Mathematical models and health economic aspects of microbicides

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Purpose of review

This paper reviews the literature of mathematical modeling and health economics of microbicides. These analyses can aid decision-making for microbicide development, usage in a population, and allocation of limited resources to maximize HIV prevention.

Recent findings

Mathematical models initially forecasted the large positive impact of moderately effective microbicides. These models also predicted that condom replacement would not be a significant concern in most populations. Modeling studies have also considered biophysical interactions of HIV with microbicide gels, the impact of rectal microbicides among gay men, and behavioral and epidemiological factors that are likely to be important. Recent innovative modeling has shown that second-generation microbicides, containing antiretroviral drugs, could lead to high rates of drug resistance when used in public health interventions even if resistance is not detected during clinical trials. Limited analysis of microbicide cost–effectiveness has occurred to date. We provide an analysis of microbicide cost–effectiveness and find that it is highly dependent on HIV incidence in the population and microbicide dosing frequency.

Summary

Modeling has been influential in forecasting the potential public health benefit of microbicides and in warning of possible risks. Models of microbicide cost–effectiveness provide important perspectives in guiding access to future microbicides.

Keywords

cost–effectiveness, health economics, mathematical modeling, microbicides

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Introduction

Mathematical models of infectious disease transmission are useful for understanding complex systems and to predict future epidemic trajectories based on different intervention or resource allocation strategies. Mathematical models applied to HIV epidemics have been particularly influential in public health decisions [1–9]. Any discussion of public health policy should include careful evaluation of potential risks. The utility of mathematical modeling in health policy is most evident when epidemiological or health costs and benefits require balancing or when it must be decided how to focus and administer resources; an obvious extension to mathematical modeling is cost-effective analysis, which evaluates the financial cost of an intervention with respect to its expected impact. Modeling and cost-effective analyses are most influential when conducted proactively to guide product development, program development or policy decisions to a more beneficial or valuable outcome.

Microbicides are products designed for the prevention of sexual transmission of HIV [10–12]. Vaginal microbicides will provide an alternative protection option for women whose partners are unwilling to use condoms, and could be applied in addition to condoms. Condoms and male circumcision are highly effective preventive interventions but they are not widespread, and a safe and effective HIV vaccine has proved elusive [13,14]. Consequently, preexposure prophylaxis (PrEP) and microbicides are currently considered as promising biomedical interventions for preventing HIV transmission. Initial microbicide candidates were designed around nonspecific modes of action (intended to inhibit viral entry). They were surfactants that shear HIV membranes and sulfonated polyanions that rely on binding between the weak positive charge on the membrane surface proteins of HIV and the negative charge of the microbicide molecules to inhibit cell entry [15,16] but their efficacy to date has not been found in clinical trials [17,18]. A newer group of microbicide products that use more targeted mechanisms is now in clinical development and there is more reason for optimism surrounding their effectiveness. Thus, it is an appropriate time for mathematical models to evaluate the potential impact of microbicides.

Mathematical modeling of microbicides

The first mathematical models of microbicides did not include modes of action but simply forecasted the possible impact of a product if it had certain efficacy. The model developed by Watts and Vickerman [19] received large attention. Many papers, reports, and presentations have quoted their result that '2.5 million HIV infections would be avoided by the use of a 60% effective microbicide by 20% of the eligible population'. Nevertheless the people who cite the result largely neglect the underlying assumptions of the simple model. This result has, however, been influential in promoting sponsorship and development of microbicides. This work was extended to develop a static model to compare how different combinations of condom and microbicide use affect individual risk of HIV and STD infection [20].

There is concern that the introduction of microbicides could lead to replacement of condoms and thereby microbicides could increase HIV risk. Three groups have addressed this concern. Both ourselves [21] and Foss *et al.* [20] have used risk equations, with differing emphases [22], and Karmon *et al.* [23] used a simplified dynamic approach [24]; all analyses have predicted that microbicides could substantially reduce the risk of HIV acquisition and condom replacement will not be a significant concern in populations in which condom use is low. These analyses have explored the break-even threshold in which sexual disinhibition increases HIV risk and shown that the licensure of microbicides could result in increased risk for people who currently have high condom use if there is significant condom replacement. These analyses did not consider the direction of transmission between men and women, which may have resulted in slight underestimation of the effect of condom replacement [25]. Nevertheless the central focus of discussions surrounding this issue should be on the clinical efficacy of microbicides [26]. The overall effectiveness of a microbicide will depend on its coverage in a population. Our modeling has also shown that once a moderately efficacious microbicide is licensed, promoting high usage would have greater impact on reducing risk than developing microbicides with higher efficacies [21].

A key initiative for developing an effective microbicide is to provide a female-controlled protection option. Rectal microbicides, however, may also be beneficial for reducing HIV transmission among men who have sex with men (MSM). Breban *et al.* [27] developed a model to describe transmission dynamics in a gay bathhouse. Similar to the heterosexual modeling analyses, they found that even moderately efficacious microbicides could be very effective prevention tools for reducing HIV incidence in MSM.

Vickerman *et al.* [28] explored the behavioral and epidemiological factors that are likely to be important in determining the impact of a microbicide. They used a deterministic ordinary differential equation model, fitted to epidemiological data in two African settings, and showed that microbicides could have a greater relative impact on HIV incidence in less generalized HIV epidemics than in regions of high HIV prevalence.

Second-generation vaginal microbicides, containing antiretroviral drugs (ARVs), are now being tested for efficacy in phase III clinical trials. The first trials of this microbicide class contain dapivirine (TMC120), which belongs to the nonnucleoside reverse transcriptase inhibitor (NNRTI) class of ARV [29•] and tenofovir, which is a nucleotide reverse transcriptase inhibitor (NRTI). Other ARV-based microbicides are in earlier trial phases [12,30–34]. PrEP is a similar intervention to ARV-based microbicides for preventing HIV transmission using oral rather than intravaginal delivery of the ARV and is currently being tested in clinical trials [35]. It is hoped that PrEP and ARV-based microbicides will be effective; however there is concern that, if used by HIV-positive people, they may select for the emergence of drug-resistant strains of HIV for the class of ARV in the products, which reduces future therapeutic options [36,37•]. These drug-resistant strains can also be sexually transmitted. The most extensive mathematical modeling of microbicides to date surrounds the clinical trials and potential population-level impact of these second-generation microbicides. This modeling analysis involved constructing a dynamic transmission model of a phase III clinical trial of ARV-based microbicides and showing that planned trial designs of testing all participants monthly could mask the true resistance risks of these products and, therefore, enable high-risk microbicides to pass clinical testing [38•]. A mathematical model of heterosexual transmission was also parameterized to predict the epidemiological impact of wide-scale usage of ARV-based vaginal microbicides for different coverage and adherence levels and estimate potential levels of drug resistance that may emerge in a population due to ARV-based microbicides [38•]. These modeling results also indicate that although microbicides will be used by women to protect themselves against infection they are actually likely to result in greater reductions in incidence and lower drug resistance levels for men than for women. This analysis highlights the importance of establishing surveillance systems for regular management and monitoring of users of ARV-based microbicides.

Mathematical modeling can provide valuable contributions at other levels of microbicide development. Geonnotti *et al.* [39] developed a spatio-temporal model to simulate the biophysical interaction between HIV in semen and the topical microbicide coating applied on the

lining of a woman's vagina. Their findings suggest that microbicide formulations can function not only as vehicles to deliver functional drugs, but also as physical barriers to viral penetration at postcoital coating thicknesses of approximately 100 μm.

Cost–effectiveness of microbicides

Cost–effectiveness analysis can bring substantial value to the field of microbicide development. First, cost–effective analyses are used to guide funding decisions on a societal or population level by third-party financial sponsors of healthcare [40]. Prospectively establishing the willingness-to-pay thresholds for a successful microbicide by potential sponsors such as the World Bank, national governments of developing countries, Pepfar, and USAID, can assist developers in better selection and design of microbicide candidates. Second, analysis of the cost–effectiveness of different strategies for employing a successful microbicide within a population can identify the best way to allocate limited financial resources for maximal HIV preventive benefit. For example, screening for cervical cancer is effective in preventing deaths from the condition, but screening annually rather than every 2 years was estimated to cost more than US$1 000 000 per life-year gained in the USA because the health gain from annual versus biennial screening is small [41]. The cost–effectiveness of implementing a microbicide-based intervention will be important in their public health assessment. Third, cost–effectiveness considerations can aid allocation of resources in manufacturing, packaging, and transporting a successful microbicide. Cost–effectiveness evaluation is particularly important for second generation ARV-based microbicides as they are likely to be more effective than first generation microbicides (their IC_{50} concentrations indicate much more potent anti-HIV effects than first generation products), but may be costly to manufacture and administer in public health programs.

Cost–effectiveness research of microbicides to date is limited, reflected by the little available in a search on *Medline* and published abstracts from the Conference on Retroviruses and Opportunistic Infections, Microbicides 2008, 2006, 2004 conferences, and World AIDS conferences. There may be several possible reasons for this. First, demonstrating proof of efficacy for microbicides has had numerous setbacks and cost–effectiveness models may have appeared premature. Second, various organizations have indicated their support for microbicide demand as an encouragement to nonprofit developers. For example, World Bank representatives publicly stated in the opening ceremony keynote address of the Microbicides 2004 Conference in London the that the World Bank will pay for effective and affordable microbicides. Third, there is no benchmark threshold of acceptable cost–effectiveness of microbicides to use in interpreting model output. In developed economies, a cost–effectiveness of US$50 000 per year of life saved has been used as a benchmark threshold of adequate societal value gained for paying for a new health technology [42], but this threshold is not applicable in more resource-constrained environments. Fourth, the different categories of microbicide compounds [43] will have unique cost–effectiveness profiles. For example, the cost of second-line ARV regimens, should resistance develop to first-line regimens, may be a consideration for some microbicides [44].

Much can be learned from the cost–effectiveness models for other HIV prevention and treatment options, such as models for HIV vaccines [45–49]. A model of a partially effective HIV vaccine given to adolescent girls in South Africa reported that a vaccine costing US$20 per dose could save the South African government US$120 million over 10 years [48]. A pediatric HIV vaccine that cost US$5 per dose introduced into the Expanded Immunization Programme would cost US$3.4 per disability-adjusted life year gained [48]. The repeated dosing with microbicides, however, compared with a few doses of vaccines changes the cost–effectiveness.

HIV vaccine models can be adapted to investigate microbicide cost–effectiveness by considering microbicides as a special case of vaccines for which the duration of effect is several hours per dose instead of 5–20 years for vaccines. Some vaccine models have assessed country-specific strategies for rolling out limited initial vaccine supply, such as priority vaccination of sex workers, youth, or high prevalence areas [46].

Several models have shown that antiretroviral therapy (ART) for HIV-infected individuals is cost-effective [50–54]. For example, the provision of ART in Thailand was estimated to cost US$736 per life year saved with first-line drugs and US$2145 per life year if second-line drugs are included [55]. Provision of ART with prophylaxis in Côte d'Ivoire was estimated to cost US$620 dollars per life year gained [56]. The cost–effectiveness of ART among South African women who had received single-dose nevirapine to prevent mother-to-child transmission was US$800 per life year saved for nevirapine-based ART, US$4400 for lopinavir–ritonavir-based therapy, and US$2300 per life year saved for lopinavir–ritonavir followed by nevirapine-based ART [44]. The number needed to treat to prevent a case of AIDS or death, however, is substantially different for ART provided to HIV-infected individuals versus microbicides provided to uninfected individuals.

A cost–effectiveness analysis for microbicides

We provide a cost-effective analysis of microbicides, based on a simple but novel model. Consider a population

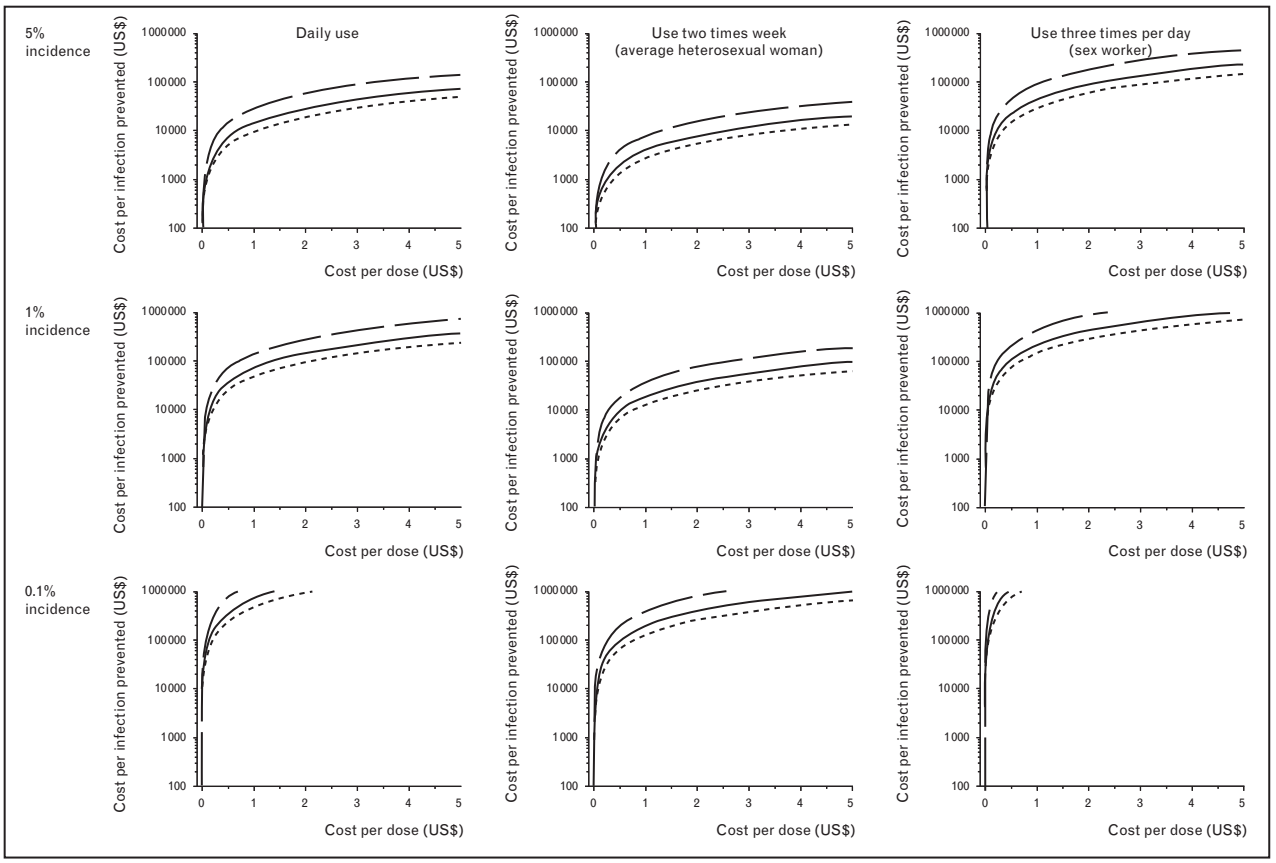
of N people. If the annual incidence of HIV is λ and the efficacy of the microbicide is ε, then $N\lambda$ people are expected to become infected each year without the microbicide and $N\lambda(1-\varepsilon)$ with the microbicide, assuming 100% adherence. Then the number of infections prevented per year is $N\lambda - N\lambda(1-\varepsilon) = N\lambda\varepsilon$. If the cost per dose is US$$c$ and n doses are required per person per year, then the total cost over all N people, ignoring supply chain and other indirect costs, is Ncn. Then,

$$\text{the cost per infection prevented} = \frac{cn}{\lambda\varepsilon}.$$

Given that prevention of HIV infection is equivalent to approximately 30–40 life-years saved, scaling the cost per infection prevented by 30 is a conservative estimate of the cost per life-year saved. We explored a range of values for several variables that may influence cost–effectiveness. Figure 1 shows three levels of product efficacy (25%, 50%, and 75%), annual population HIV incidence (0.1%, 1%, and 5%), and dosing frequency: daily, twice weekly (e.g., precoitally for an average heterosexual woman), and three times daily (e.g., precoitally for an average commercial sex worker). The model identified HIV incidence as a strong driver of cost–effectiveness. For example, a microbicide that is 50% effective requiring daily use with a US$1 cost per dose has a cost–effectiveness of US$730 000, US$73 000 and US$14 600 per infection prevented in populations with 0.1%, 1% and 5% incidence, respectively. This corresponds to costs per life-year saved of $24 333, $2 433, and $487 respectively. Dosing frequency is also a strong driver of cost–effectiveness. In a population with 5% incidence, a 50% effective microbicide that costs US$1 per dose has a cost–effectiveness of US$14 600, US$4160 and US$43 800 per infection prevented for daily, twice weekly, or three times daily posology, respectively (or $487, $139, and $1460 per life-year saved). Therefore, microbicides costing US$1 per dose are likely to be highly cost-effective.

The effectiveness of a microbicide is a moderate driver of cost–effectiveness. Microbicides will be most cost–effective in regions of high incidence and when the required dosing frequency is low. One debate in the microbicide field has focused on whether daily or pericoital

Figure 1 Cost per infection prevented versus the cost per dose



The cost per infection prevented versus the cost per dose for dosing frequencies of daily use, use two times per week, or use three times per week and for incidence rates of 0.1%, 1%, and 5%. In each case the effect of microbicides that are 25% (long dash curves), 50% (solid curves), or 75% (short dashed curves) effective are shown.

application of tenofovir gel will provide greatest efficacy when used by women at high risk of infection from migrant laborer partners who return home infrequently [29•,57•]. From a cost–effectiveness perspective, trading less frequent application for lower efficacy is likely to enhance cost–effectiveness.

Conclusion

Mathematical modeling has been influential in promoting microbicide development and in providing warnings about potential drug resistance in the general population post-licensure. Modeling of microbicide cost–effectiveness is an underresearched area that could yield valuable insights for microbicide development and access. Willingness to pay elicitation from payers would guide target costs of viable microbicides, thereby guiding the posology and selection of microbicide candidates. Our analysis shows that microbicides are generally cost effective, but cost–effectiveness is highly dependent on HIV incidence in the population and microbicide dosing frequency.

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