Preparing for Microbicide Introduction, Rollout, and Sustained Access

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Abstract Two topical vaginal microbicide candidates for HIV prevention are at an advanced stage of clinical testing, with efficacy results from three clinical trials expected within the next 2 years. Therefore, preparations for introducing and ensuring access to these products in the event that they are proven safe and effective now require increased attention. Microbicides are expected to fill an important global public health need for HIV prevention options for women. They have been developed almost exclusively with public and private funding through academic and nongovernmental institutions and minimal involvement of commercial pharmaceutical partners. Efficient and rapid introduction of a new public health technology requires a broad range of expertise and collaborations, some of which are new to the microbicide field as products are at last completing late-stage pivotal licensure studies. Strong leadership, political commitment, and considerable financial investments will be required to ensure successful distribution as well as uptake and continued access to this new product class. This paper highlights work conducted since 2000 by scientists, advocates, and public health officials to prepare for microbicide introduction, and discusses some of the needed actions to ensure that products will become readily accessible to the women who need them.

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1 Background

The path to the development of a safe and effective vaginal microbicide has been long, with numerous setbacks as well as promising developments. Microbicides are a new product class, and only one trial to date has demonstrated efficacy. Thus, preparations for introducing and ensuring access to future microbicide products have received less attention in the scientific literature than preclinical and clinical development. Research findings must be effectively applied to achieve product introduction, rollout, and sustained access, and the need for the translation "from research to reality" is increasingly apparent (AVAC 2013).

Microbicides are positioned as public health goods that are expected initially to be used by women in low and middle income countries in high HIV incidence settings. Product development has been funded almost exclusively through public and philanthropic sources, with limited financial involvement of the pharmaceutical industry. The processes for introduction and marketing of public health goods must follow similar steps to those for commercial products, but additional challenges are expected for microbicides. These include the lack of established regulatory or logistical processes for introduction of novel products, and poor healthcare infrastructure in the countries where microbicides will be introduced. While all partners are aligned around the common goal of increasing HIV prevention options for women and reducing the high incidence of HIV infection in this vulnerable group, the main cohesive factor that drives private sector collaboration—maximizing commercial return on investment—is not present. With three late-stage trials (IPM 2012; FACTS 2013; MTN 2013) of the safety and effectiveness of topical microbicide products nearing completion in five sub-Saharan African countries, the planning and work for microbicide introduction and rollout now requires increased efforts.

Delays in bringing new health technology to low and middle income countries are well documented (Brooks et al. 2012). UNITAID/WHO's recent "HIV Preventive Technologies and Market Landscape" report (WHO 2013a, b) states that "delays in roll-out of new HIV prevention technologies have stemmed from numerous factors, including insufficient financial and human resources, inadequate

political support, technical uncertainty regarding optimal programme implementation, and systemic weaknesses, including problems with commodity procurement and supply management… market factors also often play a role in impeding scale-up. These factors include unfavourable commodity prices and insufficient demand" (WHO 2013a, b, p. 67). Although it is not possible to control all of these factors, nor anticipate how they will play out for microbicides, it is incumbent upon those working in the microbicide research arena to contribute to the work needed for introduction, rollout, and continued access.

Considerations for the process of microbicide introduction have been ongoing since the initial conceptualization of these novel products. In 2000, the Rockefeller Foundation provided support for the formation of working groups charged with accelerating microbicide development, including an Access Working Group. The passage below from this group (McGrory and Gupta 2002) provides a comprehensive highlight of what is necessary to bring microbicides to those who need them.

> In order for a woman or girl to use a microbicide, she must perceive herself at risk, the product must be acceptable to her, and she must know how to use it properly. The products must be available in locations that users can easily access at a price they can afford. A woman's ability to access and use microbicides will be facilitated if there is a political and social environment that supports women's use of those products by actively promoting and incorporating them into policies and programs. For all this to be possible, microbicide products will need to be approved by relevant regulatory authorities and promoted as an essential component of a comprehensive HIV prevention package. (McGrory and Gupta 2002, p. 9)

Though the products under development as well as the landscape of HIV prevention and treatment have changed significantly since publication of that report, the issues remain salient. This paper provides an overview of work conducted since 2000 by scientists, advocates, and public health officials to prepare for microbicide introduction, rollout, and access, and discusses some of the actions that will be needed between the time a product is demonstrated to be safe and effective in clinical research settings to when it becomes readily accessible to the women who need it. Following a description of the trajectory of clinical testing which has led to the ARV-based microbicide products that are currently in advanced trials, we briefly review the efforts made to date to prepare for microbicide introduction and then discuss the broader areas needed for successful microbicide introduction and access.

2 Progress in Microbicide Clinical Testing

The first large Phase 3 clinical study of a candidate microbicide was conducted in four countries between 1996 and 2000 under the aegis of the World Health Organization Global Program on AIDS and tested the safety and efficacy of the spermicide nonoxynol-9 (N-9) for the prevention of HIV infection. N-9 had been

shown in the laboratory to prevent HIV, gonorrhea, and chlamydia infections (Van Damme et al. 2002) and was registered as a nonprescription over-the-counter spermicide for pregnancy prevention in many countries. If the trial had confirmed that the product was safe and effective in preventing HIV infection, a change in product labeling, registration in additional countries, manufacturing and distribution scale-up, and increased access would have likely been straightforward. Distribution, marketing, and promotion mechanisms were in place through family planning services, the private sector and social marketing programs, global manufacturing capabilities were scalable, and the cost of goods and finished product were modest. However, these assets were never put to the test. The results from the clinical study showed that women assigned to the active product acquired HIV infection at a 43 % higher rate than women assigned to the matching placebo, putting an end to further research on N-9 for HIV prevention.

Subsequent candidate products that have been developed and clinically assessed for use as topical microbicides involved either novel uses of already registered products or new chemical entities. The latter required preclinical and clinical safety profiles to be established de novo before definitive Phase 3 clinical safety and efficacy trials could be conducted. The "first generation" of candidate microbicides that progressed to clinical safety and efficacy testing were gels containing surfactants, buffering agents, or large polyanions that either broke down the viral envelope, maintained the low pH of the vagina making it inhospitable to HIV, or prevented the virus from coming into contact with target cells—Savvy (Feldblum et al. 2007), BufferGel™ and PRO2000 (Abdool Karim et al. 2011), Carraguard™ (Skoler-Karpoff et al. 2008), and cellulose sulfate (Van Damme et al. 2008). In 2009 the first study of PRO2000 showed a promising but not statistically significant 30 % reduction in HIV incidence compared with placebo, yet a parallel Phase 3 trial showed no reduction in incidence (McCormack et al. 2010). Trials of the remaining first generation products failed to demonstrate any reduction in HIV incidence, and as the disappointing results of these early trials accumulated, there was an increased focus on microbicides containing antiretrovirals (ARVs) that directly targeted HIV entry and/or replication.

The first microbicide study to demonstrate a statistically significant reduction in HIV incidence was the CAPRISA 004 trial, conducted in South Africa in 2007–2010. This study tested a vaginal gel containing a 1 % concentration of the ARV tenofovir used before and after sexual intercourse. Results showed a 39 % reduction in the incidence of HIV among women allocated to active gel compared with those allocated a matching placebo gel (Abdool Karim et al. 2010). A confirmatory Phase 3 placebo-controlled study (FACTS 001) using the same product in the same dosing regimen is currently underway in nine South African sites (FACTS 2013). A parallel study (the VOICE trial) was conducted in 2009–2013 by the Microbicide Trials Network (MTN) at 15 sites in Uganda, South Africa, and Zimbabwe, and included an arm testing daily use of the same 1 % tenofovir gel product. No efficacy was demonstrated in the trial. However, subsequent analysis indicated that this was likely due to low adherence (Marrazzo et al. 2013). Currently, the International Partnership for Microbicides (IPM) and MTN are each

Table 1 Microbicide products in efficacy trials

Active ingredient	Clinical trial and trial site locations	Product delivery mode	Use requirements
Tenofovir gel	CAPRISA 004 Phase IIb South Africa *(study completed in 2010)*	Prefilled single-use plastic HTI vaginal applicator	Single application applied within 12 h before sex and a second application applied within 12 h after sex
	FACTS 001 Phase 3 South Africa (ongoing)		
Dapvirine ring	IPM 027 Phase 3 Uganda, South Africa (ongoing)	Silicone vaginal ring	Vaginal ring inserted and worn continuously for 28 days, then removed and replaced
	MTN 020 Phase 3 Malawi, South Africa, Uganda, Zimbabwe (ongoing)		

conducting parallel Phase 3 safety and efficacy trials testing a vaginal ring that releases the ARV dapivirine over a 30-day period (IPM 2012; MTN 2013). Research sites for these dapivirine ring studies are in Malawi, South Africa, Uganda, and Zimbabwe.

Table 1 provides some comparisons of the two microbicide products that are furthest advanced—tenofovir gel, a 2-dose coitally associated product in prefilled applicators, and the dapivirine ring, which is replaced every 28 days.

At the time of this writing, it appears likely that results from the efficacy trials of dapivirine ring and tenofovir gel will be available at about the same time. Assuming that plans for introduction, rollout, and access continue to progress, and appropriate supportive activities take place according to plan, it is also possible that these two very different products could enter the market at similar times. Preparations for introduction and access must be made in anticipation of successful results from these trials, even though these plans may never be implemented if the products are not proven safe or effective. Such preparations require significant resources and time, but concerns about the cost of investment in an uncertain product must be weighed against the potential public health and political costs of delays in making an effective product rapidly available.

3 Conceptualizing Microbicide Introduction

Microbicides have the most potential for vulnerable women with inadequate options to reduce their risk of HIV infection. It is recognized that a complex alignment of interests and expertise is required to facilitate introduction, ensure sustained product availability, maximize demand, and ensure that resources are available to meet that demand. For example, royalty-free licenses and subsidized access to the products

have been key components of development plans from the beginning (Mandelbaum-Schmid 2004; Ratzan 2007). This has been reflected in mathematical forecasting models that consider cost, supply, and demand, offset by infections averted at different levels of efficacy and use-adherence, in multiple international settings (Watts 2001; Vickerman et al. 2006; Wilson and Coplan 2008; Verguet and Walsh 2010; Hankins and Dybul 2013; Terris-Prestholt et al. 2014). The costs and regulatory requirements for microbicides are major concerns for sponsors and advocates, and numerous consultations have occurred to discuss these issues and chart the way forward (Stone 2009; Stone and Harrision 2010). Social science and behavioral research has steadily built upon experiences with the introduction of new sexual and reproductive health technologies such as contraceptives and the female condom to provide a body of information to contribute to development of service delivery programs, counseling messages, and social marketing strategies to strengthen introduction, initial uptake, and continued use (Darroch and Frost 1999; Elias and Coggins 2001; Severy 2005; Woodsong et al. 2013).

A large number of not-for-profit research groups and universities have conducted microbicide preclinical and clinical research and engaged in studies, projects, and programs with the aim of supporting microbicide introduction, rollout, and access (Alliance for Microbicide Development 2007). Three organizations were formed expressly to support microbicide development, and their remit included aspects of introduction, rollout, and access – the Global Campaign for Microbicides, the Alliance for Microbicide Development, and the International Partnership for Microbicides.

The Global Campaign for Microbicides, founded in 1998, was "a civil society organization that worked to ensure the ethical and accelerated development and widespread access to new and existing HIV-prevention options—especially for women" (www.global-campaign.org). The Alliance for Microbicide Development was also formed in 1998 "to advocate for and educate about microbicide development, track and communicate product development and regulatory status, contribute to enhanced efficiency in preclinical and clinical processes and, later, help establish a base for matching funds to support combination and comparative studies" (Harrison 1999, p. S39) It also served as the Secretariat for the Quick Working GroupQuick Working Group, convened in 2004 to provide a platform for information exchange amongst those working on advanced microbicide trials, including scenarios for the work that will be needed for introduction once efficacy results are achieved. (Harrison 2007). In 2002, the IPM was established as a product development partnership (PDP) charged with accelerating the development and availability of microbicides for use by women in low and middle income countries. IPM's mission to support the pipeline includes efforts to secure royalty-free licenses, and work with organizations at the global, national, and local levels to provide support for microbicide introduction and access (www.ipmglobal.org).

One of the first efforts to outline the elements necessary for successful microbicide introduction and access was spearheaded by the Access Working Group of the Rockefeller Foundation Microbicide Initiative (McGrory and Gupta 2002). Observing the history of lengthy delays between drug approval and availability in

low and middle income countries, the Working Group encouraged the scientific agenda for microbicides to include priorities to ensure access. The group built on work of other partnerships designed to develop and bring public goods to market, such as the Medicines for Malaria Venture and the International AIDS Vaccine Initiative (Widdus 2005) and laid out a framework of goals, objectives, and activities to facilitate women's access to microbicides. Fundamental elements included (1) considering the acceptability, preferences, and needs of users as important for product development, (2) creating a supportive policy and public health environment for microbicide delivery, (3) ensuring availability of products through appropriate and well-functioning distribution channels, (4) establishing an affordable price for individuals and/or governments, and (5) achieving regulatory approval and licensing.

These concepts are also reflected in conceptual frameworks that have helped focus thinking about microbicide introduction and access. One of the most widely cited adaptations is Frost and Reich, which conceptualizes the "Architecture," that supports the "Access" needed to accomplish successful microbicide introduction and rollout (Frost and Reich 2009). Three pillars of this architecture are:

- "Availability"—ensures that there is sufficient high-quality production and supply of the microbicide product, and reliable channels for distribution, to meet user demand.
- "Affordability"—directs attention to the costs of microbicide products and programs to deliver them, and seeks to ensure products are affordable to purchasers, funders, and end users.
- "Adoption"—considered at multiple levels, from individual to global. Adoption also includes the notion of "Acceptability"—that microbicides are satisfactory to end users (women and their sexual partners) as well as the gatekeepers who control access to them.

In 2006, the Alliance for Microbicide Development produced the Microbicide Development Strategy (Alliance for Microbicide Development 2006), which included considerations for manufacturing, commercialization, and access, noting that "the process will have to be actively and jointly managed by sponsors, product developers, industry partners, and donors" (p. 12). It was recognized that pharmaceutical industry experiences with introduction must be effectively applied to a public health setting, with attendant social marketing, cost and demand forecasting models, manufacturing scale-up in a government-subsidized environment, and financing for product procurement and distribution provided by a range of public and private partners.

Although the Microbicide Development Strategy stated that these costs and the related demand issues would continue to be informed by the process of preclinical and clinical research, it encouraged efforts to plan and execute pilot studies for introduction strategies, drawing on experiences from other health technologies such as female condoms, diaphragms, vaccines, and over-the-counter products. The strategy document also called for concerted efforts to ensure communication with the US Food and Drug Administration (FDA), the European Medicines

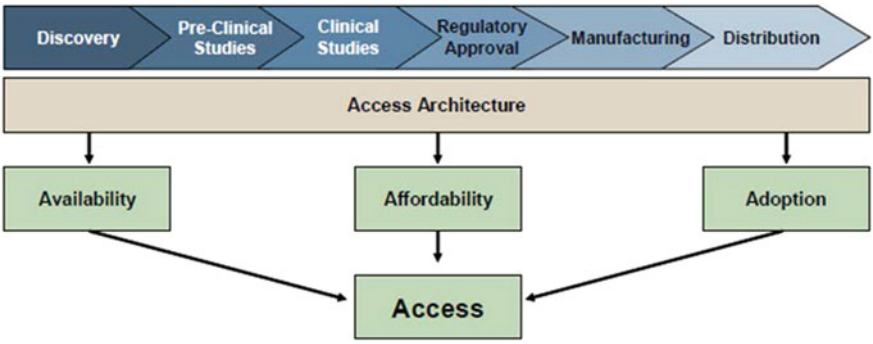

Fig. 1 Access framework and the product development process Herman and Oudin 2010. Reprinted with permission from the Product Development Partnership Access Group (www.pdpaccess.org)

Agency (EMA), and regulatory authorities in the countries where microbicides trials were being conducted.

In 2008, a Product Development Partnership (PDP) Access Group was formed to serve as a forum for access information exchange among 12 PDPs working on new technologies for diseases affecting people in low and middle income countries (notably, malaria, tuberculosis, and HIV/AIDS). Microbicides were one of the technologies included, through IPM's membership in the group. The PDP Access Group maintains a website to improve performance and facilitate efficiencies in access activities (www.pdpaccess.org). Building on the Frost and Reich framework, the PDP Access Group, added a conceptualization of the process pathway from "Discover" to "Distribution," shown in Fig. 1 (Herman and Odin 2010). This framework was used in an assessment of the roles that PDPs will play in post-licensure access to the health technologies they develop. The assessment noted that product developers' specific activities in support of Access varied according to where their technology sits in the pathway, but it was stressed that developers should keep the complete pathway in mind, and be prepared to contribute throughout the process.

4 Progress in Planning for Microbicide Introduction

Dialogue and linkages with regulatory authorities from developing countries with high HIV incidence were brokered by the World Health Organization (WHO). WHO sponsored a series of workshops beginning in 2002 to discuss minimum preclinical requirements to be met before initiating clinical research, and the sequence of clinical studies necessary before launching pivotal Phase 3 studies to establish safety and efficacy for HIV prevention. These workshops served to underline the importance that regulatory authorities in low and middle income countries place on the thorough review conducted by better-resourced national regulatory authorities

with sufficient resources to carefully examine all elements of the dossier, while nevertheless conducting a final assessment of risks and benefits in the context of their own country setting. It was noted that health care systems in countries with high incidence and generalized HIV epidemics are severely stretched to provide care to individuals living with HIV. As a result, the balance of risks and benefits for investment in microbicides for HIV prevention in countries with generalized epidemics differs markedly from the situation in the USA or in European countries.

A series of "Access Forums" were convened in 2007, 2008, and 2010 by the World Health Organization Department of Reproductive Health and Research (WHO/RHR), IPM and the Population Council to flesh out understandings and agreements about what is needed for microbicides to be accessible (WHO 2007, 2008). Informed by experiences with introducing and improving access to sexual and reproductive products, these forums analyzed the challenges and successes of HPV vaccines, the female condom, subdermal implants, and intrauterine contraceptive devices. The candidate microbicide products in efficacy testing at that time were gels designed to be used before sex. The other lead candidate was IPM's vaginal ring, which was similar to those used for contraceptive delivery.

Introduction of the female condom, as a family planning as well as HIV prevention product, was considered particularly relevant. The experiences with introducing the female condom in South Africa and Zimbabwe highlighted the importance of public and private sectors and social marketing structures working synergistically using consistent technical information and promotional materials, as well as supporting programs long enough to allow users to become comfortable with the product. Lessons from the female condom are useful, although current ARV-based products like tenofovir gel and dapivirine ring will likely need to be delivered through a more formal health system. The female condom also illustrated the complexity of product pricing; the price the user was willing to pay was well below the cost of producing the product, let alone distributing it. Subsidies by national governments and/or bilateral donors were able to bring down the cost to the user, but had to compete with other demands on HIV prevention resources, such as male condoms with a unit cost 10–20 times lower. Lessons from contraceptive introduction provided numerous similar and additional insights (Brown 2007).

Over the past decade, the roadmap for specific streams of work needed for microbicide introduction has become clearer. The Bill and Melinda Gates Foundation sponsored a conference in 2009 to outline processes for implementation of new HIV prevention technologies, including topical microbicides, noting that clinical trial results are "only the beginning" (Kim et al. 2010). WHO convened meetings to establish a consultative process for introduction of Pro2000 (WHO 2010), which proceeded until the Phase 3 trial results failed to show efficacy (McCormack et al. 2010). Nevertheless, this work provided instructive, if sobering, insights into the process and timelines to be expected for other microbicide products advancing through the pipeline (Stone 2010). Conceptual frameworks were revisited, and vulnerabilities identified. The positive results of the CAPRISA 004 tenofovir gel trial spurred efforts to address these gaps and timeline needs, and again, WHO convened consultative meetings. A steering committee was formed in 2011 to coordinate

preparation for the introduction of tenofovir gel, and facilitate communication between the research teams, license holders, manufacturers, and donors (WHO/UNAIDS 2010), while the FACTS001 efficacy trial is underway. Some of the key knowledge gaps identified in the Pro2000 and tenofovir consultative process are reflected in USAID's "Shared Vision and Strategic Plan for Microbicide Introduction" (USAID 2013) which overviews a portfolio of projects to be funded by USAID. To-date, a number of these projects have been completed, are ongoing, or planned.

5 Components of Microbicide Introduction

This section briefly summarizes critical components of the architecture that will be needed for microbicide introduction, rollout, and access. These include:

- clinical and regulatory issues,
- social and behavioral science,
- community participation,
- policy and advocacy
- operations and implementation research,
- marketing, and
- manufacturing/supplychain/distribution.

Figure 2 provides a schematic for these components, adapted from Walker (Walker 2006) and benchmarked for demonstration of efficacy.

These components are not discrete, and work in these areas is best done concurrently. AVAC (Global Advocacy for HIV Prevention) has observed that although the prerequisite steps for microbicide introduction follow a linear process (such as that outlined in Fig. 1), feedback between these steps is fluid, and often iterative (AVAC 2013). For example, as ARV-based microbicides have moved forward in the development pipeline, an understanding of what will be needed for their introduction is becoming clearer. The architecture for their delivery will require a health care delivery system capable of providing periodic HIV testing. This will be necessary to monitor and manage the potential for drug resistance among women who become infected while using the ARV prophylactically. If non-ARV microbicides, which are at earlier stages of development, are introduced, service delivery requirements and distribution options will differ.

The sub-Saharan countries where microbicide trials have been conducted will be priority countries for introduction. This sets a geographic stage for where introduction policies and programs will be needed, even though it is not yet clear how or if introduction efforts will focus on women at highest risk. Since the geographic setting, dosing strategy, and active ingredients can now be taken into consideration for tenofovir and dapivirine products, the manufacturing, supply, and distribution costs can now be more accurately forecast (Wilson and Coplan 2008). Furthermore, it is now possible to work more concretely on expected regulatory and policy requirements.

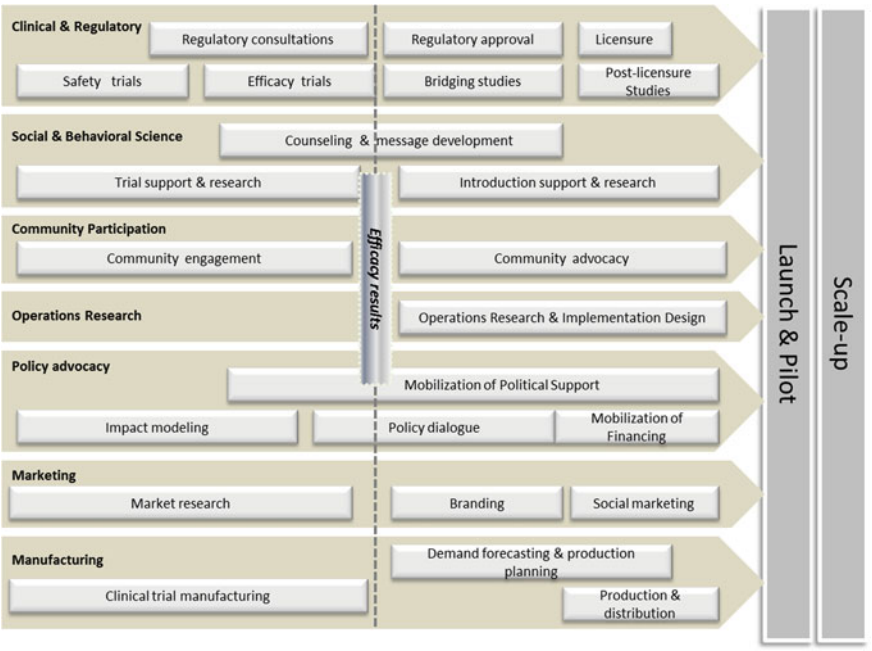

Fig. 2 Process flow for components of microbicide introduction

5.1 Clinical and Regulatory Issues

As a new product class, to be introduced to women in low and middle income countries, the regulatory requirements for approval and licensure for microbicides have yet to be clearly specified (see Nardi et al. 2014, this volume). Initial guidance from the US FDA and the EMA detailed aspects of trial design needed to provide sufficient evidence for licensure. There are multiple regulatory pathways that could be used for microbicide licensure, based primarily on FDA or EMA requirements, and these should in turn be considered by national regulatory authorities in the countries where microbicides will be introduced. EMA's article 58 provides for the EMA, in cooperation with WHO, to provide a scientific assessment of a new drug, yet leave authorization to the national regulatory authorities. Some countries have decided to recognize FDA's assessments, and adopt products that have FDA approval. Guidance for microbicide development continues to be developed and is available on the EMA and FDA websites (FDA 2012; EMA 2012).

It has been observed that although the regulatory bodies in some of the countries where microbicides will be introduced continue to develop their expertise and strengthen the resources needed to approve first-in-class products, many countries will need considerable support (Coplan et al. 2004; Stone 2009). In recognition of these challenges, organizations developing microbicides have

engaged in consultations with regulatory authorities, to keep themselves apprised of the evidence that will be expected of them as well as to provide information to aid in agency deliberations. For example, in 2008, IPM began convening annual meetings that brought together representatives of the ethics and regulatory bodies in the African countries where microbicide research is being conducted. The meetings update these bodies on progress in microbicide development, and serve as a forum for considering the requirements for microbicide registration and licensure in the countries represented.

As microbicide products advanced through clinical trials, communication between research teams was facilitated by the Quick Working Group, and meetings convened by WHO, as mentioned above. Consultations with regulatory bodies, particularly the FDA, the EMA and the South African Medicines Control Council have also occurred, and are the furthest advanced for tenofovir gel and dapivirine ring. These bodies have indicated additional data that will be needed to support licensure, and as a result, a range of supportive clinical studies have been fielded or planned. These include studies of drug–drug interactions, use by women with specific health conditions (e.g., Hepatitis B, impaired liver function), female and male condom compatibility, and use by adolescents and postmenopausal women. Pregnancy registers have been developed for those who became pregnant while using microbicides, as well as studies enrolling women who became infected with HIV while participating in a microbicide trial. These clinical studies have been carefully developed with feedback from the regulatory bodies that requested them, to ensure that the data that will be required are collected. Finally, bridging or follow-on studies are being planned for the post-efficacy/prelicensure period, if the trials show the product(s) are effective, including those that will provide trial participants with continued access to the products they helped to prove effective.

Normative guidance provided by WHO is widely accepted and has a strong influence on policy, accelerates implementation in resource-limited settings, and is necessary for accessing funding for implementation from some donors such as the Global Fund. WHO guidelines contain clinical, public health, or policy recommendations about health interventions, and provide information about what policy makers, health care providers, or patients should do (WHO 2012b). While national regulatory authorities have the mandate and responsibility to allow a product into the market in their jurisdiction, WHO Guidelines provide advice on issues to consider when national program managers and policy makers decide whether and how a product should be used, whether and how it should be prioritized to certain segments of the population or risk groups, and how to deliver the new product in an efficient and cost-effective manner with due consideration to other priority health interventions. The process to develop normative guidance on microbicides is underway and is aimed to be published soon after the products are first licensed. The guidance will be informed by pilot introduction and acceptability research conducted in high priority settings and communities if the new products have been shown to be safe and effective in the late-stage clinical studies.

A parallel procedure that will accelerate introduction and availability of the new microbicide products is the WHO prequalification process which is applied to

medicines and medical devices in priority areas (WHO 2013a, b). This procedure is usually focussed on medicinal products with established markets and several generic manufacturers, and prequalifies specific manufacturing sites and facilities to supply product for international procurement agencies for distribution in resource-limited settings. In this respect the prequalification program concentrates on the quality of the manufacturing process and the finished product. However, when applied to novel pharmaceutical products, the WHO prequalification process also assesses the safety and efficacy of the product in a similar manner to national regulatory authorities. This assessment will be strongly influenced by the result of any reviews by and decisions from stringent regulatory authorities. At present, prequalification requirements have not been developed for microbicides but the procedures should be initiated once data on the safety and efficacy of the new microbicide products are available.

5.2 Social Science and Behavioral Science Research

A decade ago, a landmark social and behavioral science study on preparing for microbicide introduction provided an overview of issues relevant to community, service delivery, policy development, and advocacy (Becker 2004). This work highlighted the range of potential contributions from social science and behavioral research. Earlier social and behavioral science research focused on acceptability of hypothetical vaginal products, and conceptual models framed acceptability as influencing adherence to use of microbicides proven effective (Woodsong and Koo 2002).

As experience with clinical trials increasingly pointed to adherence problems, significant effort has been devoted to measuring and motivating adherence to product use (van der Straten et al. 2012; Woodsong 2013; Tolley in press), and further understanding how (or if) acceptability and adherence are related (Montgomery, Gafos et al. 2010). Microbicide clinical trials include collection of behavioral data on acceptability and adherence, and provide behavioral counseling for risk reduction and adherence to the study protocol. Additional ancillary studies have further investigated factors influencing use within clinical trials, collecting data from trial participants as well as their male partners, health professionals, and community stakeholders (Pool et al. 2010; Whitehead et al. 2011; van der Straten et al. 2012; Woodsong et al. 2012). This body of research provides data that can inform much of the workstreams portrayed in Figure 3, particularly once a product with demonstrated clinical effectiveness becomes available outside of a research setting.

For example, the adherence counseling approaches used in microbicide trials are being further scrutinized and studied to ensure quality counseling in trials as well as provide an evidence base for operations research to develop future counseling on use of an effective product (Hoffman et al. 2008; Evangeli et al. 2009; Amico 2012). Social and behavioral science has identified gender issues (Mantell et al. 2009; FHI360 2014) and traditional sexual practices (Hilber et al. 2007; Braunstein et al. 2011) that could influence uptake and use of microbicides

proven effective. Marketing research will benefit from what has been learned about user perceptions of microbicide products and their use within sexual relationships (Bentley et al. 2004; Tolley et al. 2006; Morrow et al. 2007; Woodsong and Alleman 2008). Community engagement, education, and advocacy all require an understanding of social, cultural, and behavioral factors that will influence initial uptake and use, and it is expected that social scientists and behavioral scientists will be engaged in this work.

5.3 Community Engagement and Education

Community engagement is an essential component in the process of developing new health technologies, and facilitating introduction, uptake, and sustained use. It will be critically important for microbicides, as they will be introduced in settings where non-Western health belief systems are common, and the products are to be used for prevention (not treatment) of a highly stigmatized disease which is frequently associated with rumors, misinformation, and suspicion. Community stakeholders serve as an interface between government policy makers, program developers, civil society groups, and potential microbicide users. The HIV care and treatment field has demonstrated that community stakeholders and other influential individuals must be involved from the initial stages of human trials, and preferably even earlier (Tindana et al. 2007; Tedrow et al. 2012; AVAC 2013). Guidance and training in "Good Participatory Practice" has been developed by UNAIDS/AVAC to provide basic tools for effectively educating and engaging with communities in research (UNAIDS/AVAC 2011).

Microbicide trial researchers have routinely solicited community input, by working with existing community advisory groups or forming new ones. Initially, microbicide activities with communities were focused on increasing awareness of the need for a woman-centered HIV prevention product. As clinical research has progressed, community engagement has expanded to strengthen local knowledge about scientific research, as well as provide education on HIV prevention that can support the emergence of demand for microbicides. There is considerable variability in the form and function of community advisory groups (Morin et al. 2003), but the community groups currently engaged with microbicide trials are poised to provide support for a wide range of introduction activities.

5.4 Policy and Advocacy

The timing for policy and advocacy work is critical, and must be synchronized with the product development process. Microbicide advocates focused initially on the basic concept of a vaginal method that women can use for protection, followed by details about the products that advanced to large-scale efficacy testing. Next

will be concerted efforts to champion the development of policies and programs to deliver the microbicides that prove efficacious. The process of policy development, and attendant national guidelines and budgets, requires lengthy and multitiered discussions. Although policy makers may be reluctant to engage in serious consideration of a new class of product that is not yet proven effective, past experiences with developing HIV and population policies demonstrate that the policy process is lengthy and requires consultation and buy-in from many sectors (Stover 1998). Thus, it is appropriate to engage with policy makers and other influential parties during the clinical research process, to set the stage for action once efficacy is demonstrated. The possibility exists that a microbicide trial could be discontinued early because of high levels of efficacy, and in such a situation, advocates and policymakers will be keen to take advantage of the momentum of such a positive situation and move for speedy introduction.

The policy development process varies between countries, but the steps in this process are generally known, and approaches for engagement in these steps have been articulated. A number of assessment tools, techniques, and templates useful to organize information for policy makers to use in decision-making can be used for development of microbicide policies (Schwartlander et al. 2001; Stover 2003). Furthermore, policy development must be done in parallel with regulatory development, as the policies will reflect the regulations for how, who, when, and for what the products can be made available. For innovations in the international public health sector, the interface between product developers and policy makers has historically been supported by international aid agencies, and it is likely that such agencies will provide support for microbicide introduction in sub-Saharan Africa.

5.5 Operations Research and Implementation Science

International aid agencies, particularly USAID, provide funding support for operations and implementation research, and will likely be instrumental in microbicide introduction. This work will draw from all the streams of activity shown in Fig. 2 to plan programs in accordance with the capacity and requirements of local health service delivery systems. The Population Council, with funding support from USAID, has convened consultative meetings with nongovernmental, governmental, advocacy, and donor organizations to consider how experience with introducing other healthcare technologies, particularly contraceptives, can inform development of pilot and demonstration projects, and operations research for microbicide introduction (Brady and McGrory 2007, 2012). FHI 360, with funding support from the Bill and Melinda Gates Foundation, has completed a "proof of deliverability" study, to highlight issues that could facilitate or hinder introduction of new HIV prevention methods, including microbicides (Evens et al. 2012).

Since the current lead microbicide candidates are ARV-based, the products will initially be available as prescription-only medicines. Thus, they must be delivered through formal health care delivery systems, and the service provider must be able

to provide HIV testing to ensure that users are and remain uninfected. The service delivery avenues that have been discussed most frequently are family planning services and/or HIV services. Both types of service delivery points have advantages and disadvantages, which vary considerably in different country settings and with different target populations.

In addition to requiring that users be HIV negative, the first microbicide delivery services will likely require that users be on contraceptives until the safety of the products during pregnancy has been established. Family planning centers are generally "woman friendly" service delivery settings that could provide both contraceptives and microbicides. An open-label follow-on study to CAPRISA 004 is providing tenofovir gel in family planning clinics to assess provision of microbicides in this service delivery setting, compared to the research clinic setting (Karim and Baxter 2013), and study results will inform decisions about co-locating microbicide delivery with family planning.

Not all women who are at risk of HIV infection access family planning services. HIV service delivery facilities reach out to general or targeted at-risk populations, and may provide a range of testing, care, and treatment services. However, such facilities are primarily resourced to provide care, and are less well-resourced to provide the necessary counseling and support for HIV prevention. In addition, the stigma that may be associated with HIV treatment and care facilities could be a deterrent to potential microbicide users. Furthermore, in order to deliver microbicides, an HIV service facility must have capacity to provide more than voluntary counseling and testing. Operations and implementation research will be needed to inform decisions about locating microbicide in these settings, to ensure that both practical and socio-cultural issues are addressed. Making microbicides available to young women will be a particular challenge as they already have limited access to family planning and other reproductive health services. Yet this high HIV incidence group is one of the populations most in need of new HIV prevention approaches and should be prioritized for access.

Regardless of the type of service delivery setting used for microbicide delivery, the basic elements of microbicide delivery programs will include determining potential users' eligibility (e.g., must be HIV negative) and contraindications for use, establishment of testing requirements (e.g., STI, pregnancy and HIV testing), and a resupply schedule. The products will require resources and space for storage, tracking, disposal, etc. Training programs will be needed to encompass service provision and counseling. Although in most settings, processes and systems for meeting needs are generally understood by in-country program developers, adding a completely new technology will require creativity and flexibility.

Microbicides are intended to fit within a range of HIV prevention options with different levels of use-effectiveness (Nuttall 2004; Brown 2007), and preferably be used with other effective methods, such as condoms. Thus health professionals must be able to provide information so that prospective users can combine microbicide use with other prevention methods, if they wish. Lack of provider support is cited as a significant factor contributing to poor uptake of female condoms and intrauterine contraceptive devices (Hubacher 1994; Kerrigan 2000; Hoffman et al. 2008;

Mantell et al. 2011). This underscores the importance of leadership and guidance from national and international health professional associations, as well as the promulgation of clear national policies and service delivery protocols. It is likely that microbicide introduction and delivery will require additional scarce resources in health care delivery systems that are already stretched very thin.

5.6 Marketing

It is likely that microbicides will be introduced in government-subsidized programs in sub-Saharan Africa. Social marketing campaigns will be needed for microbicide introduction, and establish the initial positioning of these products. Some market research has been conducted during the microbicide development process to inform decisions about product formulations and means of delivery to the vagina. For example, market research studies assessed user preferences for the different types of products being considered for further development (e.g., gels, rings, vaginal tablets) (Nel et al. 2011), and studies assessed user preferences for products and their delivery modes (e.g., gel applicators) (Cohen et al. 2007, 2013). These studies provide information relevant to user interests and the products' appeal to potential users, which can inform marketing strategies.

Past experiences with condom social marketing campaigns and HIV prevention messages illustrate the importance of getting the introduction message right (Hanson et al. 2001). Doing so requires tailoring the message to the setting and potential user group. Social and behavioral science research, advocacy experiences, and community engagement activities conducted to date provide important insights into how to position microbicides as women's HIV prevention products (Boyce 2008). In the early days of microbicide development, they were referred to as "woman-controlled" and claims were made that they would empower women (Elias and Coggins 1996). It is now more common to use the term "woman-initiated" and to temper claims for the impact of microbicides on gender roles. Positioning microbicides as products to improve women's sexual pleasure could have negative ramifications if women's sexual pleasure is not a culturally appropriate topic for open discussion, but for some populations it could increase interest in the product.

Although preliminary work on product branding and social marketing research can be conducted earlier in microbicide development and be included in the regulatory dossiers, realistically it is probable that the main thrust will be conducted once efficacy is demonstrated. It is likely that these branding and marketing activities will include commercial firms with experience in marketing health products in low and middle income countries, as well as not-for-profit groups that have previously conducted social marketing campaigns for HIV prevention and contraceptives. Since the initial positioning of microbicides could have a long-term impact on perception and uptake (Brady and McGrory 2012), there is keen interest in making sure this receives thoughtful attention. The basic concept of

asking women to insert a microbicide product in their vagina and keep it there when having sexual intercourse, possibly without the partner's knowledge or approval, could become negatively sensationalized. It will be also important to monitor negative and erroneous publicity about health interventions and new technologies, and take appropriate steps to counter this when necessary (Robinson 2010; Larson et al. 2013).

5.7 Manufacturing, Supply Chain, Distribution

Manufacturing products for testing in clinical trials is done on a much smaller scale than will be required for introduction and rollout. Careful coordination will be needed to manufacture and deliver the increasingly larger amounts of products that will be needed for introduction and scale-up. Processes that are compliant with Good Manufacturing Practice must be achieved and validated, incremental increases in quantities must be estimated, and supply must be ensured through distribution channels that are monitored to ensure quality is maintained. As tenofovir gel and dapivirine ring advance in development, and potential manufacturing firms are identified, these considerations are becoming clearer. For example, there may be advantages to in-country manufacturing, both in terms of cost of production and transport, and because governments may require it. With improved clarity in the manufacturing process, the determination of microbicide cost per unit is also becoming more focused.

Microbicides are unlike other drug products that have been introduced in low and middle income countries long after being made available in the USA, Europe and other developed country markets, and they will require significant subsidies for manufacture and distribution. Demand forecasting and economies of scale are governed by policy and program, in accordance with funding for procurement. Again, the female condom experience is instructive, since low demand hindered economies of scale and potential cost reductions, and even when cost reductions were achieved, low demand persisted in areas where potential users, health professionals and policymakers continued to think of them as too expensive (Bertrand 1995, 2002; Horn 1998; Shane 2006). The importance of sustained supply is highlighted by contraceptive experiences in low and middle income countries, where sustained use of contraceptive products has been impeded by stock-outs, and these interruptions have affected use-effectiveness as well as provider and user-confidence in plans to continue to use the method (Bertrand 1995; Horn 1998).

Finally, women's experiences in clinical trials point to the importance of developing simple user-friendly instructions about how to correctly and consistently use microbicides (Woodsong et al. 2013). Increasingly, trials have used illustrated instruction sheets, with minimal text in the local language, to supplement the instructions given by clinical staff. These materials can be adapted for use with licensed products, as has been done by PATH for development of package inserts and labeling for the SILCS diaphragm and Woman's Condom.(PATH 2005;

PATH 2005; PATH 2006; Major et al. 2013) PATH conducted studies to assess women's ability to use the products by following the package instructions and work is currently underway to develop prototype packaging that meets regulatory requirements for labeling and package inserts in such a way that the preponderance of required information will not confuse users and that key messages are kept clear and comprehensible for users and providers. Similar user tests will be needed for microbicide packaging and use-instructions.

6 Conclusion

There is widespread agreement that women need more options for HIV prevention, and that vaginal microbicides could help meet this need. The challenges of introducing a new product class into overstretched healthcare systems in low and middle income countries are sobering, but work that is needed has become more clear since microbicide research first began.

Much of the work conducted thus far for the explicit purpose of planning for microbicide introduction focuses on the supply side, and as candidate products advance in efficacy testing, this type of planning will become more concrete. Certainly, there is much to be done to ensure that a reliable supply of quality products gets to where they are needed. However, the demand side of microbicide access also requires significant attention and planning. There is currently no space for microbicides on the shelves in public health clinics, people don't ask for them, and providers don't recommend them—this demand will have to be created. Furthermore, their use may challenge existing norms for sexual behavior (Becker 2004; Mantell et al. 2009). This has led to calls for a new paradigm for product introduction (Nuttall et al. 2007).

A compelling reason why microbicides are needed is that the cornerstones of HIV prevention—sexual abstinence, mutual sexual fidelity, and condom use—which have been so successful in reducing HIV incidence in many communities and populations, are inadequate for many women at risk of infection. This is evidenced by the stubbornly high HIV incidence in young women in sub-Saharan African countries. By intention or design, microbicide introduction could become a leverage point for empowerment and other broader improvements in women's positions in those regions targeted for microbicide introduction. In order to accomplish this goal, microbicides must be introduced in a way that provides appropriate access to those who need them most, and ensures that users are adequately empowered to use them correctly and consistently so that they can better protect themselves against infection.

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