OPTIONS CONSORTIUM: Optimizing Prevention Technology Introduction On Schedule

Core Implementers: FHI 360, Wits RHI, AVAC

Primary Partners: Avenir Health
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Dapivirine Ring Modeling Literature Review

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Prepared by: Jack Clancy, AVAC
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Summary

The aim of this literature review is to identify the scope of completed dapivirine ring and microbicide modelling to date, to inform modeling work OPTIONS intends to undertake in 2017. This body of work will feed into a broader dapivirine ring investment case the OPTIONS team intends to complete as open label ring studies progress and product rollout nears. This review focuses primarily on dapivirine ring-specific models from Imperial College, Applied Strategies, and the Cleveland Clinic/University of Pittsburgh; however, it also includes more general microbicide models that may be useful to consider, including the model created by the London School of Hygiene and Tropical Medicine.

Findings – Dapivirine focused modeling summary of findings

There have been relatively few models created specifically for the ring, and none that have been adjusted or published findings since the results from the Ring Study and ASPIRE were released. Below details high level findings from each of the ring models as well as general trends across models.

The **Cleveland Clinic** conducted dapivirine ring focused modeling analysis for South Africa in 2016. It compares the combined scale-up of ART, medical male circumcision (MMC), and the dapivirine ring to a baseline scenario of only ART and MMC. At the baseline, 80% of HIV+ individuals with a CD4 count <500 would be on ART, and 80% of men would receive MMC by 2017. Overall, this model found that the dapivirine ring, "could have considerable impact on HIV prevention at compelling economic value when prioritized to women by age and could decrease drug resistance, even if adherence is modest" (Glaubius, 2016).

The model simulates four scenarios on top of the baseline: un-prioritized to women aged 15-54, age-prioritized to women 15-24 years old, age-prioritized to women aged 20-29, and risk-prioritized to female sex workers (FSW). Each scenario looked a high adherence (95%) and low adherence (50%) outcome. From an impact standpoint, 15% overall ring coverage prioritized to women aged 20-29 averted the highest number of infections. Rollout to 80% of FSW averted the fewest infections, but required less than 0.1% overall coverage which may be more realistic. The model demonstrates the importance of adherence, predicting the ring will prevent 86-106% more infections if high adherence occurs compared to low adherence outcomes. From a cost effectiveness standpoint, rollout to FSW exhibited the greatest amount of cost savings. Cost per infection averted decreased by 52-57% in high adherence situations compared with low adherence situations.

The model from **Imperial College** similarly looked at rollout and scale-up in South Africa in 2016. As with the Cleveland model, Imperial found that the ring "could substantially and cost-effectively generate health among women in South Africa". The findings of this model stress that highly targeted rollout to those at greatest risk, such as sex workers, young women, and those with multiple partners, will have greatest impact in South Africa.

Imperial's model focuses on variable outcomes based on 25%, 50%, and 75% efficacy levels, noting the success of the product will vary significantly depending on ultimate efficacy of the product. However, "even a low efficacy IVR product with uniform coverage across all women is considered borderline cost-effective" which is important as we now know the results of ASPIRE and the Ring Study were underwhelming, demonstrating 27% and 31% effectiveness. The model acknowledges that "real world factors" such as end user demand, product preference, and adherence tendencies are largely uncertain at this point, but critical to understand. As answers to these questions become clearer, the modeling will become more relevant and usable.

The **Applied Strategies** model, built in 2015, provides a framework to project out impact and cost-effectiveness with data across 35 countries. The model compares 3 scenarios: introduction of oral PrEP only, introduction of oral PrEP and the dapivirine ring, and introduction of oral PrEP, the dapivirine ring, and a long acting injectable. It is malleable; users are able to adjust/edit the following inputs: Country scope, prevention demand (demand cascade by country, facility, year), market share and price, product adherence, cost, and health impact. The model generates outputs for: prevention demand, product demand, cost, health impact, and cost-effectiveness. It differs from the Cleveland Clinic and Imperial work in that it is not a dynamic model, meaning it did not actually model changes in HIV incidence over time or interaction of different factors.

This model is available for use and has collated a large amount of data into the manipulable spreadsheet. Applied Strategies utilized UNAIDS data on incidence, transmission, and treatment to model health impact, and IPM provided data on procurement prices to understand costing. The model concludes that, given its base assumptions, "annual demand for the 1 month dapivirine ring is expected to range from 50M-125M rings by 2035" (Applied Strategies). It also assumes that the dapivirine ring will increase the prevention product marketplace by 5% when introduced alongside oral PrEP, but that the incremental cost effectiveness of the 1-month ring will be high, at $149,000/case averted and $630,000/death averted. The model suggests follow on analyses should focus on targeting higher risk populations as well as the benefits of a 3-month vs. 1-month ring (Applied Strategies).

All studies highlighted a strong need to prioritize populations for rollout, but differ on which populations should receive top priority (depending on model assumptions and rollout goals). The ring modeling conducted thus far has emphasized that cost-effectiveness will improve with a highly targeted rollout. For the ring to have impact it will be crucial to identify and effectively reach these sub-populations, as resources for rollout and sustained supply will be limited. The Imperial College model highlights sex workers, young women, and those with multiple partners as "most at-risk", but further segmentation within those groups will be needed, and will differ from country to country. The Cleveland Clinic model specifies ring rollout will be most cost effective if age-prioritized to women ages 20-29, and risk-prioritized to female sex workers. Both models are able to segment broadly but more detailed data will allow for better accuracy in future models.

End user demand, adherence, and product preference will have large effect on impact and cost-effectiveness of the ring. Sufficient research does not exist to understand how demand, adherence, and product preference will materialize as the ring is rolled out. The Imperial College research states that the ultimate success of the dapivirine ring will be determined by, "user demand and adherence, and new and forthcoming data on women's preferences will be critical for determining its use across different settings". While we do have initial adherence results from the Ring Study and ASPIRE, the follow on open label studies will further illuminate imperative data. AVAC conducted a literature review on social and behavioral findings from ring studies, which details completed, ongoing, and planned studies to this point. The review found that, with the conclusion of the Ring Study and ASPIRE, there has been a host of research released on social and behavioral implications for dapivirine ring use. This "first cut" at understanding the preferences and needs of users, their partners, and communities has illuminated trends and questions to be investigated further, but is not enough to comprehensively inform rollout of the product when approved for widespread use. Continued close monitoring of the follow on open label studies for ASPIRE and the Ring Study, as well as others mentioned, will help shape an actionable and accurate investment case for the dapivirine ring.

Study Parameters

Measures/includes	*Total*	*Ring-Specific*	*General Microbicide*
Impact	**11**	**3**	**8**
Cost/cost-effectiveness	**6**	**3**	**3**
Drug resistance	**2**	**1**	**1**

Population Focus

Population	*Total*	*Ring-Specific*	*General Microbicide*
Women	**5**	**3**	**2**
FSW	**5**	**3**	**2**
Generalized	**6**	**0**	**6**
Heterosexual Couples	**2**	**0**	**2**
Young Women	**3**	**3**	**0**

Geographic Focus

Region	*Total*	*Ring-Specific*	*General Microbicide*
Sub-Saharan Africa	12	3	9
South Africa	7	3	4
Other	6	1	5
North America	1	0	1
Asia	2	0	2

Generalized	2	0	2

Gaps in existing modeling – Questions to investigate further to inform OPTIONS modeling and investment case

1. What is the projected health impact of adding the ring to the current available suite of prevention and treatment options?
2. How will ring impact vary when other prevention options are introduced, scaled-up, or scaled-down?
3. How will ring introduction impact existing prevention options, and what will total market share be?
4. How will adherence levels effect cost-effectiveness and impact?

How OPTIONS modeling will build on other modeling conducted to date

Dapivirine specific models have begun to identify trends and important areas for further exploration; however, they are not sufficient to adequately prepare for product approval and scale-up. Because of this, OPTIONS is conducting impact and cost-effectiveness modeling of the ring using multiple scenarios in selected high prevalence countries. Whereas the Applied Strategies model looked at overall ring uptake, the OPTIONS modeling, using the GOALS model, will allow the contexts to be changed in each scenario: ring uptake by subpopulation (high risk vs. general population), different levels of adherence for different populations and different conditions, and in context of large/small PrEP uptake or antiretroviral treatment uptake. In this way, the model will help to answer the question: What would be the impact and cost-effectiveness if I added ring to the suite of HIV interventions? Using a variety of assumptions about uptake of different interventions, the model will project what might happen if, for instance, ring is introduced *and* treatment is also scaled up, or if ring is scaled up alongside PrEP scale up. This type of modeling has been used to help countries prioritize HIV programming. The OPTIONS modeling will be dynamic, allowing exploration of multiple scenarios.