Workshop Summary:

Scientific Evidence on Condom Effectiveness

for Sexually Transmitted Disease (STD) Prevention

June 12-13, 2000

Hyatt Dulles Airport

Herndon, Virginia

EXECUTIVE SUMMARY

Background

Sexually transmitted diseases (STDs), including HIV, are common, important, and preventable causes of morbidity, mortality, disability, lost-productivity, and health care costs. In the United States, more than 65 million individuals are living with an STD, the majority of which are incurable viral infections. Approximately 15 million new sexually transmitted infections occur annually in the U.S. In the United States, approximately 493,000 individuals have died from AIDS, and 800,000-900,000 people are living with HIV disease. Many sexually transmitted infections can cause adverse pregnancy outcomes including miscarriages, stillbirths, intrauterine growth restriction and perinatal (mother-to-infant) infections. Some STDs can cause infertility or lead to ectopic pregnancy among women and one, the human papillomavirus, can cause cervical and anogenital cancer. Furthermore, other STDs facilitate HIV transmission.

The Problem and the Process

Primary prevention of STD infection is an important health priority. Unfortunately there are no STD vaccines, except for hepatitis B vaccine, and topical microbicides to prevent STDs are not available. Beyond mutual lifelong monogamy among uninfected couples, condom-use is the only method for reducing the risk of HIV infection and STDs available to sexually active individuals.

Recently, a number of Federal agencies sponsored a workshop to answer the following question: "What is the scientific evidence on the effectiveness of latex male condom-use to prevent STD transmission during vaginal intercourse?" This workshop was attended by 180 persons, and the data from numerous peer-reviewed published studies were discussed. Following the workshop, a panel of 28 experts worked to develop this report.

The sessions included review of published information on the properties and user patterns of the male latex condoms for vaginal intercourse and included data from studies on pregnancy prevention. Focused research studies have documented the high effectiveness of condoms for prevention of pregnancy. The data associated with condom use in eight specific STDs were considered in detail, including HIV infection, gonorrhea, chlamydial infection (including gonococcal and chlamydial pelvic inflammatory disease), syphilis, chancroid, trichomoniasis, genital herpes, and genital HPV infection and associated diseases (i.e. cervical dysplasia, cervical cancer and genital warts).

The meeting was not intended to make public health policy recommendations regarding the role of condoms in HIV/STD prevention policy and programs.

Assessment of the Data

In general, the Panel found the published epidemiology literature to be inadequate to definitively answer the question posed to the workshop participants. Most studies reviewed did not employ a prospective design, which is the optimal method to assess the effectiveness of condoms in preventing infection.

Conclusions on STDs Transmitted by Genital Secretions

The published data documenting effectiveness of the male condom were strongest for HIV. The Panel concluded that, based on a meta-analysis of published studies "always" users of the male condom significantly reduced the risk of HIV infection in men and women. These data provided strong evidence for the effectiveness of condoms in preventing HIV transmission in both men and women who engage in vaginal intercourse.

The Panel also concluded that the consistency of findings across four epidemiological studies of gonorrhea indicated that the latex male condom could reduce the risk of gonorrhea for men.

The strongest evidence for potential effectiveness of condoms on other STDs transmitted by genital secretions (i.e. gonorrhea in women, chlamydial infection and trichomoniasis) was the laboratory-based studies on the properties of the male latex condom and the strength of the evidence for condom use reducing the risk of HIV transmission in men and women and gonorrhea in men. The Panel concluded, however, that because of limitations in study designs there was insufficient evidence from the epidemiological studies on these diseases to draw definite conclusions about the effectiveness of the latex male condom in reducing the transmission of these diseases.

Conclusions on Genital Ulcer Diseases

The Panel agreed that the published epidemiologic data were insufficient to draw meaningful conclusions about the effectiveness of the latex male condom to reduce the risk of transmission of genital ulcer diseases (genital herpes, syphilis and chancroid).

Conclusions on HPV

For HPV, the Panel concluded that there was no epidemiologic evidence that condom use reduced the risk of HPV infection, but study results did suggest that condom use might afford some protection in reducing the risk of HPV-associated diseases, including warts in men and cervical neoplasia in women.

Summary

The Panel stressed that the absence of definitive conclusions reflected inadequacies of the evidence available and should not be interpreted as proof of the adequacy or inadequacy of the condom to reduce the risk of STDs other than HIV transmission in men and women and gonorrhea in men. To definitely answer the remaining questions about condom effectiveness for preventing STD infections will require well-designed and ethically sound clinical studies.

Workshop Summary:
Scientific Evidence on Condom Effectiveness for STD Prevention

1.   Introduction

Sexually transmitted diseases (STDs), including the human immunodeficiency virus (HIV)/AIDS, are important and preventable causes of morbidity, mortality, disability, and associated lost-productivity and health care costs. One in five adults in the United States has an STD (170). In the United States, approximately 450,000 individuals have died from AIDS, and 800,000-900,000 people are living with HIV infection. Approximately 15 million new sexually transmitted infections occur annually in the U.S. Many go undiagnosed, and therefore untreated. The health repercussions of STDs, particularly undiagnosed infections, can be serious. Asymptomatic infections, which can result in unknown transmission of STDs, are important factors in perpetuating STD/HIV infections. Many sexually transmitted infections can cause adverse pregnancy outcomes including, but not limited to, miscarriage, still birth, intrauterine growth restrictions, and perinatal (mother-to-child) infections. Some STDs are associated with infertility among women and one, the human papillomavirus, can cause cervical cancer among women. In addition, studies have shown that both ulcerative and non-ulcerative STDs promote HIV transmission by augmenting HIV infectiousness and HIV susceptibility. Multiple prospective studies have estimated this risk to be between 2 and 5 fold (178).

STDs can be prevented. Current prevention/risk reduction strategies include, abstinence, mutual monogamy with an uninfected partner, use of condoms and engaging in sexual activity that does not result in the transfer of bodily fluids or cell-to-cell transmission.   There are no marketed microbicides or vaccines (with the exception of hepatitis B vaccine) for the prevention of STDs, although research to develop them is underway. All STD prevention and risk reduction strategies involve the complex interplay of biological, behavioral, social and structural factors. These issues have been elucidated in the Institute of Medicine report on STDs, *The Hidden Epidemic* (118), and the recent IOM report on HIV prevention, *No Time To Lose* (144).

2.   Process: Scope of Workshop

On June 12-13, 2000, four government agencies (U.S. Agency for International Development, Food and Drug Administration, Center for Disease Control and Prevention, National Institutes of Health) responsible for condom research, condom regulation, condom use recommendations, and HIV/AIDS and STD prevention programs, co-sponsored a workshop to evaluate the published

evidence establishing the effectiveness of latex male condoms in preventing HIV/AIDS and other STDS. [1]

Representatives of the sponsoring agencies and outside experts were asked to work as a panel to review and discuss the existing literature and write a report. The expertise of the panel members included STDs, genitourinary tract anatomy, contraception, condoms, behavioral science, epidemiology, medicine, and public health. This report was developed by the panel members. The names and affiliations of the 28 panel members are listed in Appendix A.

The workshop examined only peer-reviewed literature because these studies have been subjected to independent scientific evaluation prior to publication. Based on literature searches and papers identified by the speakers, discussants, meeting attendees and panel members, 138 peer-reviewed papers, published on or before June 2000, were compiled and reviewed. From this selection, the individual presenters determined which papers to consider based on their assessment of the quality of the evidence contained within the papers. Presenters varied in their criteria for inclusion or exclusion and, in general, the Panel's deliberations were focused on the papers deemed sufficient for inclusion by the individual presenters. Because the workshop was structured to examine the level of protection afforded by condom use for individual STD pathogens, presenters responsible for reviewing and summarizing the data for each infection generally excluded studies that presented outcomes for multiple infections in aggregate. The reader is referred to the bibliography for a more complete view of the issues discussed at the workshop. Additionally, for those interested in a broader discussion, a tape recording of the two-day meeting is available and can be ordered[2]. The bibliography appears in Appendix B and includes the reviewed papers (numbered 1- 138) as well as other papers cited in this summary (numbered 139 – 180).

The agenda for the workshop is provided in Appendix C.

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[1] The focus on the latex male condom for the prevention of HIV/AIDS and STDs during penile-vaginal intercourse reflected the predominance of the latex male condom in current condom usage, its FDA labeling for this purpose, and the preponderance of available effectiveness literature. The focus was not intended to diminish the need for research on other forms of male condoms, on female condoms, and on prevention of HIV/AIDS and STDs associated with other forms of sexual activity, such as oral or anal intercourse.

[2] Cassettes can be obtained from:
Audio Transcripts, Ltd.
3660-B Wheeler Avenue,
Alexandria, VA 22304
Conference #1561
June 12-13, 2000
Scientific Evidence on Condom Effectiveness and STD Prevention sponsored by National Institute of Allergy and Infectious Diseases

The scientific scope of the workshop was deliberately limited to three areas:

(1) The device. This workshop examined evidence only for the male condoms made from natural rubber latex. According to sales data, the latex male condom accounts for 97% of all United States condom sales (per unit).

(2) The route of infection. The workshop addressed condom effectiveness in preventing infections transmitted via penile-vaginal intercourse. The U.S. Food and Drug Administration (FDA) permits manufacturers to label latex condoms for use during penile-vaginal intercourse as follows, "If used properly, latex condoms will help reduce the risk of transmission of HIV infection (AIDS) and many other sexually transmitted diseases." Other routes of infection were not evaluated.

(3) The diseases. The workshop examined evidence related to eight STDs: HIV infection, gonorrhea, chlamydial infection, [including gonococcal and chlamydial pelvic inflammatory disease (PID)], syphilis, chancroid, trichomoniasis, genital herpes caused by herpes simplex viruses (HSV) 1 and 2, and genital human papillomavirus (HPV) infection and HPV diseases.

3.   Evaluation Parameters

Efficacy versus Effectiveness

The protection condoms afford against STDs can be examined from three perspectives, including:

(1) The product;

(2) The individual users, who may include those who use the device properly, improperly or intermittently whenever they are at risk for transmitting or becoming infected with an STD; and

(3) The population in which the prevalence of sexual behaviors, including condom use and exposure to different STDs, may vary.

Regarding the product, protection depends on the physical properties of the device, breakage and slippage rates, and the parts of the body it covers. From the perspective of the individual user, protection also depends on whether the device is used properly for every act of intercourse or, in the parlance of condoms and STDs, whether it is used "correctly and consistently." It is important to distinguish between condoms' efficacy, which is the protection that the users would receive under ideal conditions, and their effectiveness, which is the protection they provide under actual conditions of use. Efficacy depends primarily on the properties of the device, whereas effectiveness depends on the

characteristics of the device and the user. Since multiple studies were evaluated, study groups and their condom use behaviors varied. The accuracy with which condom use was defined and measured also varied from study to study.   Thus, in all the studies reviewed in this workshop, the observed relationship between reported condom use and STDs reflects both product characteristics and user behaviors that may fall short of ideal and also may not represent "typical" for the population at large. For the purpose of this report, the term "condom effectiveness" will be used to mean the level of protection against STDs when condoms are used consistently and correctly.

Methodological Issues

To make a valid empirical assessment of condom effectiveness for STD prevention, appropriate study design, accurate measurement, and appropriate analyses are necessary. The panel considered the particular methodological challenges posed by condom use studies to determine the quality of the data and to evaluate the strength of the evidence/conclusion. A variety of study designs were used in the literature reviewed and they differed in their ability to provide strong evidence of the relationship between condom use and STDs. The ideal design, a prospective randomized controlled clinical trial, has not been used in evaluating condom effectiveness because of ethical concerns associated with non-use of condoms in high-risk populations. In this design, factors that could bias results are minimized because participants are randomly assigned to treatment and control arms. All published studies reviewed in this document are observational studies, that is, participants were not assigned to use or not use condoms. Instead, the presence or occurrence of infection was compared between those who reported using or not using condoms.

Each observational design carries its own strengths and weaknesses. Prospective cohort studies collect information on events as they occur. A cohort study can provide the strongest evidence among the observational designs. To do so, this design requires following a relatively large number of sexually active participants for an extended period of time and can be quite costly. This design is also vulnerable to attrition of subjects, but errors associated with recall and selection bias can be minimized, as the cohort is assessed in real time. It can also establish the order of events (exposure, infection, disease).

Retrospective case-control studies or cross-sectional prevalence studies can be relatively more economical because individuals who have or had the disease of interest (cases) can be selected and compared with those without the disease (controls), with data collected on possible exposure and use of protective measures during previous intervals. However, these studies are vulnerable to errors in recall and selection bias. These designs also make it difficult to determine the temporal ordering of events because exposure to infection, data on condom use, and outcome are measured at the same time.

The population chosen for study, the incidence and prevalence of disease in the population, and the numbers of subjects also have important implications for a study's ability to detect significant effects and to generalize these effects to other populations. In observational studies, the ability to measure and account for differences in risk between two groups (i.e. condom users versus non-users) is critical. If such "confounders" are not taken into account, the estimate of effectiveness will be biased.

Appropriate measurement of key exposures and infection or disease outcomes is also critical. Ideally, highly specific and sensitive diagnostic techniques for detection of infectious agents should be employed. It is also essential to ascertain whether the condom was used consistently and correctly, including occurrences of slippage or breakage, during the entire period of exposure. Because direct observation and objective measurement of condom use are not possible, all studies must rely on self-reported use, a potential source of error due to recall bias.[3]

The panel's review of the existing literature on condoms and STD transmission revealed that the majority of the studies were not optimally designed to answer the specific questions posed at this workshop; as such, a number of common problems in study design were noted including:

(1) In some STD studies, clinical manifestation of disease rather than the more infection-specific diagnostic tests were used as the outcome measures in evaluating condom effectiveness. Consequently, the study designs were not optimal to ascertain all incident infections and, therefore, to address the objectives of this conference.

(2) Many studies lacked sufficient numbers of subjects to have adequate statistical power to evaluate condom effectiveness.

(3) Many studies were done in special populations, such as commercial sex workers or STD clinic patients, who are at far higher risk for infection than are other sexually active individuals. Therefore, generalizability to other populations is somewhat limited.

(4) Gender differences with respect to infectivity and susceptibility were not taken into account in many studies. For example women are more susceptible than men to gonorrhea and chlamydia.

(5) Insensitive or non-specific methods were often used to detect specific infections.

(6) Most studies did not use the optimal interview methods or questionnaires to elicit complete and accurate information, especially with regard to sexual histories and condom usage.

(7) Factors associated with the outcome disease that are also associated with condom usage can confound and bias estimates of effectiveness. Bias can either over-estimate or under-estimate effectiveness.

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[3] New tests using biological markers assessing the presence or absence of seminal fluids in the vagina after intercourse may offer the possibility of better measurements of condom use and/or effectiveness. The use of these biomarkers is promising but remains developmental.

(8) Many available studies had limited data regarding condom use in relation to exposure to infectious agents. In many, quantitation of condom use was imprecise and did not distinguish between correct and incorrect use, e.g. timing of donning of the condom during sexual activity and use of the condom during the entire sexual act. Slippage and breakage events were also not quantified and some studies measured only "ever" use and some failed to specify how condom use was measured.

(9) For most studies the ability to document exposure to disease in relationship to condom use was uncertain.

4.   Findings: The Device

The Latex Male Condom

Most male condoms are made from natural rubber latex. When used consistently and correctly and without slippage or breakage, male condoms cover the penis and will contain pre-ejaculate emissions as well as semen following ejaculation, thus protecting the female reproductive tract. Condoms also may prevent penile exposure to cervicovaginal secretions and tissues under similar conditions and use. Condom shape, thickness, and other specifications, including the latex formulation itself, have been engineered to produce a product that is placed easily (onto the penis), minimizes slippage and breakage during vaginal intercourse, and contains the collected fluids.

The FDA regulates manufacturers who sell condoms in the U.S., primarily through 510(k) premarket notification (premarket) and compliance with the Quality System Regulation (postmarket). Through premarket notification, FDA can ensure that condoms marketed in the U.S. are designed properly with appropriate specifications. As a postmarket regulatory control, the Quality System Regulation requires manufacturers to:

   (1) Employ quality assurance standards for new condom designs;
   (2) Employ validated processes in condom manufacture; and
   (3) Apply strict product release criteria to condoms.

As a quality assurance step, condom manufacturers sample each lot of finished packaged condoms and visually examine them for holes using a water leak test. FDA recognizes domestic and international standards that specify that the rate of sampled condoms failing the water leak test, for each manufacturing lot of condoms, be less than 1 in 400 (ASTM D3492 and ISO 4074) (http://www.fda.gov/cdrh/ode/oderp399.html). Manufacturers also test lots for physical properties using the air burst test and the tensile (strength) property test. These latter tests provide a measure of consistent condom quality.

The FDA also requires manufacturers to determine condom stability over time and to provide an expiration date of the condom for the labeling. This is done

using accelerated stability tests of packaged condoms at elevated temperatures. In addition, manufacturers must conduct real-time studies to confirm the expiration date (21 CFR 801.435) (http://frwebgate.access.gpo.gov/cgi-bin/get-cfr.cgi). Properly packaged and properly stored, condoms maintain their physical integrity over several years.

FDA researchers have also developed an assay for condom leakage using high concentrations of a laboratory virus (78). The laboratory virus penetration assay is not used routinely as a quality control test, but its sensitivity and relevance are arguably greater than the conventional water leakage test. Using this virus assay, FDA scientists tested many different types of male condoms and showed that condoms are highly effective barriers to virus passage with a very small chance of leakage (76, 77). Intact condoms (i.e., pass the water leak test) are essentially impermeable to particles the size of STD pathogens (including the smallest sexually transmitted virus, hepatitis B). Moreover, these studies show that fluid flow, not virus size, is the most important determinant of viral passage through a hole. Even holes many times larger than the virus impeded fluid flow such that few of the test particles passed through (78).

Applying results from the laboratory tests (12, 76, 77, 78), the hypothetical relative risk of exposure to semen, as a function of semen volume attributable to various independent condom use events, was presented and is shown in the table below. The purpose of this relative risk assessment is to model the expected degree of protection of exposure to semen afforded by condom use, condom non-use, and condom use in the events of breakage or leakage.

Hypothetical Relative Risk Model of Condom Use

Condom Use Event	Semen Exposure (Volume, averaged over event probability)	Relative Risk Compared to Non-Use
Failure to Use a Condom	3.3 ml	1.0
Condom used, but it breaks	1 ml $\times$ 2/100	0.006
Condom used, No break but has visibly detectable hole (by water leak test)	10^{-2} ml $\times$ 1/400	0.000008
Condom used, No break, No visibly detectable holes, but still passes virus	6 x 10^{-6} ml $\times$ .023	0.00000004
Condom used, no break, no leak	0.0 ml	0.0

For example, if a condom breaks during intercourse, the associated volume of fluid leaking out of the condom is estimated to be approximately one-third of the total ejaculate, i.e., about 1 ml. Therefore, assuming a 2% breakage or slippage rate during actual use, the relative risk of semen exposure from the infrequent condom breakage (compared to using no condom at all) would be .006 (1 ml $\times$ 2/100 $\div$ 3.3 ml).

Under this risk assessment, failure to use a condom would obviously result in certain exposure (1.0 probability). Conversely, condom use without breakage or slippage would reduce (if not eliminate) exposure dramatically (0.0 probability). However, and perhaps just as importantly, condom use – even in the event of breakage, leakage, or slippage – would also result in greatly reduced exposures.

It should be noted that, for many STDs, risk of infection might not be proportional to exposure to a *volume* of semen. Estimation of risk requires further extrapolation because it depends on additional variables, especially the infectious agent of interest. The concentration, infectivity, and mode of transmission of the specific STDs clearly need to be considered (12).

Conclusion

Natural rubber latex condoms for men are manufactured to conform to limits specified within consensus standards, including water leakage. Laboratory studies show that manufactured condoms meet these specifications. Other studies, based on viral penetration assays, have demonstrated that condoms provide a highly effective barrier to transmission of particles of similar size to those of the smallest STD viruses. These data also provide a strong probability of condom effectiveness when used correctly, where the etiology of STD transmission is linked to containment of pre-ejaculate and seminal fluids or barrier coverage of lesions on the penis and there is no slippage or breakage.

Condom Use Data

Condom use patterns

National surveys that monitor contraceptive behaviors among Americans have documented increases in condom use throughout the 1980s and 1990s, coincident with increased awareness of AIDS and increased prevention efforts. The largest increases in condom use have occurred among adolescents and young adults, the age groups most at risk for infection with HIV and other STDs. The National Survey of Family Growth reported that condom use among American women 15-44 years of age increased from 12% in 1982 to 15% in 1988, and to 20% in 1995 (98). Reported condom use in women is higher among those who are unmarried and younger. The trends in National Survey of Family Growth data are corroborated by data from national representative sample surveys of youths. Two surveys of young men, completed in 1988 and 1995 document that in 1988, 33% of youth ages 15-19 report always using a

condom when having sex, and in 1995 that proportion increased to 45%. In 1988 the proportion of those who had sex and never used condoms was 18.4%, while in 1995, only 9.5% reported never using condoms (112). The Youth Risk Behavior Survey (youth in grades 9-12) also documents significant increases in reported condom use between 1991 and 1997, from 55% to 62% for males and from 38% to 51% for females (180). That study reports use at the last act of coitus, but does not address correct or consistent use nor slippage and breakage. A 1990 re-interview of participants in the 1988 National Survey of Family Growth assessed the reasons for condom usage in a representative sample of 932 sexually experienced unmarried women (aged 17-44). In this group 41% reported using condoms for protection, at least some of the time, against STDs; 18.5% reported "every time" use (4).

Condom Slippage and Breakage during Use

For a condom to be fully effective, it must stay on the penis during sexual intercourse, and it must not break. However, condoms sometimes do slip or break during use. Many studies have looked at condom slippage and breakage, but most were conducted ten or more years ago and, therefore, do not represent higher quality condoms being manufactured today. Moreover, most employed methodologies led to questionable relevance or reliability of reported rates. Such methodological drawbacks included inexact definition of terminology, selection bias, study size (e.g., <100 couples; <1000 uses), populations that are less generalizeable (e.g., commercial sex workers, low STD risk, etc.), and reporting methods (e.g., retrospective surveys relying on memory of events six months earlier). None of the studies considered by the panel evaluated condom slippage and breakage rates in sexually active teenagers less than 18 years of age. Only three published articles report results from recent prospective sizeable trials of latex condoms in the U.S. and provide reliable slippage and breakage rates (44, 45, 80). Estimates of condom breakage from these studies range from 0.4-2.3%. Slippage rates from these three studies ranged from 0.6% to 1.3%. Slippage rates include both slippage during intercourse and slippage during withdrawal. The combined method failure (slippage plus breakage) is estimated at 1.6% – 3.6%.

These and other studies show that factors affecting slippage and breakage are related to user familiarity and knowledge, including user experience, selection of condom size (width), and proper use of additional (exogenous) lubricant (2, 51, 81, 123). With increased education and improved experience, one can expect condom slippage and breakage rates to decrease.

One additional drawback of all these studies is reliance on self-reports for tallying the events themselves, i.e., slippage, breakage, and use. More recently, study methodologies have provided for improved logs of coital activity to be used by study participants, as well as careful study monitoring techniques to encourage their consistent use. It is believed that this has added to the reliability of slippage and breakage rates numbers. Still, these studies may inherently be hindered by

relying on the self-assessment of study participants. Over the past 2-3 years, researchers have begun to use biological markers and postcoital testing of the vaginal pool as a potentially more objective measure of method failure. The eventual success of these efforts remains to be seen (75, 79, 129).

Overall, results from clinical slippage and breakage studies, when coupled with results from laboratory studies, suggest that condoms provide a reliable barrier for the areas covered (the penis) and touched (vaginal and cervical mucosa) and that the level of protection is greatest when used correctly.

Lessons from Pregnancy Studies

Information on consistent and correct condom use for the prevention of pregnancy has also provided valuable insights on the importance of consistent use. Approximately 3% of couples who reported using condoms consistently and correctly (considered "perfect use") are estimated to experience an unintended pregnancy during the first year of use (123), based on results of one rigorous controlled trial as well as modeling based on rates of condom breakage and slippage. In a recent well-controlled randomized clinical trial of monogamous couples using latex male condoms for contraception over six months, the pregnancy rate during "typical use" was reported at 6.3%, with a 1.1% pregnancy rate during "consistent use" (45). Most of these couples had experience using condoms. However, based on estimates from National Surveys of Family Growth (123), 14% of couples are estimated to experience an unintended pregnancy during the first year of "typical" use, a failure rate that includes both inconsistent (non-use) and incorrect use, as well as breakage and slippage. Failure rates in the second year of typical use are about 50% lower (167).

Conclusions

Condom use in the U.S. has increased over the past 20 years. Recent studies conducted in the U.S. show condom breakage rates during use to be in the range of 0.4% to 2.3%, with comparable rates for slippage. Use factors such as experience, condom size, and use of lubricant can affect condom slippage and breakage.

Information on condom use for pregnancy prevention indicates that, at least in the population described above, as condom experience and facility in use of condoms increases in couples using condoms as their primary method of birth control, unintended pregnancies decrease.

5.   Findings: The Diseases

The eight STDs addressed in this report are HIV infection, gonorrhea, chlamydial infection, (including PID caused by gonococcal and chlamydial infections), syphilis, chancroid, trichomoniasis, genital herpes caused by HSV 1 and 2, genital HPV infection and HPV diseases including genital warts, cervical dysplasia and cervical cancer. These infections span the spectrum of medical microbiology, including viral, bacterial, and parasitic infections. Each of these infectious diseases is unique; variation in transmissibility, duration of infectivity, co-morbidity, and clinical manifestations are well described. Variations in the modes of transmission and the transmissibility of the different infections will affect the level of protection that condoms can be expected to provide.

Seven of the eight STDs fall into two categories: discharge diseases and ulcerative diseases. The discharge diseases include HIV infection, gonorrhea, chlamydial infection and trichomoniasis. The infectious agents of discharge diseases are present in genital secretions (i.e., semen and cervical-vaginal fluid). In genital ulcer diseases (genital herpes, syphilis, and chancroid), the infectious agents are present in sores or ulcers; however, the infectious agents may also be released or "shed" into secretions. HPV infection cannot be classified in either category; this virus is probably transmitted via contact with infected cell surfaces in the presence or absence of fluid or tissue exchange. Organism-related factors that influence transmission include infectiousness of virus, bacterium or parasite, duration of infectiousness, and variation in infectiousness based on stage of disease.

In addition to causing symptomatic disease, most of these infections cause diseases with no symptoms (asymptomatic) or with very mild symptoms; these infections are called "silent." People who have silent infections do not seek health care and consequently, most remain undiagnosed and untreated. Not all STDs respond to treatment. The curable diseases include four bacterial infections (gonorrhea, chlamydial infection, syphilis, and chancroid) and the one parasitic infection (trichomoniasis). Appropriate treatment eliminates these infections. In contrast, the viral infections (HSV, HIV, and HPV) either persist for life (HSV and HIV) or are cleared spontaneously (approximately 90% of HPV infections). However, HSV and HIV infections may be controlled or ameliorated with anti-viral therapies.

The likelihood of spreading these infections during sexual intercourse varies. Multiple factors influence transmission, including characteristics of the infectious organism and the site(s) of infection, the health of the infected individual and the uninfected partner, the couple's sexual behaviors, and the prevalence of STDs in different populations will affect the likelihood of exposure to STDs.

A number of biologic factors, specific to the infected individual and his or her partner influence transmission rates including age, sex, and nutritional status.

Based on genetic make-up and history of previous infections, individuals may vary in non-specific defenses and specific (immune-mediated) defenses. These defenses will alter susceptibility to infection if exposed. If the person is infected, host defenses may alter that person's infectiousness by reducing the frequency of shedding of the infectious agent, the concentration of the infectious agent in secretions or lesions, and the duration of infection. Whether or not a host becomes symptomatic during infection may influence health care seeking behaviors that would also influence infectiousness.

A couple's sexual behavior is important; specifically foreplay, the types of sexual intercourse (e.g. anal and/or penile-vaginal), abrasions, the number of acts of intercourse and intercourse during menses may influence exposure and transmission rates. Importantly, the duration and perceived seriousness of the relationship and the gender roles and empowerment, will affect the use of condoms, choices of contraceptive, and choices regarding sexual monogamy.

General population factors that influence transmission rates include prevalence of infection and access to health care. The risk of transmission of infection can vary widely in observed populations because actual exposure depends upon the choice of individual sex partner and that person's risk characteristics.

To complicate matters, a change in one factor may lead to other changes that counter-act the anticipated change in risk of transmission. For example, anti-herpes therapies (e.g., acyclovir) reduce the amount of genital herpes virus that is shed in the genital tract fluids. The expectation is that the person is less infectious since these secretions may not contain much virus. However, if infected individuals do not use condoms during intercourse because they believe that they are not infectious, the rate of HSV transmission may not be reduced. In aggregate, both biomedical and behavioral factors determine whether or not infection is transmitted.

Measurement of condom effectiveness is affected by transmissibility; the relative ease of transmission in part determines how "forgiving" the method is if user- or device-failure occurs. If infection is transmitted easily, for example gonorrhea, failure to use a condom or incorrect use even one time may result in exposure and infection. In contrast, if an infection is hard to transmit, for example HIV, failure to use a condom or incorrect use may not result in infection because the probability of transmission is lower per exposure.

Infections Transmitted by Genital Secretions

With penile-vaginal intercourse, HIV/AIDS, gonorrhea, chlamydia and trichomoniasis are transmitted from infected males to uninfected females via exposure of the cervix and vaginal epithelium to semen and from infected females to uninfected males via exposure of the male urethra to female genital secretions. The effectiveness of the latex male condom in reducing the risk of infection is, in large part, dependent upon preventing exposure to fluids that may

be infectious. If used correctly and without slippage or breakage, the latex male condom contains the male pre-ejaculate and ejaculate and thus reduces the risk that the female will be exposed to these secretions. Likewise, if used correctly and without slippage or breakage, the latex male condom should adequately cover the male urethra and protect the penis from exposure to female genital secretions.

HIV (Human Immunodeficiency Virus)/AIDS

Background

In 1999, an estimated 6 million adults and children around the world were newly infected with HIV. Approximately 40,000 of these infections occurred in the U.S; 70 percent of new infections were diagnosed among men and 30 percent among women. Notably, more than 80 percent of all adult HIV infections throughout the world have been transmitted during heterosexual intercourse.

HIV is found in the blood and virtually all other body tissues and fluids. Stage of disease as well as co-infection with other STDs can increase HIV shedding in genital secretions and thereby increase risk of transmission. HIV/AIDS can be sexually transmitted by anal, penile-vaginal, and oral intercourse. The highest rate of transmission is through anal exposure. In addition, secretions from ulcerative lesions (associated with other STDs) on the penis may also be a source of infected male-to-uninfected female transmission of HIV/AIDS, and ulcerative lesions may be sites for uninfected male exposure to HIV/AIDS from infectious female secretions.

Key Research Findings on Effectiveness

HIV infection is the only STD for which formal meta-analyses have been published (28, 166). The most recent analysis by Davis and Weller (28) was evaluated. This analysis, in which only longitudinal or cohort studies were included, used the following criteria to select studies related to condom use and HIV/AIDS prevention:

(1) Sample included serodiscordant, sexually active, heterosexual couples;
(2) HIV status was determined by serology (so that exposure to HIV was known);
(3) Data collection included self report about condom use; and
(4) Study design afforded longitudinal follow-up of HIV uninfected partner.

Studies with insufficient condom use information and/or duplicate or interim reports on the same cohort were excluded.

Davis and Weller found twelve studies, which met these criteria (139, 29, 30, 150, 155, 158, 160, 161, 165, 108, 171, 173). The meta-analysis noted the direction of transmission (male-to-female, female-to-male, and unstated) and

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date of study enrollment. Condom usage was classified into the following three categories: always (100% use), sometimes, and never.

Among participants who reported always using condoms, the summary estimate of HIV/AIDS incidence from the twelve studies was 0.9 seroconversion per 100 person years. Among those who reported never using condoms, the summary estimate of HIV/AIDS incidence from the seven studies was 6.7 seroconversions per 100 person years. Overall, Davis and Weller estimated that condoms provided an 85% reduction in HIV/AIDS transmission risk when infection rates were compared in always versus never users.

Conclusions

The methodological strength of the studies on condoms to reduce the risk of HIV/AIDS transmission far exceeds that for other STDs. There is demonstrated exposure to HIV/AIDS through sexual intercourse with a regular partner (with an absence of other HIV/AIDS risk factors). Longitudinal studies of HIV- sexual partners of HIV+ infected cases allow for the estimation of HIV/AIDS incidence among condom users and condom non-users. From the two incidence estimates, consistent condom use decreased the risk of HIV/AIDS transmission by approximately 85%. These data provide strong evidence for the effectiveness of condoms for reducing sexually transmitted HIV.

Gonorrhea (Neisseria gonorrhoeae)

Background

Gonorrhea causes significant morbidity in the U.S. and around the world. Every year an estimated 650,000 cases occur in the United States and 62 million cases occur worldwide. Gonorrhea is one of two major causes of pelvic inflammatory disease (PID); the other cause is chlamydial infection. Although PID is often silent and therefore difficult to diagnose, PID is a serious disease in the upper reproductive tract of women. PID causes tubal scarring and can result in ectopic or tubal pregnancy, tubal infertility, and chronic pelvic pain. Like most other STDs, gonorrhea may cause adverse pregnancy outcomes, such as neonatal ophthalmia, with loss of vision.

Infection results from exposure to *Neisseria gonorrhoeae* in infectious cervical/vaginal secretions or ejaculate during oral, vaginal, or anal intercourse. Although the infectious dose is unknown, one ejaculate from an infected man contains approximately 6 million live bacteria (157). Although limited, data suggest an average transmission of 1 infection for every two exposures. Transmission efficiency is gender dependent. Females are at greater risk of acquisition, with 0.6 to 0.8 infections following a single exposure with an infected male. Males are at less risk (0.2) from a single act of vaginal intercourse, with cumulative risk increasing from 0.6 to 0.8 with four or more exposures (61, 172).

Among men, symptoms typically appear within 2-5 days following infection. Estimates from screening studies suggest that asymptomatic disease occurs in approximately 10% of infected men. Among symptomatic women, incubation periods vary. Asymptomatic disease occurs in 20 to 80 percent of infected women.

Three methods are generally used to diagnose gonorrhea – gram stain, nucleic acid amplification tests, and culture. However, since gram staining is not sensitive for detecting infections in women nucleic acid amplification tests, or laboratory culture are usually used to diagnose gonorrhea. The sensitivity and specificity of these two tests are extremely high (approaching 98%) (147). Gonorrhea is curable with single-dose therapy; currently cephalosporin or fluoroquinolone antibiotics are used.

Key Research Findings on Effectiveness

Key Research Findings on Effectiveness

The panel reviewed thirteen studies on gonorrhea and condom effectiveness. Four studies in men and two studies in women were deemed acceptable for assessing gonorrhea transmission. The single prospective study, among U.S. sailors having sex with commercial sex workers, demonstrated that 0% (0/29) of men who sometimes or always used condoms acquired gonorrhea compared to10.2% (51/498) of non-users; however this difference was not statistically significant (61). Two cross-sectional studies and one case-control study found between a 49-75% reduction in risk of gonorrhea among men reporting condom use compared to non-users (8, 96, 110**).** Only one of these studies (8) reported measuring consistent and correct condom use.   In this study, a 71% reduction in relative risk for gonorrhea was observed in men who reported correct condom use (4/106) compared to men reporting incorrect use (20/153). One case-control study found no significant risk reduction in gonorrhea cases when women who had ever used condoms without other methods (98/706) were compared to women who had never used condoms (126/889) during the previous three months (O.R 0.90) (6). Another cross-sectional study found a 39% relative risk reduction in gonorrhea infection comparing women attending an STD clinic who reported using condoms as a method of contraception (93/984) to those who did not use condoms, sponges, or diaphragms as a birth control method (521/4068) (105).

Two case control studies that used either pelvic inflammatory disease (PID) or tubal infertility as outcome measures were also evaluated.   Although the PID study did not distinguish between PID due to gonorrhea or chlamydia, a 55% relative reduction in the risk of PID was observed among women who had ever used a condom in the previous three months; 32/279 of women with PID reported condom use in the previous 3 months compared to 213/959 who did not have

PID (absolute risk reduction 13.7%, relative risk reduction 55%) (69). The

second study found a statistically insignificant effect on the risk of tubal infertility

when at least three months of continuous condom use was compared to non-use of condoms; 48/200 women with infertility reported three months of continuous condom use compared to 679/2538 women without infertility (absolute risk reduction 2.5%, relative risk reduction 30.5%) (25).

Conclusions

Several of the available studies on effectiveness demonstrated a protective effect of condoms for men, although they were limited either by retrospective design, inadequate measures of condom use, or small sample sizes. The panel deemed, however, that the collective strengths of these studies demonstrated that correct and consistent condom use would reduce the risk of gonorrhea for men. The available epidemiologic literature does not allow an accurate assessment of the degree of protection against gonorrhea infection in women offered by correct and consistent condom use.

Chlamydial Infection (Chlamydia trachomatis)

Background

Chlamydial infection is the most common bacterial STD in the United States, with an estimated three million new cases per year. Infections caused by *Chlamydia trachomatis* are usually asymptomatic. This disease is most common in sexually active adolescents and young adults. Chlamydia is transmitted from infected male-to-uninfected female via semen and from infected female-to-uninfected male via exposure of the male urethra to infectious female genital secretions. Chlamydia is transmitted more easily to women (179). Infected women may also transmit chlamydia to their babies during birth resulting in neonatal eye infection and/or pneumonia. Although curable with appropriate antibiotic therapy, most chlamydial infections are asymptomatic and thus go undiagnosed and untreated. Persistent infection often results in PID; common sequelae include chronic pelvic pain, tubal pregnancy, and infertility. Epididymitis in men is well documented, although other chronic sequelae in men have not been thoroughly studied.

Key Research Findings

Review of the literature revealed twelve papers (10, 38, 42, 48, 63, 91, 101, 105, 107, 110, 137, 138) that, to some degree, addressed condom effectiveness for prevention of chlamydial infection. However, virtually all twelve studies were compromised by design weaknesses (from the perspective of measuring condom effectiveness and identifying exposure to infection).

Twelve studies, six were deemed sufficient for inclusion. Three prevalence studies, two retrospective case-control analyses, and one prospective study measured the relationship of self-reported condom use and *C. trachomatis* infections. Of the three studies of infection in women, two (63, 105) failed to

demonstrate a protective effect of condoms among high risk populations including commercial sex workers in Indonesia who had ever used a condom during the previous week (63) and women attending a STD clinic in the U.S. who reported they were using condoms (105). Of the 1873 commercial sex workers, only 14% reported using condoms in the previous week. In this study 10 % of 397 condom uses and 13% of 1005 non-users were diagnosed with chlamydia. In the cross-sectional study of women attending a STD clinic, chlamydia infection was seen in 2/157 women who reported using condoms as a method of contraception and in 111/823 who did not use condoms, sponges or diaphragms as a birth control method (105). The third study among 13,204 new female military recruits found a statistically significant increase in chlamydial infections associated with self-reports of no condom use or inconsistent condom use (O.R. 1.4) (48).

Three studies, one prevalence (cross-sectional) study (137), one case-control (110), and one prospective study (138) evaluated the relationship between condom use and the risk of chlamydial infection in men. The cross-sectional study found no evidence of reduction of chlamydial infections associated with self-reported consistent condom use among 356 heterosexual men attending a London hospital clinic (137). For the subset that reported having "changed partners" in the 3 months prior to visiting the clinic, 11% of men (4/37) who reported "always" using condoms and 12% of men (7/59) who reported "never" using condoms were diagnosed with chlamydia infection. The case-control study among 4,848 men attending a STD clinic in Seattle found a 33% risk reduction among consistent condom users (which represented approximately 12% of the clinic men) compared to any other patterns of condom usage/non-usage, however this reduction was not statistically significant (110). The third study, a prospective design (138), found 0% (0/72) of men who reported always using a condom developed chlamydial infections compared to 6.3% (16/251) of men who reported sometimes or never using condoms, a statistically significant effect.

Conclusion

The one study employing a prospective design found a protective effect of condoms against female-to-male transmission of chlamydia. Other studies in men and women demonstrated either no or some protection and are inconclusive. Taken together, the available epidemiologic literature does not allow an accurate assessment of the degree of potential protection against chlamydia offered by correct and consistent condom usage.

Trichomoniasis (Trichomonas vaginalis)

Background

Trichomoniasis is caused by *Trichomonas vaginalis*, a protozoan parasite. It is responsible for an estimated 5 million symptomatic cases of vaginitis per year in

the United States and 160 million cases worldwide. In men, infection is associated with urethritis, prostatitis, and other syndromes. *Trichomonas vaginalis* is transmitted from infected males to uninfected females and from infected females to uninfected males via exposure of mucosal surfaces to genital secretions. Asymptomatic infection occurs in both men and women. Diagnosis is commonly made by direct microscopic examination of genital specimens, but this method has low sensitivity when compared with culture. As with other STDs, trichomoniasis has been associated with increased transmission of HIV/AIDS. Transmission rates for *T. vaginalis* have not been measured but are estimated to be high. The infectious dose is also unknown. Treatment with single-dose, inexpensive, oral therapy (metronidazole) results in high cure-rates.

Key Research Findings

A statistically significant reduction in trichomonas infection (30%) was reported in women attending a STD clinic who reported using condoms as a method of contraception (106/1021) compared with those who did not use condoms, sponges or diaphragms as a birth control method (525/4660) (105). Other published data employed designs that rendered them inadequate to allow evaluation of the effectiveness of condoms in preventing transmission of trichomoniasis.

Conclusions

One limited study demonstrated a 30% protective effect for women. The paucity of epidemiologic studies on condom effectiveness for trichomoniasis does not allow an accurate assessment of the reduction in risk of trichomoniasis offered by condom usage.

Genital Ulcer Diseases

In genital ulcer diseases (genital herpes, syphilis, and chancroid), the infectious agents are present in sores or ulcers. However, these infectious agents may also be released or "shed" into secretions. The potential of the latex male condom to reduce the risk of transmission, even when used correctly and without slippage or breakage, would be expected to depend on the site of the sore/ulcer or infection and the ability of the condom to fully cover the lesion.

Genital Herpes (Herpes Simplex Virus Types 1 and 2)

Background

HSV 1 and HSV 2 cause oral and genital herpes. Using HSV-2 serology as a surrogate marker, at least 45 million Americans are infected with genital herpes, with 500,000 new infections and 10 million recurrences occurring every year. Genital herpes can also increase the risk of HIV/AIDS transmission and acquisition.

Lesions on anogenital sites and surrounding areas (buttocks and thighs) are common in symptomatic infections. However, it is estimated that more than 80 percent of primary and recurrent genital infections are undiagnosed because the infections are usually asymptomatic or unrecognized. Genital herpes is transmitted from males to females by contact with infected genital skin or mucosal surfaces, including either apparent lesions or areas with inapparent infection. For the male, the penis (skin and urethra) is the genital area most often affected, but other genital areas may also be affected (145). Herpes is transmitted from females to males by contact with infectious secretions or infected genital-area lesions, which are usually vulvar, vaginal, or cervical and which may be apparent or inapparent. Viral shedding occurs in the presence or absence of symptoms. Recent studies have suggested that viral shedding can occur, on the average, 28% of days that subjects are followed; asymptomatic shedding can result in transmission (175). Furthermore, genital herpes can result in maternal-to-infant transmission of infection at delivery, which can be fatal (142).

Because other infections cause genital ulcers, the gold standard for diagnosing genital herpes is by culturing the virus from ulcers. Other diagnostic procedures that utilize samples from lesions are polymerase chain reaction and antigen detection tests. Given a history of genital lesions, if a patient is examined after lesions have healed, serological testing may help to diagnose genital herpes and to differentiate between primary or recurrent infection. Based on viral culture and/or nucleic acid detection, HSV-1 infection causes one-third of genital herpes infections, and HSV-2 infection causes two-thirds of genital infections (145).

An adequate study design to assess the effectiveness of condom use in reducing the risk of genital herpes must take into account the natural history of HSV infection, as follows:

> (1) Most people with genital HSV infection do not know they have genital herpes.
> (2) HSV causes a latent, persistent infection that reactivates and can cause recurrent disease (both clinical and subclinical).
> (3) People with genital herpes cannot always tell when the virus reactivates.
> (4) New infections can only be measured by evidence of seroconversion using accurate tests.

Key Research Findings on Effectiveness

A search of the literature revealed five prevalence (cross-sectional) studies that allowed for assessment of condom effectiveness for preventing HSV transmission. None of the studies reviewed was designed specifically to measure condom effectiveness for preventing HSV, but all did include some measure of condom use. A cross-sectional survey of 766 women in Costa Rica showed a partial protective effect (approximately a 30% reduction in herpes

seroprevalence) among women who reported their male partners ever using condoms (28.9%) compared to those reporting never using condoms (44.3%) (90). Another population-based study of 1600 randomly selected women done in Greenland and Denmark showed a non-significant relationship between HSV-2 infection among women who reported ever using barrier contraceptive methods, either condoms or diaphragms, and those that did not use barrier methods (O.R .85) (72). Two serological studies, one in 1,115 young Thai army conscripts (149) and the other a random sample of 259 women and 231 men in rural Tanzania (162) evaluated the history of condom use and its association with HSV seroprevalence. In the Thai army study, although the consistent use of condoms in the previous 3 years during sex with commercial sex workers was associated with significantly increased seroprevalence for either HSV-1 or HSV-2, (O.R.1.8), seroprevalence decreased consistently with increasing regularity of condom use (O.R. .79).   In the Tanzania study, reported rates of condom use were too low in women to examine their association with HSV-2 infection. Among Tanzanian males, the prevalence of HSV-2 was higher in men who used condoms (O.R. 2.99) but condom use among males was reported to be a marker for high-risk relationships, e.g. intercourse with sex workers. Because the study did not report data on high-risk relationships, no meaningful conclusions were drawn regarding condom effectiveness (162).   A study of 135 adolescents in juvenile detention facilities showed no relationship between regular condom use (defined as used in >50% of sexual contacts) and current HSV-2 status (156). Measurement of condom use varied widely across these studies. None of the studies assessed consistency of condom use over the entire period during which exposure to HSV could have occurred.

Conclusions

The limitations in epidemiologic study designs and the lack of primary outcome measurements found in the above studies prevented the Panel from forming any conclusions about the effectiveness/ineffectiveness of correct and consistent condom usage in reducing the risk of genital herpes infection.

Chancroid (Haemophilus ducreyi)

Background

Chancroid is a bacterial infection caused by *Haemophilus ducreyi.* It is a major cause of genital ulcer disease in many areas of the world, especially Asia and Africa. Chancroid is transmitted from infected male to uninfected female via genital-area lesions that are usually, but not always, on the penis, and from infected female to uninfected male via exposure of the penis to genital area lesions that are usually, but not always, in the vagina. Approximately 1,000 cases of chancroid are reported in the United States per year. However, because the organism is difficult to culture, it is likely that some cases are not diagnosed. In the Southeastern region of the United States, periodic outbreaks of chancroid have occurred.

In experimental models, the infectious dose is only a few *H. ducreyi* organisms, if applied to abraded skin (176). Predictably, transmission efficiency is high during sexual contact; transmission occurs in approximately 70 percent of sexual exposures (177).

If untreated, lesions may persist for up to 3 months. In patients who do not have syphilis, chancroid is often presumed to be the cause of genital ulcer disease. Since culturing this organism is very difficult, diagnosis by culture is not generally available. As a consequence, a broad-spectrum antibiotic is used to treat these patients. Like other genital ulcer diseases, chancroid facilitates HIV transmission and acquisition.

Key Research Findings on Effectiveness

A limited number of studies are available due, in part, to the low incidence of disease in the U.S. and in part to diagnostic difficulties. Only two studies are relevant to this review. In Thailand, an HIV/AIDS control program that consisted of multiple interventions including sanctions against sex workers if they did not use condoms, mass distribution of condoms, mass media campaigns and establishment of 140 new STD clinics, resulted in increased condom use among sex workers and was associated with a 23%/year decrease in chancroid cases over 4 years (53). From 1989 to 1993, there was a reduction in reported chancroid cases from 29,675 to 1,990. However, in this study the direct effect of condom use in the over-all reduction in chancroid infection was not evaluated (53). In a point prevalence study of sex workers in a chancroid endemic area of Kenya, there were less GUD cases for those who always used condoms (18%, N=28) compared to those who never used condoms (47%, N=17) (11). Since neither study included microbiological confirmation of the disease, attributing the effect of condom use to reduced risk of chancroid is not possible.

Conclusions

Although both reviewed epidemiologic studies suggest an association between condom use and the reduction in risk of chancroid infection, the lack of microbiological confirmation prevented the panel from drawing conclusions with respect to correct and consistent condom use and the acquisition of chancroid.

Syphilis (Treponema pallidum)

Background

Syphilis is a major cause of genital ulcer disease. In 1995, an estimated 12 million new cases of sexually acquired syphilis occurred globally. Following the epidemic of the 1990s, the rates of syphilis in the United States have declined steadily. Currently, the United States is experiencing its lowest rates of syphilis (2.2/100,000) since the advent of effective antibiotic therapy. However, since

1997 increases in the incidence rates have been observed in cities among men who have sex with men (e.g., Seattle, San Francisco, New York). Furthermore, the reported rate of primary and secondary syphilis among African Americans remains approximately 30 times higher that the rate among whites (148).

The infectious bacterium, *Treponema pallidum*, is transmitted easily through contact with moist, infectious lesions. The spirochete does not invade intact skin and particles of the same diameter do not pass through intact condoms. However, only a few organisms in contact with skin abrasions are required to transmit infection. Acute disease, which is communicable, includes the primary stage (ulcers) and secondary stage (various lesions that may involve skin, mucous membranes, or other tissues). The primary ulcers are often painless and can be located on/around the genitals, mouth or, perianal area. Women may have subclinical cervical/vaginal lesions. Chronic disease (after the secondary stage) can be latent or develop into a systemic illness affecting many organs. Infection during pregnancy can cause fetal death or congenital syphilis. The diagnosis of primary syphilis can be made by microscopic examination of material scraped from the ulcers or by detecting antibodies in blood. Early stages of syphilis are curable with single or multiple antibiotic injections. Secondary, latent, and tertiary syphilis are diagnosed with blood tests. The ulcers of early syphilis increase the risk of HIV acquisition and transmission.

Non-sexual transmission may occur through body fluids such as blood, lesion exudates, and breast milk. Transmission risk is greatest in the first few months of infection, but may theoretically extend up to 2 to 5 years of latency, albeit at reduced and intermittent infectiousness.

Key Research Findings on Effectiveness

There were eight reports available for the purposes of this review. These studies included case-control, cross-sectional, and ecologic designs. All of these studies were limited by inadequacy of the data on condom use, presumed limited exposure (because of low prevalence of infection), and in several, small sample sizes reduced statistical power. Two cross-sectional studies (8, 96) showed a 60-70% reduction in the prevalence of syphilis infection among condom users compared to others, although the results were not statistically significant. Both studies assessed condom use in STD clinic patients, although one study (8) compared correct and consistent use to incorrect use or no use. In this study, 1.02% of all clinic patients (36/3543) had a syphilis diagnosis compared to 0.39% (1/259) of patients who reported correct and consistent use of condoms. Pemberton (96) evaluated the distribution of STDs in males as they related to condom use. Of the 1,173 diagnoses, 51 cases of syphilis were identified. When cases were evaluated based on condom use, 0.9% (1/112) of patients who reported using a condom had syphilis compared to 2.7% (23/855) of non-condom users. A third cross-sectional study (47), showed no significant association between consistent condom use in the past year and a positive syphilis serology among transvestite prostitutes. Among those reported "always" use of condoms

there was a 72.2% (13/18) sero-positivity compared with 81.6% (40/49) of those reported "inconsistent or never" use of condoms. A fourth cross-sectional study (125) reported no association between condom users (not further specified) and syphilis serology in female commercial sex workers in Mexico City. A fifth cross-sectional study among female commercial sex workers in Indonesia found that women reporting "any condom use in the past week" had a statistically significant lower prevalence of syphilis than those reporting no condom use (8% {30/380} versus 14% {141/1006}) (63). A cross-sectional study of 693 men and women attending municipal health centers in Peru found no significant association between a history of ever-using condoms (58%) and infection with STDs (syphilis, chlamydia, or HSV-2); however, this study did not separately examine the relationship between syphilis and condom use (107). A case-control study among 144 STD clinic attendees found a statistically significant reduction (59%) in syphilis infection for persons reporting "any" versus "no" condom use in the past 3 months (39). Lastly, in an ecologic analysis of trends in syphilis and condom use among 824 commercial sex workers in Japan, a decline in syphilis infection (from 7.5% to 0.5% between 1990-1993) occurred while condom use increased (6.3% to 25.3% during the same period); however, this study did not directly assess the relationship between condom use and syphilis infection among individual women (117).

Conclusions

While most of the studies suggest a protective effect, all are hampered by design limitations. Due to these limitations, the panel found that no rigorous assessment of the degree of reduction in the risk of syphilis transmission offered by correct and consistent condom use could be made.

Non-classified modes of Transmission:

Human Papillomavirus (HPV)

Genital HPV infection cannot be classified exclusively as either an STD which is transmitted by genital secretions or which is transmitted through contact with open sores. HPV is probably transmitted through contact with infected epithelial surfaces and/or genital fluids containing infective viruses.

Background

An estimated 20 million Americans are currently infected with genital HPV (170). More than 50% of sexually active adults are estimated to have once been infected with one or more genital HPV types, significant majorities of which are subclinical, unrecognized and benign (146).

There are more than 100 different types of HPV (174), differentiated by their DNA and identified by number (e.g. HPV type 6, 11,16). A subset of specific HPV types commonly infects the mucosal epithelium of the genital tract and is sexually

transmitted.   Genital HPV types can be further separated into high-risk and low-risk HPV types. High-risk types are defined as causally associated with cervical cancer (141), as well as forms of anal/genital cancer and pre-cancerous tissue changes of the cervix (cervical intraepithelial neoplasia or CIN) (143, 146). The low- risk types cause genital warts and flat wart-like lesions of the cervix called condylomata and/or low-grade Pap smear abnormalities (dysplasia) (146). Low-risk types are rarely, if ever, associated with cancer in immune-competent individuals, although multiple types of HPV can often occur together.

The current definitive method of detecting HPV infection is laboratory diagnosis by nucleic acid detection using tests such as DNA polymerase chain reaction (PCR) or Hybrid Capture II (Digene Corp., Gaithersburg, MD). Nucleic acid (DNA) testing for HPV is far more sensitive than presumptive diagnosis of HPV infection through cytology (Pap smears) or through clinical examination (observation of genital warts, cervical condylomata, and/or cervical pathology determined through colposcopy and biopsy). Older research literature on HPV and condoms involves incomplete case ascertainment, as it relied only on cytology or clinical examination prior to availability of HPV-DNA technology.

The natural history of HPV infection in men is poorly understood (146). In women, genital HPV infections are common, but the vast majorities are self-limiting (154, 60, 146, 168). Cross-sectional studies have demonstrated that prevalent HPV infection of the genital tract can be detected in approximately 30% of sexually active adolescent girls and young women (140, 143, 151, 169). Studies on the natural history of HPV in women of this age group indicate that the majority of HPV infections (both high risk and low risk) result in transient cervical tissue changes that are spontaneously cleared. Persistent HPV infection may reflect an inability of the immune system to clear the infection; persistent HPV infection is a prerequisite to cervical disease progression (143). Studies have also consistently supported a long duration of HPV infection prior to development of cervical cancer (120, 146).

Unlike other STDs, HPV infection has not been associated with an increased risk of HIV/AIDS acquisition. However, persons already infected with HIV/AIDS appear to be at greater risk of acquiring or reactivating HPV infection (146). Further, it is reasonable to assume that the normal duration and natural history of concurrent HPV infection may be altered as HIV infection damages the immune system, leading to an increased incidence of cervical neoplasia in women (146) and anal cancers in HIV-positive individuals (164).

Genital HPV infection is transmitted primarily by sexual contact. Transmission occurs through contact with infected genital area skin or mucosal surfaces/fluids, from either apparent or subclinical lesions. HPV infection in women can occur on the cervix, vagina, vulva, inner thighs, and perianal area (146). For the male, infections can occur on the penis, urethra, scrotum, inner thighs and perianal area. Finally, genital HPV types have also been isolated from skin and nail samples of the hand in persons with genital warts (113); thus, digital transmission

of HPV may be possible. Given that HPV infections can occur in and be transmitted by areas not covered or protected by the condom, correct use without breakage or slippage of the male latex condom could at most be expected to partially reduce the risk of HPV transmission.

Key Research Findings on Effectiveness

Twenty-four papers were provided for consideration; 16 were found adequate and are discussed in this review. These include 11 case-control studies (9, 31, 56, 59, 68, 70, 85, 111, 120, 131, 134), four cross-sectional studies (1, 58, 62, 135), and one cohort study (60).

The primary outcomes that were measured in these studies differed as noted below, but include HPV infection, genital warts, low- and high-grade cervical intraepithelial neoplasia (CIN), and invasive cervical cancer.   The 16 studies listed above investigated HPV infection and/or HPV-associated disease outcomes only in women, with the exception of one study that investigated HPV prevalence and risk factors in only men (58), and one that measured genital warts in both men and women (134).

Four of these studies looked at condoms as a factor in the risk of acquiring HPV infection (60, 62, 68, 135). None of these four studies reported a risk reduction for HPV infection associated with condom use, including the one cohort study (60). Genital warts were investigated in two retrospective studies (58, 134). In both studies, investigators found that condom use provided some risk reduction from warts among men (risk reduction of 30% and 52%). The one study (134) that examined the effect of condom use on genital warts among women found no statistically significant evidence for risk reduction (risk reduction of 30%). Cervical dysplasia, carcinoma *in situ*, or invasive cancers were examined in relation to condom use in 10 case-control or cross-sectional studies (1, 9, 31, 56, 59, 70, 85, 111, 120, 131).   Of these 10, six studies reported that condom users had statistically significant reductions in risk, ranging from 39% to 80% (1, 59, 70, 111, 120, 131*).* Among the remaining four studies, two noted risk reductions that were not statistically significant (9, 31), and two found no evidence of partial protection (56, 85).

Conclusion

The Panel found interpretation of the studies on condom use and HPV infection/disease to be more difficult than for the other STDs. This is due, in part, to the conflicting evidence reported by different studies and the various different outcomes requiring evaluation.   Furthermore, most of the reviewed studies did not obtain sufficient information on condom use to allow careful evaluation of the association between correct condom use without breakage and HPV infection or disease. For retrospective studies that focused on the long-term disease outcomes, this was also complicated by the difficulty in ascertaining condom use at relevant time points (i.e., years preceding the diagnosis of disease).

The HPV data were evaluated separately for the various outcomes of interest (HPV infection, genital warts, and cervical neoplasia). There was no evidence that condom use reduced the risk of HPV infection, but study results did suggest that condom use might afford some reduction in risk of HPV-associated diseases, including genital warts in men and cervical neoplasia in women.

6.   Research Needs and Challenges

The foregoing review underscores the need to conduct better-designed studies to assess condom effectiveness for STD prevention. Such studies will continue to face complex design and ethical challenges.

Critical design elements include the following:

(1) A description of the type of condom used during each sex act. Ideally, this would include the brand, type and physical properties of condom as well as information on lubricant usage.
(2) Frequency and specificity of specific sexual acts.
(3) Frequency and specificity of condom use, including correctness of use, timing of donning and removal and any slippage and breakage.
(4) Validated and sensitive measurements (e.g. biomarkers) of exposure, infection and/or disease outcome.
(5) Prevalence of infection in the population.
(6) Selection of study population and the generalizability of this population's results to other relevant populations.

In addition, there are important, potentially confounding variables that need to be considered, such as concurrent contraceptive use, other sexual acts (besides penile-vaginal intercourse) hat may result in infection transmission, relationship characteristics (e.g., long- or short-term; single partner or not) and partner characteristics (history of STDs, injection drug use or other possible source of infection).

The choice of study design will influence the inferences that can be made from the data collected. As previously discussed, a prospective randomized design provides the strongest clinical evidence for effectiveness. However, because randomly assigning participants to a condom non-use control condition is not ethical, observational study designs must be used to assess the effectiveness of condom use to prevent STDs.

Study design issues, already complicated by the limitations imposed by an observational design, are made even more complex by the need to address fundamental ethical principles, including the following:

(1) Research participants with curable STDs must receive timely treatment. Studies of couples in which only one partner is infected with an incurable STD (e.g., HIV/AIDS or HSV) must include the best available preventive services, including provision of condoms and condom counseling to the couples.
(2) All study participants must be informed of and have access to the best available preventive measures.
(3) Because consistent condom use has been shown to reduce the risk of some STDs, research participants cannot be ethically randomized to use and non-use groups to assess the effectiveness of condoms. Withholding condoms would be similar to withholding available treatment.

There are multiple distinct challenges to designing future studies that could draw clear conclusions about effectiveness of condom use in preventing STDs. STD treatment can reduce infectiousness, making conclusions about condom effectiveness less certain and increasing the necessary sample size. Effective prevention services, including counseling and education, might increase participants' ability and intention to use condoms, perhaps moving some participants from the inconsistent-user category to the consistent-user category during the course of the study.

Conclusions

The ability to definitively demonstrate the presence or absence of a relationship between consistent and correct condom usage and the reduction in risk of STDs was significantly hampered by the lack of adequate study design in most, but not all studies under review. Exceptions to this generalization are the studies that demonstrated that the consistent use of male condoms protects against HIV/AIDS transmission between women and men. Gonorrhea transmission to men was also found to be reduced with consistent and correct condom use. Better research is necessary to adequately answer the question about condom effectiveness in reducing the risk of acquiring other STDs.

Notwithstanding numerous design and ethical challenges, it is important that robust research be pursued to ascertain the true benefits and limitations of an available risk reduction technology—latex male condoms--for preventing the transmission of STDs. At the same time, research on additional prevention technologies and behavioral interventions must also be pursued in order to advance the health of the public in the U.S. and abroad.

Appendix A

Scientific Evidence on Condom Effectiveness for STD Prevention

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Appendix B

Scientific Evidence on Condom Effectiveness for STD Prevention
June 12-14, 2000

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Appendix C

Scientific Evidence on
Condom Effectiveness and STD Prevention

Hyatt Dulles Airport
Herndon, Virginia

June 12-13, 2000

Agenda

Monday, June 12, 2000

7:30a.m.	Registration
8:15 a.m.	Chair: **Colin Pollard** Overview and Charge to the Group – **Penny Hitchcock**
9:00 a.m.	The Male Condom – **John Gerofi, Speaker; David Lytle, Discussant**
10:00a.m.	Break
10:30 a.m.	Methodological Issues – **David Kanouse, Speaker; Freya Sonenstein, Discussant**
11:30 a.m.	Chair: **Susan Newcomer** Panel Discussion
12:30 p.m.	Lunch (no-host buffet)
1:30 p.m.	Chairs: **Judith Auerbach** & **James Buehler** Overview of STDs – **Allen Ronald**, **Speaker**
2:30 p.m.	HIV Infection – **Timothy Schacker** & **Susan Weller**, **Speakers**
3:30p.m.	Break
4:00 p.m.	Gonorrhea – **Donald Orr, speaker; Jonathan Ellen, Discussant**
5:00p.m.	Adjournment

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Tuesday, June 13, 2000

8:00 a.m.	Chairs: *JoAnn Luoto* & *John Santelli* Chlamydial Infection – *Edward Hook, Speaker; Richard Stephens, Discussant*
9:00 a.m.	Trichomoniasis – *Jane Schwebke, Speaker; John Krieger, Discussant*
10:00 a.m.	Break
10:30 a.m.	Genital Herpes – *Lawrence Stanberry, Speaker; Timothy Schacker, Discussant*
11:30 a.m.	Other Genital Ulcer Diseases (Syphilis and Chancroid) – *George Wendel, Speaker; Stanley Spinola, Discussant*
12:30 p.m.	Lunch (no-host buffet)
1:30 p.m.	Chair: *Jeff Spieler* HPV infection – *Robert Burk, Speaker; Laura Koutsky, Discussant*
2:30 p.m.	Chair: *Heather Miller* Open Discussion: The Condom; the Methods; the Diseases.
3:30 p.m.	Break
4:00 p.m.	Chair: *Allan Hildesheim* Answered and Unanswered Questions; Research Needs.
5:00 p.m.	Adjournment