INTERNATIONAL PARTNERSHIP for MICROBICIDES

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Draft Meeting Report

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FOREWARD

The first Microbicide Access Forum provided an important opportunity to engage experts within and beyond the microbicide field in a dialogue on future microbicide access.

While there has been considerable progress in microbicide research and development (R&D), uncertainty remains about when a first product will be registered for use. Results from the Population Council's Phase III trial will be announced by the end of 2007. Two further Phase III microbicide trials are due to announce results in 2009. The next generation of microbicide candidates, based on antiretroviral agents, are already in clinical trials. In parallel, other new HIV prevention approaches are being tested or, in the case of male circumcision, now being introduced. Countries have also committed to expanding existing HIV prevention programmes. In such a rapidly changing and complex environment, opportunities to exchange clear and up-to-date information and engage in a dialogue with country and international stakeholders are essential.

Although it is important not to raise expectations prematurely, there is much that can be done now to build a platform for microbicide introduction and raise awareness among key country stakeholders. Participants highlighted both the considerable experience that already exists in introducing new health technologies and the unique challenges that will be faced by microbicides.

There was strong support from those attending for future opportunities to continue these discussions. The dialogue initiated in Nairobi will be continued with a larger range of participants at the forthcoming Microbicides 2008 conference in Delhi in February 2008. The International Partnership for Microbicides and World Health Organization will also continue to co-convene the Microbicide Access Forum on an annual basis, in order to provide a forum for discussion of timely issues in planning for future microbicide introduction and use.

Saul Walker
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EXECUTIVE SUMMARY

The International Partnership for Microbicides (IPM) and World Health Organization (WHO) co-hosted the first annual Microbicide Access Forum on July 2-3, 2007 in Nairobi, Kenya. The Forum brought together more than 45 government representatives, programme implementers, advocates, social science researchers and clinicians from the HIV/AIDS and reproductive health fields to discuss approaches to microbicide introduction and delivery scale-up.

The objectives of the Forum were to:

- identify strategies to support microbicide introduction, scale-up and access, with an emphasis on country-level perspectives;
- facilitate shared planning and collaboration; and
- support a common understanding of likely timelines and scenarios resulting from trials of microbicides and other HIV prevention technologies.

The meeting began with a reminder of the urgent need for female-initiated HIV prevention methods, which must be balanced against realistic expectations regarding the likely timeframe for first product approval. Drug development is inherently uncertain which makes predicting product introduction timelines difficult.

Participants discussed experiences of past introduction programmes for contraceptive technologies, and more recently, male circumcision and antiretroviral therapy. The rapidly evolving HIV prevention and treatment environment was also discussed. In particular, participants noted the challenges faced by countries that are grappling with the scale-up of existing interventions, while trying to anticipate results from a range of ongoing HIV prevention trials.

The agenda included two working groups on: a) designing early introduction programmes and b) informing country decision-making. In both groups, participants contributed their experiences with introducing, delivering and scaling-up existing health technologies and interventions.

The key themes from the meeting were:

- New prevention options should be integrated into a comprehensive programme that expands choice within an enabling environment.
- Phase III trials in developing countries provide an important opportunity to build community support and country ownership of a product.
- Microbicide advocates must set realistic expectations about when microbicides will become available and the scope and speed of initial introduction. Building demand will take time.
- Engaging policy-makers at country-level early and building local constituencies prior to product introduction will be critical to successful microbicide adoption. However, country-specific advocacy and localised communication strategies will be needed.

- WHO and other normative agencies will play a critical role in issuing guidance and facilitating policy discussion.

- Policy-makers will need technical assistance and clarity on how to interpret clinical trial results and cost-effectiveness comparisons between various HIV prevention tools and interventions.

- While microbicides will provide an important additional HIV prevention tool that women can use, they should not be seen as a panacea for gender inequalities in HIV and sexual and reproductive health.

Participants identified the following next steps and areas for future research:

- Identifying key gatekeepers at the country-level and keeping them informed as research progresses.
- Identifying appropriate international financing and technical cooperation mechanisms to support product introduction.
- Agreeing on realistic targets and indicators for the success of initial introduction programmes.
- Developing tools and guidance for country decision-makers to determine criteria for microbicide introduction in different settings, including on features such as effectiveness, level of coital dependence and cost.
- Developing messaging that is both consistent and appropriate to different audiences. This includes conveying concepts of 'partial efficacy' at population- and an individual-level

The Forum ended with two participant-led discussions on the a) WHO Gender, Sexuality and Vaginal Practices Study and b) roles of advocacy and social science research in microbicide introduction and scale-up. A description of these sessions is included as Appendix I and II respectively.

Presentations from the meeting are available online at:
http://www.ipm-microbicides.org/ensuring_future_use/english/2007_microbicide_access_forum.htm

1. PLENARY SESSION I

1.1. HIV Prevention Research and Implementation- Challenges and Opportunities on the Horizon: Emily Bass, AIDS Vaccine Advocacy Coalition

In the dynamic field of HIV prevention research, there are more new technologies and interventions in the pipeline than ever before.[i] At the same time, efforts to expand coverage and improve the delivery of existing HIV prevention programmes are urgently needed.[ii]

Within this rapidly changing context, a mechanism is needed to translate new research findings into action. This need has been self-evident in the relatively slow rollout of male circumcision (MC) for HIV prevention and plans for the introduction of new HPV vaccines that prevent cervical cancer.

Laying the groundwork for microbicide access and asking difficult questions now will speed up eventual product introduction. In particular, the presentation identified the following as key issues:

- Determining the minimum effectiveness threshold(s) for new health technologies, and designing trials in order to be able to provide these answers.
- Determining decision-making criteria or processes for who will receive new prevention tools and when.
- Developing a multi-stakeholder partnership, including researchers, communities and advocates, to communicate the implications of research successes and failures.
- Identifying new funding streams and ensuring that existing instruments, such as PEPFAR and the Global Fund, are able to quickly respond to new trial results.
- Determining and setting new technical standards for comprehensive prevention services.
- Building better bridges between prevention research and implementation of existing technologies and services.
- Informing the agenda for ongoing HIV prevention research following the introduction of multiple new approaches and first generation products.

1.2. The WHO Strategic Approach to Strengthening Reproductive Health Policies and Programmes: Kim Dickson, WHO

The Strategic Approach (SA) is a toolkit developed by WHO that a number of countries have successfully utilized to prioritize their reproductive health needs and develop services to meet them.[iii] It was cited as an example of a comprehensive,

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[i] AVAC. "HIV Prevention Research: A Comprehensive Timeline." Accessed Aug 2007. http://www.avac.org/timeline-website/index.htm

[ii] Global HIV Prevention Working Group. "Global HIV Prevention: The Access and Funding Gap." Accessed Aug 2007. http://www.kff.org/hivaids/upload/pwg062807factsheet.pdf

[iii] For a full description of the Strategic Approach, see http://www.who.int/reproductive-health/strategic_approach/principles.html

public health approach that could be deployed for microbicide introduction and was revisited several times during the meeting.

The approach has three stages focusing on assessment, action research and scaling up. It has a participatory process, encourages country ownership of decisions and emphasises rights-based and gender-equity approaches. Key issues explored in the toolkit include: assessing the coverage and quality of existing services and deciding whether methods should be added or removed from the service mix; assessing the capacity of the service delivery system to add a new product, while providing high-quality services and supporting informed user choices; and estimating the resource needs for introducing new methods.

1.3. Male Circumcision and HIV Prevention Recommendations- Implications for Microbicide Introduction and Access: Kim Dickson, WHO

In March 2007, WHO and UNAIDS issued guidance recognizing the importance of MC as an additional prevention strategy, after three clinical trials concluded that the procedure reduces HIV risk by approximately 60 percent. Eleven recommendations were made including that MC should be made part of a comprehensive HIV prevention package; public health impact is likely to occur most rapidly if MC services are first provided in areas of high heterosexual transmission; effective communication on the role of a partially effective method as part of HIV prevention choices is important; health systems need to be strengthened in order to deliver quality MC services; and ongoing research must guide further programme implementation.[iv]

The consultation process and subsequent technical recommendations provide a recent example from which the microbicide field can draw. MC recommendations were supported by three trials with unequivocal results. This raises the question of what evidence burden will be required by the normative agencies in order to issue policy and programme guidance for microbicides. The repeat-use nature of microbicides and the challenge of supporting consistent use could complicate such guidance.

Microbicides will be introduced into a prevention mix that may include MC and other new prevention approaches. Policy-makers will need guidance on how new and existing methods can be combined. Both MC and microbicides are partially effective methods that emphasise the importance of communication and counselling of users, and the need to understand and address prevailing gender and social norms within communities.

[iv] WHO and UNAIDS. "New Data on Male Circumcision and HIV Prevention: Policy and Programme Implications." 30 April 2007.

1.4. Insights and Evidence from Product Introduction to Inform Microbicides: Martha Brady, Population Council

Girls and women build their protection strategies using available technologies and services, social power and economic opportunities. The availability of technology will not, in itself, adequately equip girls and women to protect themselves. Thus, new technologies, such as microbicides, must not be viewed as a magic bullet that will single-handedly empower women.

Successful microbicide introduction will require a safe, effective, and affordable product; a clear understanding of product benefit (for policy-makers, providers and women); demonstrated early introduction[v] success; targeted health systems strengthening; and engagement and support of stakeholders at various levels.

An early introduction phase will need to pilot routine provision through different distribution channels, identify product champions, train providers, develop communication and marketing strategies, conduct programme costing exercises, and design monitoring and evaluation frameworks.

To illustrate the steps involved in product introduction, an example was provided of the pre-introduction approach developed by Population Council to launch Norplant, a hormonal implant contraceptive, in the early 1990s. Early introduction phases proved useful during Norplant's rollout as a bridge between clinical trials and incorporation into national programmes as they provided opportunities to gain experience and provide training under normal field conditions. They also allowed time to build stronger community ties and mobilise politically. Being the first contraceptive implant on the market provided opportunities to shape user experiences but also posed challenges in terms of anticipating provider and user responses to the product outside a trial setting.

Drawing on lessons learned from the introduction of emergency contraception, female condoms and Norplant, the presentation identified the following issues to consider during microbicide introduction planning:

- the need to understand and navigate industry, political and public health goals and recognising that these may not be aligned;
- the importance of working with women to get past the initial learning curve in product use;
- recognizing the potential tensions between providing quality of service and expanding service delivery points;
- addressing potential provider bias upfront;
- utilizing an early introduction phase to field test products prior to national roll out; and
- recognizing that product introduction takes time, and that the speed of uptake is dependent on how much behaviour change is required, product price and the level of commitment to establishing and building demand.

[v] Pilots, early introduction, pre- introduction, Phase IV, Phase V, post-marketing or registration studies are variants of the same concept, involving post-Phase III clinical trials and surveillance studies to obtain additional information on safety, efficacy, acceptability, optimal dosage, patient eligibility criteria, distribution and communication strategies etc.

1.5. Discussion (Plenary Session I)

Participants emphasised the importance of countries building ownership of programmes. The failure of prevention-of-mother-to-child-transmission (PMTCT) programme scale-up was offered as an example of how lack of ownership and political will at the country-level have resulted in poor coordination of implementing agencies at the country-level.

Participants also stressed the importance of looking at societal factors defining sexuality. Understanding the overall status of women and how this impacts their ability to make decisions concerning sexuality and reproductive health is essential. This should include identifying other members of the family - such as husbands or mothers - who may influence women's decisions, so that they can be included in communications strategies.

2. PLENARY SESSION II

2.1. Update on Microbicide Development: Zeda Rosenberg, IPM

Early-generation microbicides, which are currently in Phase III trials, are coitally-dependent and will probably have low efficacy against HIV. Results from the Phase III trial of Carraguard are due at the end of 2007, with findings for PRO 2000 and BufferGel due in 2009. The next generation of antiretroviral (ARV)-based, highly HIV-specific microbicides are likely to be more potent. These products can be formulated in a variety of ways and have longer durations of action, providing opportunities for less dependence on use just before sex. An efficacy trial of the ARV-based PMPA gel has now started in South Africa. Dapivarine, formulated as both a gel and a vaginal ring, is in clinical safety studies. A number of organisations have additional ARVs with a variety of viral targets in early stage development.

The drug discovery, development and testing process is long and complicated and few compounds progress from the laboratory into clinical trials. Those that do are not always successful. Drug development can start with as many 10,000 potential compound leads to yield just one approved drug.[vi]

In addition, microbicide R&D faces a number of particular challenges. Firstly, as no microbicide has been approved, there are no validated surrogate markers that can predict in early tests whether a candidate will prove successful in clinical trials. This reduces the certainty with which choices can be made when progressing products into efficacy trials. Secondly, HIV prevention trials must take place in communities where there are high rates of HIV incidence. However, incidence is difficult to measure and usually falls when women enrol in trials due to increased access to HIV prevention services, which are provided to all participants. If incidence rates are lower than anticipated, it may be difficult for a trial to give a definitive result. Thirdly, if women become pregnant during clinical trials then they leave the study. If too many women leave a trial then a decisive result may be difficult to obtain. Pregnancy rates have been higher than expected in existing trials. Fourthly, microbicide

[vi] DiMasi, J.A., 2001b. Risks in new drug development: approval success rates for investigational drugs. Clinical Pharmacology & Therapeutics 69, 297–307.

effectiveness depends both on the potency of the product and on the consistency with which it is used. Assessing levels of adherence (consistency of use) is challenging and can complicate the interpretation of clinical trial results. Finally, there is limited clinical trial capacity in communities in which HIV incidence is highest and where new prevention options are urgently needed.

As with any R&D process, it is likely that the years ahead will see some disappointing results from microbicide trials. It will be very important to manage expectations regarding trials and to increase understanding of the nature of the R&D process.

2.2. 'Access' to Microbicides- Key Challenges and Possible Scenarios: Saul Walker, IPM

The objective for microbicide introduction should be to maximise health impact for women in developing countries over time. There will be many challenges to this, especially as the timing of first product registration and the profile of early candidates are still unclear. Additional challenges include marketing a product in the presence of HIV stigma and understanding the impact of gender roles on decisions over the use of sexual health-related products.

While it may be relatively easy to gain funding for initial introduction of microbicides, securing long-term commitments will require demonstration that the product is widely acceptable and its use is having an impact in reducing HIV incidence. However, it will be difficult to demonstrate population-level impact of microbicides as such effects take time to emerge and, in an evolving HIV environment, are difficult to attribute to any one intervention.

The manufacturing costs of first-generation microbicides are likely to be similar to those of a female condom, but scale-efficiencies are likely to bring this price down as volumes increase. Microbicides are likely to be licensed as prescription-only products at first, which will limit distribution and may raise programme costs. The potential for second-generation products to cause ARV resistance may be an issue and would have implications for programme delivery. The potential for resistance is currently unknown but will be examined during Phase III studies.

Based on lessons from other products, microbicide introduction will be staggered with rollout with initial introduction in a few countries. It will require the integration of microbicide provision into HIV and/or sexual and reproductive health programmes. And activities to build awareness, knowledge and demand for microbicide among women and communities will be both essential and take time.

2.3. Discussion (Plenary Session II)

It was noted that the current design of microbicide trials test the effectiveness of the product, which depends on both the efficacy of the drug as well as how consistently is was used during the trial. Therefore, the perfect-use efficacy of the drug (i.e. its ability to prevent HIV infection when used consistently and correctly), although unknown, is likely to be higher than the effectiveness calculated from trial data.

It was also noted that before 2002, pharmaceutical companies had little engagement with microbicides. The high costs of development were seen to be unjustified by potentially low market returns. On establishment, IPM actively sought partnerships

with pharmaceutical companies, and provided a mechanism through which promising candidates could be licensed for development as microbicides, without companies incurring development costs. Access to such compounds is essential for driving the microbicide development pipeline. IPM has been successful in securing royalty free, non-exclusive licensing agreements with four international pharmaceutical companies, and is in advanced discussion with two additional companies. These agreements provide flexibility for future manufacturing and pricing strategies.

Some of the participants noted that it was relatively easy to generate funds for female condom early introduction programmes but scale-up has proven a challenge. The female condom programmes lacked adequate funding to do significant outreach to policy-makers. Building constituencies at country-level that can support microbicides will provide an important platform for subsequent introduction.

Participants raised the importance of reaching married couples in stable relationships and a discussion followed on product positioning – for instance, positioning as an HIV prevention product might stigmatize microbicides. Market segments within countries were also discussed. Products can be branded, positioned and priced differently for various socio-economic, demographic or epidemiological groups. This can help maximise uptake across diverse populations.

The discussion ended with a reminder that there were many things to learn from the contraceptive field, which has evolved over time from a few options to a wide range of increasingly efficacious products with different formulations and modes of action that enable choice, and hence increase use.

3. WORKING GROUP SESSIONS

In the afternoon, participants broke into two working groups, one to discuss "Designing Early Introduction Programmes" and the other to discuss "Informing Country Decision-Making".

3.1. Working Group A: Designing Early Introduction Programmes

The first working group focused on identifying elements of an early introduction programme for microbicides. Previous experience indicates that building demand for a new product, establishing the systems to deliver it, and understanding how to use it most effectively takes time and considerable perseverance.[vii] Early introduction programmes aim to help identify optimal programme strategies and systems that can be successfully scaled-up at national-level. Early introduction should also help quantify programme costs and support the development of an investment case for governments and donors for scale-up and long-term funding commitments. A further objective may be to collect additional information required by regulators on safety, efficacy, optimal dosage, and acceptability in the local populations in order to obtain licensure or to change a product's designation, e.g. from prescription-only to over-the-counter.

[vii] Brown, GF, V Raghavendran and S Walker. 2007. "Planning for Microbicide Access in Developing Countries: Lessons from the Introduction of Contraceptive Technologies." *IPM Policy Paper.* Silver Spring, MD: International Partnership for Microbicides.

To aid discussion, Dr. Michael Thuo from Management Sciences for Health made a brief presentation on the experiences of MSH in designing and implementing pilot programmes.

The group then discussed a hypothetical early introduction programme of a 30 percent effective first-generation microbicide in a sub-Saharan African country with a generalized epidemic. It was agreed that such a programme would typically focus on distinct geographic areas such as districts. The programme would need to demonstrate the following:

- Capacity of the system and providers to deliver a product;
- Affordability to the consumer, programme, and funder;
- Access to and use of the product in different groups; and
- Longer term outcomes such as how microbicides will fit into a broader HIV prevention package.

Discussion

a. Efficacy Threshold

Participants discussed what minimum level of product efficacy would be required before a product should be introduced. Current efficacy trials are powered to report a minimum level of trial effectiveness of 30 percent. However, this does not mean that regulators or decision-makers will automatically regard this as sufficient to introduce a product. There was no consensus among participants. Some felt that the limited options currently available to women should justify the introduction of even limited efficacy products for use with existing methods. Others argued that it would be difficult to market a limited efficacy product, particularly if it is also coitally dependent. It was noted that MC – a "once only" method - has been shown to reduce female-to-male-transmission by approximately 60% in three clinical trials, and yet responses by countries and programme managers to integrate circumcision into HIV prevention strategies have been tepid. Cultural norms and the potential for behavioural disinhibition (i.e. an increase in risky behaviour because of assumed protection of a method) may also be factors that would also impact microbicide introduction.

Participants also discussed the challenge that decision-makers and women would face in comparing microbicides to other prevention methods. Microbicide trials provide information on a combined measure of product efficacy and individual adherence under clinical trial conditions. Few other HIV prevention methods have been assessed under similarly rigorous conditions, making direct comparison inequitable to microbicides. It is also not possible to say whether use under trial conditions is likely to be more or less consistent than regular everyday use, with participants making arguments for both scenarios. On the one hand, trial participants are provided with intensive counselling which would tend to increase their adherence. On the other hand, there is a probability they received a placebo in the trial which would tend to decrease motivation to adhere.

Although no consensus was reached on whether a low efficacy microbicide should be introduced, it was agreed that countries would need to make decisions for themselves with the assistance of strong technical advice. It was also agreed that

the lower the efficacy of the product, the harder advocates would need to work to convince policy-makers to introduce a product.

b. Cost

Very little data is available on product cost, which will vary considerably depending on the formulation of the microbicide. Equally, costs for products currently in trials are likely to reduce if production volumes increase and economies of scale can be realised. There is also little information about supporting programme costs although it is likely that microbicides would be introduced within existing programmes. Several participants felt that the price to the consumer should be the same as the cheapest condom or free. This will require long-term government or donor subsidy. A strong point was made that people and policy-makers currently undervalue prevention. However, this may change as the costs of AIDS treatment programmes become unsustainable due to rising HIV transmission rates.

c. Donor Funding

Microbicide introduction will require significant funds to build health system capacity, train providers, generate demand and purchase and distribute products. Donors could help reduce manufacturing costs by committing to purchase large quantities, thereby supporting scale-efficiencies in manufacturing. Several participants recalled the early discussions on AIDS treatment where the costs were seen as impossibly high. However, the global community has overcome these challenges to implement treatment programmes on a large scale.

d. Distribution

It was agreed that if the product is prescription-only, then the delivery is more likely to be clinic-based in the initial stage, with such services largely provided by the public sector in sub-Saharan Africa (although there are other significant providers, including the mission and social marketing sectors). It may also be possible to provide prescription-only products through community-based distribution programmes. The difficulty of controlling informal delivery of prescription-only products through drug shops in many developing countries was noted. However, in general, there was agreement over using a mixed service delivery approach where possible, in order to maximize the number of women reached.

e. Comprehensive Prevention Approach

One participant suggested conducting a strategic analysis of overall prevention needs and designing early introduction programmes focusing on comprehensive prevention approaches rather than a specific product. The particular method mix should be determined based on local needs and preferences. Others argued that such integration at every service point would not be feasible, particularly given differences in target constituencies and the different support needs for each method. For example, MC services target men and require a surgical procedure, whereas microbicides would target women and do not require surgery. However, there was general agreement that there should be integrated messaging on a hierarchy of risk approach (with condoms deemed most effective, followed by microbicides, MC and other partially effective technologies) that allows people to make choices in their specific circumstances.

3.2. Working Group B: Informing Country Decision-Making

When clinical trials for successful microbicides are concluded, they will provide evidence of microbicides' efficacy in reducing HIV-infection among women who use them. This evidence is essential in order to move ahead with licensing and other regulatory authorization for manufacturing and marketing microbicides for use in developing countries. However, policy-makers in these countries are likely to require additional information to guide their decisions as to whether or not to implement microbicides as part of their HIV prevention programme. This information needs to be based on credible data. In addition, legitimate decision-makers' concerns specific to future microbicide introduction and scaling-up will need to be addressed. These concerns may include: affordability (to governments and users); reliability and consistency of supply; existence of international financing mechanisms (such as GAVI for vaccines); and the impact of introducing microbicides on health systems and existing HIV prevention programmes.

Discussion

The key criteria for decision-makers were seen as regulatory approvals, introduction programme planning, integration into existing services, transparency and the need for advocacy that is independent of trial sponsors. The importance of building constituencies and sustaining momentum at country-level following trials was stressed.

a. Cost

Cost was highlighted as a key concern. Policy-makers would eventually require information not only on the cost of the product, but also the costs of introducing and delivering it and its relative cost-effectiveness to other products. The cost to both governments and to consumers will need to be clarified. Decision-makers will also want to know what the commitment of the international community is to supporting countries that wish to introduce microbicides. Participants discussed the option of establishing an international mechanism designed to mobilise resources and provide technical support and funding for microbicide introduction.

b. Advocacy

The group discussed the importance of identifying the types of policy-makers and opinion leaders to address in seeking support for microbicide introduction. These included: official health leaders in the Ministry of Health and other relevant ministries at national, provincial, district and sub-district levels; politically elected leaders at different levels; health workers; the medical and research community; NGOs; community leaders; and religious leaders. Different decision-makers should be approached by appropriate messengers. Country-based researchers can also play a role in communicating the potential of microbicides, although this should ideally be supplemented by community advocates who are recognised as being independent from clinical trials. Technical agencies, such as WHO and UNAIDS, were highlighted as being particularly important.

Participants concluded that approaching national policy-makers does not have to wait until the microbicide introduction phase. Early engagement provides opportunities to build trust and set expectations appropriately. This can then provide a stronger basis for later consensus on microbicide recommendations and messages. It was noted that earlier engagement to familiarise policy-makers with the female condom could have established a more supportive environment for introduction.

However, it is important for dialogue to be grounded in progress in the development of actual microbicides candidates. Concern was raised that advocacy messages can sometimes be interpreted as implying that microbicides already exist. While mobilising support is important, attention must be paid not to prematurely raise expectations.

Microbicide clinical trials can provide an important opportunity to build community and country stakeholders' understanding of and support for microbicides. It is important to keep country policy-makers and programme managers abreast of progress in clinical trials as they will be among the most influential constituencies as decisions around introduction are made. Building familiarity with, and confidence in the robustness of clinical trials can provide a basis for future mobilisation.

4. AREAS FOR FUTURE RESEARCH

The meeting identified the following main areas for future research:

- Gatekeepers – from policy-makers to researchers- will play an influential role in the success of microbicide introduction programmes. *Identifying key gatekeepers and keeping them informed as research progresses will therefore be important.* A microbicide focal person within the government can serve this role.
- *The role of normative agencies such as WHO will be critical.* It will be important to identify the criteria such agencies will use to issue recommendations and technical guidance on microbicide introduction.
- Unlike vaccines which can be channelled through the Global Alliance for Vaccines and Immunizations, UNICEF and WHO, microbicides do not yet have clearly defined mechanisms or lead agencies. *Identifying the appropriate international financing and technical cooperation mechanisms for microbicides will be important.*
- In a rapidly evolving HIV prevention environment, it will be difficult to attribute population-level impact to any one method. *Identifying appropriate objectives and indicators to measure the success of initial microbicide introduction programmes will therefore be important to avoid disappointment.*
- It was noted that microbicide clinical trials, as they are currently designed, will measure the effectiveness of a product (the impact of its inherent efficacy combined with the consistency of its use by women in the trial). This information is not easily comparable to available data for existing HIV prevention and reproductive health technologies, such as condoms. *However, it will be necessary to develop tools and guidance that can inform country decisions on the minimum criteria for microbicide introduction, on characteristics such as effectiveness and level of coital dependence.*
- Clarity is needed about how to communicate potential population-level benefits of microbicides (which drive public health discussions) and benefits to individual women (which will drive their own choices about use). *Messaging that is appropriate to different audiences will be therefore be needed.*

Appendix 1: Preliminary Results of the WHO Multi-Country Study on Gender, Sexuality and Vaginal Practices (GSVP Study)

Dr Adriane Martin Hilber, Institute of Social and Preventive Medicine
Dr Matthew F Chersich, International Centre for Reproductive Health

The aims of the session were: to summarise existing evidence, and preliminary results of the WHO Multi-country Study on Gender, Sexuality and Vaginal Practices (GSVP Study); and discuss areas for future work. The potential association between vaginal practices and HIV acquisition, as well as implications of vaginal practices for microbicide safety, efficacy and acceptability were discussed.

Summary of GSVP Study

The study consisted of a Stage 1 (qualitative research) and Stage 2 (household survey) component, assessing all genital practices (not only intra-vaginal practices). Thailand, Indonesia, South Africa, Mozambique and Kenya participated. It was funded by Australian AID (Mozambique), Australia National Research Council, Flemish Government via UNAIDS, Ford Foundation, IPM, Rockefeller Foundation and WHO.

The Stage 1 and 2 components have been challenging to implement as few precedents existed to follow or build upon. A complex survey instrument had to be developed and cross-cultural adaptation and translation were required. Outputs of Stage 1 included classification of vaginal practices and the development of a measurement framework, as well as extensive qualitative and ethnographic details about women's vaginal practices, products used, men's perceptions of practices, and detail on the meanings, motivations, and effects of the practises on women's health. Population-level data from Stage 2 were being analysed at the time of this meeting and two countries (Mozambique and Kenya) were awaiting survey.

The research indicates that practices vary widely, but in all surveyed countries a combination of commercial and traditional products are used, and many products are heavily marketed. Practices vary by product, timing and frequency and are commonly linked to desired effect (or motivation for use). Therefore, documenting women's motivation for vaginal practices is key. Primary motivations are hygiene, health and sexual satisfaction for male partners. Motivations associated with sexual pleasure for male partners underlie existing gender power inequalities –a manifestation of women's economic and emotional dependence on male partners and fear of losing their partner to another woman.

Vaginal practices have also been hypothesized as facilitating heterosexual HIV transmission. The vaginal environment at the time of HIV exposure likely has an important influence on risk of acquisition. Vaginal practices markedly influence the vaginal environment, hence the potential risk for HIV acquisition and impact on the efficacy of microbicides. Overall, available evidence is limited and comparability across studies is difficult with diversity in settings and populations studied. Broad categorisation of vaginal practices in previous studies may decrease potential for detecting harm from specific practices. Evidence that Nonoxynol 9 and, possibly, cellulose sulphate products, are harmful does suggest that other chemicals could also cause vaginal inflammation or disruption.

Discussion

The potential for adverse chemical reactions between microbicides and other vaginal products warrants consideration. The efficacy of microbicides may be reduced if intravaginal cleansing lowers the vaginal concentration of the product. Randomisation of participants in clinical trials should ensure that performance of vaginal practices among sub-groups of a study population should not unduly bias results. However, improved measurement and control for such practices may still be necessary in future microbicide trials. It is also important to ensure that the candidate product and placebo don't elicit different vaginal practices.

Data collected during microbicide trials could be used to improve knowledge of vaginal practices. However, particular care is needed to ensure validity of tools and methods for measuring vaginal practices. Interviewing in community settings, appropriate selection of interviewer and probing, such as in focus groups, can improve data quality. Using views of women in the community, and cultural adaptation of terms in the questionnaire is essential. Asking questions requires sensitivity and nuance.

Women participants in microbicide trials are counselled not to insert other products in their vagina, apart from the study product. The perception, from microbicide trials to date, is that women modify their vaginal practice behaviours during the course of the trial. However, risks or potential benefits of different practices are largely unknown. Caution is needed with blanket messages that inserting products into the vagina is harmful as this may adversely affect microbicide perspectives and use.

It is important to further investigate which, if any, vaginal practices have harmful effects. However, it is likely to be very difficult for one study to investigate the relationship between vaginal practices and HIV, STI and bacterial vaginosis. Strengthening links between vaginal practices and microbicide research offers many synergies. For example, a secondary analysis of existing data from microbicide trials may provide insights on the longitudinal effects of vaginal practices.

Laboratory methods could be used to investigate potential chemical reactions between vaginal products that women insert and microbicide candidates, within a plausible range of temperature and pH. As an alternative, a cohort study could investigate effects of highlighted in existing evidence as potentially harmful, such as abrasive practices. Data from the GSVP household survey on self-reported symptoms and consequences following vaginal practices could assist in identifying which products/practices to investigate further. Men also need to be involved in this research as their perceived pleasure is the primary motivator for practices and hence a key determinant of their continuation. The potential for a programmatic interaction between microbicide and vaginal practices could be investigated. However, it was also noted that the primary focus of microbicide trials is to test the product's effectiveness and safety, and research questions that do not directly contribute to this goal should be considered as secondary.

Appendix 2: Acceptable Access- The Nexus of Social Science and Advocacy

Cynthia Woodsong, RTI International
Manju Chatani, African Microbicides Advocacy Group

This discussion focused on the role of social science researchers and advocates in developing and implementing an access strategy. Social science research can be used to help identify:

- Populations to prioritize for initial introduction
- Product positioning strategies
- Optimal distribution systems
- Stakeholders who will support and resist access

Social science can serve as a powerful tool for advocates as research findings can be used to target and refine advocacy messaging. The ensuing discussion focused on the need to balance realistic expectations of distribution (limited in early stages); timing (initial availability in limited markets) and other factors, against the ethical imperative, expressed by advocates, of making the product as widely available, as quickly as possible. The critical role that advocates play in mobilizing support for new product introduction was highlighted and it was noted that an in-country advocacy base would be crucial to building political commitment and mobilizing resources to support introduction and scale-up.

Appendix 3: Agenda

Monday, July 2

Time	Topic	Chair/ Speaker
8:00 – 9:00	Registration/Coffee	
9:00 - 9:30	**WELCOME AND INTRODUCTION**	
9:00 – 9:15	Welcome	Dr. Zeda Rosenberg, International Partnership for Microbicides
9:15 - 9:30	Introduction and Housekeeping • Agenda • Objectives of this and future forums • Housekeeping	Dr. Kim Dickson, World Health Organization
9:30 - 11:00	**PLENARY SESSION I**	Chair: Dr. Elizabeth Bukusi, Kenya Medical Research Institute
9:30 – 9:50	The Dynamic HIV Prevention Landscape • Low uptake of existing technologies but commitments to scale-up • New interventions/ methods: timelines for male circumcision, diaphragm, PrEP etc • Evolution of HIV prevention: using prevention tools and understanding contexts	Ms. Emily Bass, AIDS Vaccine Advocacy Coalition
9:50 – 10:10	Strategic Approaches to New Product Introduction • WHO Strategic Framework • Male circumcision policy and programme recommendations: issues for microbicides access and introduction	Dr. Kim Dickson, World Health Organization
10:10 – 10:30	Insights and Evidence from Prior Product Introductions • Case examples of emergency contraception, female condoms, cycle beads and implants	Ms. Martha Brady, Population Council
10:30 – 11:00	Discussion on Plenary Session I	
11:00 – 11:30	Break/ Tea and Coffee	
11:30 - 13:00	**PLENARY SESSION II**	Chair: Dr. Badri Saxena, Centre for Policy Research
11:30 – 11:50	Update on Microbicide Development • Overview of microbicide science • Current status of the research	Dr. Zeda Rosenberg, International Partnership for Microbicides
11:50 – 12:05	Discussion	
12:05 – 12:25	'Access' to Microbicides: Key Challenges and Possible Scenarios • Key dimensions of 'access' • Microbicide specific challenges	Mr. Saul Walker, International Partnership for Microbicides
12:25 – 12:40	Discussion	
12:40 – 13:00	**GENERAL DISCUSSION – PLENARY I AND II**	Facilitator: Dr. Badri Saxena, Centre for Policy Research

Time	Topic	Chair / Speaker
13:00 – 14:00	Lunch (hotel restaurant)	
14:00 – 17:00	**WORKING GROUP PARALLEL SESSION** *Tea and coffee will be available throughout the session*	
14:00 – 14:30	Instructions	Dr. Youssef Tawfik, International Partnership for Microbicides
14:30 – 17:00	Session A: Designing Early Introduction Programs Possible Issues: ▪ After completing Phase III studies, what key preparatory steps need to be undertaken before the start of an early introduction (pilot) program? ▪ Who are the decision-makers in selecting countries for early introduction programs? What should the decision-making criteria be? ▪ Who are the actors involved in designing and implementing microbicide early introduction programs? ▪ What is the role of the product developer, donors, national policy-makers, and technical agencies such as WHO and UNAIDS? ▪ What are the key steps and decision-making points in moving from early introduction to scale-up?	Facilitator: TBD Speaker: Dr. Michael Thuo, Management Sciences for Health
14:30 – 17:00	Session B: Informing Country Decision-Making Possible issues: ▪ Who are the key country-level decision-makers? ▪ What are the key decisions that they will need to make for the initial introduction of microbicides? ▪ Should/how will broader constituencies be consulted? ▪ What information will policy-makers need to make these decisions? ▪ Who would be the most effective "messengers"? ▪ What should the role of international organizations and donors in supporting country-level decision-making be?	Facilitator: Dr. Youssef Tawfik, International Partnership for Microbicides Speaker: Ms. Jayne Waweru, John Snow, Inc.
17:00 – 19:00	Free Time	
19:00 – 21:00	Forum Dinner (Sitar restaurant, Grand Regency Hotel)	

Tuesday, July 3

Time	Topic	Chair / Speaker
9:00 – 11:00	**REPORT BACK ON PARALLEL SESSIONS**	Chair: Dr. Morenike Ukpong, Nigerian HIV Vaccine and Microbicide Advocacy Group
9:00 - 10:00	Report back and discussion on Session A	Discussant: Ms. Wanjiku Kamau
10:00 – 11:00	Report back and discussion on Session B	Discussant: Dr. Elizabeth Madraa, National AIDS Commission, Uganda
11:00 – 11:30	Break/ Tea and Coffee	
11:30 – 13:00	**SUMMARY AND NEXT STEPS**	Chair: Mr. Guy Stallworthy, Bill and Melinda Gates Foundation
11:30 – 11:45	Rapporteur Feedback	Ms. Carol Bradford
11:45 – 12:30	Discussion	
12:30 – 13:00	Next Steps • Issues for Microbicides 2008 conference • Meeting report • Post meeting dialogue	Co-Chairs: Dr. Kim Dickson. World Health Organization *and* Mr. Saul Walker, International Partnership for Microbicides
13:00 – 14:00	Lunch (hotel restaurant)	
14:00 – 17:00	**OPTIONAL SESSIONS (OPEN TO ALL)**	
14:00 – 15:30	**Prevalence and Implications of Vaginal Practices for Vaginal Microbicides: Preliminary Results of the WHO Multi-country Study on Gender, Sexuality and Vaginal Practices (GSVP Study)** A synthesis of the evidence to date on vaginal practices and their implications for vaginal microbicides will be summarised to facilitate a discussion of research gaps and planned initiatives to fill those gaps.	Dr. Adriane Martin Hilber, Institute of Social and Preventive Medicine *and* Dr. Matthew F Chersich, International Centre for Reproductive Health For further information, please contact amartinhilber@ispm.unibe.ch.
15:30 – 17:00	**Acceptable Access: Lessons Learned from Social Science** This session will explore current knowledge and identify key issues that must be addressed (e.g. in early introduction studies) to ensure that access to microbicides will be socially acceptable. Some of the questions explored will be: ▪ Is there consensus on who should have access to microbicides? ▪ What groups are likely to support or block microbicide access? ▪ How and where should microbicides be made accessible? ▪ How should microbicides be described? ▪ How should the potential for covert use be accommodated?	Dr. Cynthia Woodsong, RTI International For further information, please contact cwoodsong@rti.org.

Appendix 4: Participant List

	Title	First Name	Last Name	Organization	Position	Country	Email
1	Dr	Ian	Askew	Population Council	Director, Frontiers in Reproductive Health Programme	Kenya	iaskew@pcnairobi.org
2	Ms	Anurita	Bains		Consultant	Canada	anurita@sympatico.ca
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5	Ms	Carol	Bradford		Consultant	UK	Cebradford@aol.com
6	Ms	Martha	Brady	Population Council	Programme Associate, International Programmes Division	USA	mbrady@popcouncil.org
7	Dr	Elizabeth	Bukusi	Center for Microbiology Research, KEMRI	Co-Director, RCTP	Kenya	ebukusi@csrtkenya.org; ebukusi@u.washington.edu
8	Ms	Manju	Chatani	African Microbicides Advocacy Group	Coordinator	Ghana	manju_chatani@yahoo.co.uk
9	Dr	Mathew	Chersich	International Centre for Reproductive Health	Epidemiologist	Kenya	matthewf.chersich@icrhk.org; chersich@doctors.org.uk
10	Dr	Kim	Dickson	World Health Organization	Medical Officer, Women and Youth	Switzerland	dicksonk@who.int
11	Ms	Bernice	Heloo	African Microbicides Advocacy Group/ Society for Women Against AIDS in Africa	SCM/President	Ghana	contact@swaainternational.org; bernhel@hotmail.com
12	Dr	Adrianne	Hilber	University of Berne	Senior Research Collaborator	Switzerland	amartinhilber@ispm.unibe.ch
13	Ms	Pauline	Irungu	Global Campaign for Microbicides	Programme Associate	Kenya	pirungu@path.org
14	Dr	Samuel	Kalibala	International AIDS Vaccine Initiative	Regional Representative	Kenya	skalibala@iavi.org
15	Ms	Wanjiku	Kamau	Consultant		UK	wanjiku@wkconsulting.org
16	Dr	Stanley	Luchters	International Centre for Reproductive Health	Field Director	Kenya	stanley.luchters@icrh.org
17	Dr	Pamela	Lynam	JHPIEGO/ Kenya	Country Director	Kenya	plynam@jhpiego.net
18	Dr	Elizabeth	Madraa	National AIDS Control Programme Uganda		Uganda	emadraa@yahoo.com
19	Ms	Florence	Manguyu	International AIDS Vaccine Initiative	Consultant-Senior Advisor	Kenya	fmanguyu@iavi.org
20	Mr.	Thomas	Marwa	JHPIEGO/ Kenya	HIV Technical Officer	Kenya	tmarwa@jhpiego.net
21	Dr	Jessie	Mbwambo		Consultant	Tanzania	jmbwambo@intafrica.com
22	Ms	Catherine	Montgomery	London School of Hygiene and Tropical Medicine	Research Fellow	UK	Catherine.Montgomery@lshtm.ac.uk
23	Ms	Feddis	Mumba	EngenderHealth	Country Manager	Kenya	fmumba@engenderhealth.org
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	Title	First Name	Last Name	Organization	Position	Country	Email
25	Dr	Alex	Ngaiza	Population Services International	HIV/ AIDS Manager	Tanzania	angaiza@psi.or.tz
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27	Ms.	Daisy	Nyamukapa	UNFPA		Zimbabwe	Daisy.Nyamukapa@undp.org
28	Mr.	Kingsley	Obom-Egbulem	Journalists Against AIDS	Information Resource Officer	Nigeria	kingsley@nigeria-aids.org; kingsley257@yahoo.co.uk
29	Mr.	Walter	Odhiambo	Marie Stopes International	Social Marketing Manager	Kenya	walter.odhiambo@mariestopes.or.ke
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31	Ms	Heidi	Quinn	Marie Stopes International	Senior Programme Support Manager - Africa and Latin America	UK	heidi.quinn@mariestopes.org.uk
32	Ms	Vimala	Raghavendran	International Partnership for Microbicides	Policy Associate	USA	vraghavendran@ipm-microbicides.org
33	Dr	Zeda	Rosenberg	International Partnership for Microbicides	Chief Executive Officer	USA	zrosenberg@ipm-microbicides.org
34	Dr	Badri	Saxena	Centre for Policy Research/Microbicides 2008	Honorary Research Professor / M2008 Conference Co-chair	India	bnsaxenacpr1@yahoo.co.uk
35	Mr	Guy	Stallworthy	Bill and Melinda Gates Foundation	Senior Programme Officer	USA	Guy.Stallworthy@gatesfoundation.org
36	Dr	Youssef	Tawfik	International Partnership for Microbicides	Director, Policy and Advocacy	USA	ytawfik@ipm-microbicides.org
37	Dr	Michael	Thuo	Management Sciences for Health	Head, RPM Plus Programme	Kenya	thuo@swiftkenya.com
38	Dr	Morenike	Ukpong	Nigeria HIV Vaccine and Microbicide Advocacy Group	Coordinator	Nigeria	toyinukpong@yahoo.co.uk
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44	Dr	Damien	Wohlfahrt	EngenderHealth	Programme Support Leader, Eastern/Southern Africa	Kenya	DWohlfahrt@engenderhealth.org
45	Dr	Cynthia	Woodsong	RTI International	Senior Scientist	USA	cwoodsong@rti.org
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