed at every step of the process—pre-clinical development, clinical testing, licensing, management of intellectual property rights, production, introduction, delivery, and use.

Microbicide production costs can be reduced through a variety of mechanisms, including low-interest loans for building manufacturing plants, providing tax credits and incentives, and reducing royalty payments. Procurement and distribution costs can be lowered through international tendering or bulk procurement and elimination of tariffs or duties on microbicides.

The cost of purchasing microbicides can also be lowered by negotiating price guarantees in exchange for public investment in product development or for access to publicly financed clinical trial sites.

Donors, international agencies, the new Global Fund to Fight AIDS, Tuberculosis and Malaria, and national governments will have to work together to devise funding mechanisms and purchase agreements to ensure that microbicides are both accessible and affordable in the areas where they are most needed.

Regulatory approval and licensing

Before a microbicide can be used in a country, it has to be approved by the appropriate regulatory authority. This long and complex process can vary considerably among different countries in terms of approach, criteria, standards, and requirements.

While some developing countries have approval processes for new health-care products, many have only limited regulatory infrastructure or scientific expertise. It is important, therefore, to:

- clarify the regulatory processes and requirements for marketing-approval of microbicides with different characteristics and sponsor claims;

- collaborate to help speed up the drug testing and approval process, including the shared design and conduct of clinical trials and the formats for submitting data; and
- strengthen the national regulatory infrastructure in key countries like India, South Africa, and Thailand that can potentially provide regulatory guidance and regional leadership.

In many countries, approval can be heavily influenced by the decisions of the United States Food and Drug Administration (FDA) and the European Medicines Evaluation Agency (EMA). However, given the differences in the epidemic profile between industrialized and developing countries, regulatory agencies in developed countries may take a conservative approach to microbicides. A partially effective microbicide or HIV vaccine that might not be approved in the United States or Europe could make a major difference in curbing the spread of HIV in a setting where prevalence and incidence are much higher. This may have implications for donor purchase, since regulatory approval may also be required in the donor country.

It is critically important, however, that efforts at collaboration and streamlining do not result in requirements that conform to those of the jurisdiction with the most exacting review process. The purpose of harmonization should be to accelerate product availability where it is needed most, not to hinder it.

A wide range of actors, nationally and internationally, ultimately bear responsibility for following through on these recommendations. International agencies, governments, donors and investors, politicians, policymakers, health providers, and activists all have crucial roles in ensuring access to microbicides for those who need them most. This ambitious agenda cannot be ignored or postponed if the promise of microbicides—for women's empowerment in the fight against AIDS—is to be realized.

A Call to Action for Global Advocacy for Microbicides

Why do microbicides need global advocacy? Unlike other areas of science, where profit motives are sufficient to propel innovation, microbicides will only become a reality if sufficient political will is garnered for substantial investment on the part of governments and private foundations. Advocacy creates the political will and momentum necessary to propel the scientific enterprise forward.

Advocacy plays a role in all phases of microbicide technology development and introduction—from helping to structure the research agenda to ensuring that community views and perspectives are included in the design of clinical trials. Because microbicides are a user-controlled technology, advocacy must go beyond product development to address issues of pricing, accessibility, stigma, gender bias, and women's empowerment.

The microbicide field has the advantage of operating at the crossroads of three relatively mature and vibrant movements: women's health, family planning, and HIV/AIDS. All bring to the issue a network of sophisticated NGOs, passionate constituencies, experience with policy advocacy, and media sophistication.

A global advocacy plan to accelerate microbicide development should set these priorities over the next two years:

- Strengthening existing advocacy initiatives
- Expanding advocacy, outreach, and resource mobilization in Europe
- Elevating the profile of microbicides on the global stage, among government officials and other political leaders
- Building the capacity of civil-society actors to undertake microbicide-related activities, especially in the countries where clinical trials will be taking place

- Recruiting new scientists to the field and elevating the issue's stature within the scientific community
- Using the media to raise awareness, manage scientific failure, and mobilize political will

During the next five years a portion of the monies raised for microbicide development should go toward strengthening the capacity of civil-society actors—such as women's health groups, HIV organizations, and community representatives—to participate in decision making related to the field's research agenda and clinical trial implementation.

The ultimate goal of an advocacy strategy for microbicides is to reduce the spread of HIV and other STIs by accelerating the widespread access to, and use of, a topical microbicide. For every task identified by the other Working Groups in the Microbicide Initiative, there is an advocacy component that must be recognized and adequately resourced.

Organizing globally for microbicides

To date, the greatest progress in translating growing awareness of microbicides into concrete political action has been made in North America through advocacy groups such as the Alliance for Microbicide Development and the Global Campaign for Microbicides. They have sponsored briefings at key government agencies and have ensured that microbicides have had a presence at all major conferences and venues touching on public health, HIV/AIDS, and reproductive health in the United States. With some exceptions, the issue of microbicides has penetrated the policy mainstream in the United States, but maintaining its place “front and center” on the agenda requires constant vigilance and effort.

Organizing in Europe is poised for growth through recent support from the European

Commission to International Family Health, a U.K.-based non-governmental organization that expands advocacy efforts throughout the continent and in Africa and Asia. This alliance greatly increases the opportunity for organizing among European NGOs and policymakers.

There is ample evidence in developing countries of widespread interest in microbicides among many groups and networks with substantial constituencies. These include the Society for Women and AIDS in Africa, the Latin American and Caribbean Women's Health Network, and the International Community of Women Living with HIV/AIDS (ICW), among others. While their efforts have begun to penetrate the activist and NGO discourse on AIDS, many key policymakers and scientists in developing countries are still unfamiliar with microbicides.

Internationally, a number of groups have made efforts to bring the message of microbicides and woman-controlled prevention to major international forums. Advocates have ensured a central presence for microbicides and female condoms at the global and regional HIV/AIDS conferences, as well as a number of other important venues. A high-level briefing on microbicides was held in June 2001 at the Special UN Assembly on AIDS, and UN Secretary General Kofi Annan now includes mention of microbicides in his speeches on HIV/AIDS.

Facing challenges unique to microbicides

Like vaccine advocates, microbicide proponents face the challenge of having to mobilize interest around something that does not yet exist. This is

far more complicated than the task of treatment activists, who can argue persuasively that existing life-extending HIV drugs should be made available to everyone who needs them. Treatment activists can also capitalize on the indignation aroused by the common perception that the pharmaceutical industry seeks excessive profits on these lifesaving drugs.

Moreover, vaccines and drug treatments share the advantage of being concepts readily recognized by the public and policymakers. By contrast, the notion of a vaginal microbicide is an entirely new conceptual category: in fact, the very word "microbicide" needs prior definition.

By selecting accessibility to the end user as the key criterion for claiming success, the field of microbicide development could serve as an example to be emulated by future technology development efforts. The objective, after all, is not just to develop new technologies and effective products, but also to ensure that their use contains the spread of the HIV/AIDS epidemic and saves lives.

Constructing a savvy and effective global strategy around any issue requires careful attention to specific political realities and historical antecedents. By virtue of its history, the microbicide movement inherits both the strengths and weaknesses of its affiliation with the women's health movement and the field of contraceptive research and development. It is this reality—perhaps more than any other—that distinguishes the landscape of microbicide advocacy from that of other HIV-related issues.

Mobilizing for Microbicides: Success in this Decade?

The ambitious contributions of the various expert groups of the Microbicide Initiative demonstrate how far the microbicides field has progressed. The first generation of microbicides could be available and on the market by 2007, with successive and better products to follow in subsequent years. Microbicides that meet women's needs in both developed and developing countries can garner a global market size of US\$900 million by 2011, and double that by 2020. Epidemiologists conservatively estimate that a product with 60% efficacy in preventing HIV could avert 2.5 million infections over a three-year period.

The recent US\$20 million grant to the Population Council that will launch the microbicide candidate Carraguard into large-scale, phase 3 clinical trials, is a sure sign that momentum for microbicides is building. But it will take widespread, sustained funding and political support for the hope that is microbicides to be fully realized.

Here are the ingredients that ensure timely development of, and access to, these essential products:

- **Sufficient funding**—to guarantee that money is not an obstacle to critical research, development, and related access and advocacy activities. It would increase the probability that a first-generation microbicide effective against HIV will be approved for use in at least one country by 2007, and that the remaining pipeline is well funded and product leads are moving forward in parallel.

- **A robust microbicide field**—to attract research and development efforts by one or more large pharmaceutical companies. Small biopharmaceutical companies would have access to sufficient resources and technical assistance to move their product leads forward. High-quality scientists from all relevant fields of science would become actively involved in microbicide research; prestigious scientific spokespeople would advocate on behalf of the field.
- **Collaboration among international and national agencies**—to produce a clear, expedient, and responsible pathway for approving and registering microbicides. All unnecessary delays would be eliminated. Microbicides would be widely available and affordable for those who need them. People would have the knowledge, skills, power, and social support necessary to use them.

The global community can reach these goals by seizing the moment and mobilizing for accelerated microbicides research, development, approval, and distribution—**now**.

This can be The Microbicides Decade. Millions of lives are at stake.



The Microbicide Initiative

In 2000 the Rockefeller Foundation invited key players—international scientists, research organizations, pharmaceutical industry representatives, United Nations organizations, advocacy groups, and donors—to come together to find ways to accelerate the development of safe, effective, and accessible microbicides. These experts established Working groups to examine the key elements needed to bring microbicides to market in a timely manner. Readers seeking greater detail on aspects of microbicide development and introduction should consult the individual publications of the five Microbicide Initiative Working Groups, listed below.

George Brown, MD, MPH, Associate Director–Health Equity, The Rockefeller Foundation, provided liaison with the foundation on Working Group activities and publications. Working Group chairs and others who contributed significantly to the development of this document are:

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Paula Cobb, The Boston Consulting Group: Pharmaco-Economics Working Group;

Charlotte Watts, The London School of Hygiene and Tropical Medicine: Public Health Benefits Working Group;

Elizabeth McGrory, Population Council, and Geeta Rao Gupta, International Center for Research on Women: Access Working Group;

Lori Heise, Global Campaign for Microbicides and PATH, and Susan Crane, International Family Health: Advocacy Working Group; and

Florence Camus-Bablon, PATH; Polly Harrison, Alliance for Microbicide Development; Susan Perl, Consultant; Thomas Robinson, The Boston Consulting Group; and Zeda Rosenberg, Family Health International.

Names of all the experts who participated in discussions and preparation of the documents summarized in this publication are listed in each Working Group paper. The Microbicide Initiative works closely with many organizations active in the microbicides field, including: Alliance for Microbicide Development; Biosyn, Inc.; British Medical Research Council; CONRAD/CICCR; Epicyte Pharmaceutical, Inc.; Family Health International; Global Campaign for Microbicides; International Center for Research on Women; International Family Health; National Institutes of Health; PATH; Population Council; and the World Bank.

Copies of the complete Working Group papers used as source material for this report are available at www.rockfound.org

Additional sources: UNAIDS/WHO. *AIDS Epidemic Update*, December 2001; Centers for Disease Control and Prevention. *HIV/AIDS Surveillance Report*, 2001. Vol. 13 (1).



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