This document provides a summary of the presentations, deliberations of the expert consultations and recommendations that emerged from the conference. It is anticipated that the journal supplement will be published in early 2005. Slides from authors’ presentations are available as read-only files at http://www.igh.org

Updates


Dr. Kevin DeCock from CDC-Kenya provided an overview of the history of public health surveillance for HIV and AIDS and a discussion of the current status of surveillance in generalized epidemics. Historically HIV and AIDS surveillance began in the United States in 1981. The first case definition of AIDS was “a disease, at least moderately predictive of a defect in cell-mediated immunity, occurring in a person with no known cause for diminished resistance to that disease.” While this definition reflects the limited understanding of the disease at that time, it allowed for characterizing affected groups, risk factors and modes of transmission. The AIDS case definition was changed successively in the United States in 1985, 1987 and 1993 to incorporate laboratory testing for HIV and to better capture severe morbidity associated with HIV infection. Other reasons were to simplify reporting, to be consistent with clinical practice and to better reflect the spectrum of HIV disease in minorities, women and injection drug users (IDU).

Following the development of the HIV antibody test, a meeting was held by WHO to develop an AIDS case definition for surveillance in Africa. At that time it was assumed that serological testing would not be possible on a widespread basis, and consequently, a clinical definition was developed. This Bangui case definition for AIDS was proposed in 1985 and required the presence of two major symptoms and one minor one,* which has subsequently been expanded to include additional indicator diseases and HIV antibody testing, when available. The increased availability of HIV testing and the growing recognition of the importance of tuberculosis in AIDS, led to a change in the African case definition in 1994 that included using the Bangui definition in areas without HIV testing and an expanded definition with HIV testing and one indicator condition. However, AIDS case reporting in generalized HIV epidemics suffers from a variety of limitations, including underreporting. Nonetheless, it does have some modest utility, primarily for documenting AIDS in a country or region and providing limited information on demographics and risk groups. In the developed world, the combination of active AIDS case finding, the ability to link registries and the strength of vital statistics systems has allowed monitoring of AIDS-specific mortality. However, weak vital statistics systems in most of the developing world will preclude such linkages.

* Major signs include weight loss greater than 10% of body weight, chronic diarrhea for more than one month and prolonged fever for more than one month. Minor signs include persistent cough, generalized pruritic dermatitis, history of Herpes zoster, oropharyngeal candidiasis, chronic progressive or disseminated Herpes simplex and generalized lymphadenopathy.
To reduce reliance on AIDS incidence as the primary proxy for HIV incidence, the United States instituted a family of unlinked anonymous seroprevalence surveys in 1988 that included patients with sexually transmitted infections (STI), IDUs, women of reproductive age, prisoners, students, military recruits and Job Corps entrants. These surveys had the primary advantage of eliminating non-response bias because participants had leftover serum from syphilis serologies tested anonymously and did not have to consent to testing. WHO issued guidelines on sentinel surveillance in 1990, and since then, unlinked anonymous seroprevalence surveys of women attending sentinel ANCs have become the lynchpin of HIV surveillance in much of the developing world and specifically in countries with generalized epidemics. In addition at various times and in various countries sentinel surveillance has also included blood donors, military recruits and personnel, patients attending STI clinics, commercial sex workers (CSW), tuberculosis patients and hospitalized patients. UNAIDS and WHO have used data from ANC seroprevalence surveys to estimate the prevalence of HIV infection among 15- to 49-year-old adults in countries with generalized epidemics.

Recently, population-based surveys such as the Demographic and Health Survey (DHS) in Kenya, Mali and Zambia, which have included HIV testing (or DHS+), have provided lower estimates of adult prevalence than estimates derived from ANC-based sentinel serosurveillance (Table 1). In Kenya there was close correlation between prevalence in DHS (6.7%) and ANC sentinel surveillance (9.4%), and there were consistent trends in women by urban and rural location. However, the measured male prevalence in DHS (4.5%) was lower than expected with a male-to-female ratio of 1.9:1, resulting in an estimate of 1.0 to 1.8 million infected Kenyans, substantially lower in comparison to earlier ANC-based estimates. However, there were likely problems with response bias as the response rate was only 70%.

<table>
<thead>
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<th>ANC sentinel surveillance</th>
<th>DHS survey</th>
<th>Difference (%)</th>
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<tbody>
<tr>
<td>Kenya</td>
<td>9.4%</td>
<td>6.7%</td>
<td>-28.7%</td>
</tr>
<tr>
<td>Mali</td>
<td>2.1%</td>
<td>1.7%</td>
<td>-19%</td>
</tr>
<tr>
<td>Zambia</td>
<td>21.5%</td>
<td>15.6%</td>
<td>-27.4%</td>
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Data on AIDS-related mortality have been difficult to obtain in developing countries. There are some “population laboratories” that can provide data on births, deaths, migration and orphans. One site in Asembo, Kenya, has documented life expectancy in men and women and has measured the impact of HIV by tracking the number of orphans. However, in general these data are lacking in Africa.

The expansion of VCT represents a potential additional data set that can be used to estimate adult HIV prevalence. Unfortunately these data are even more biased than ANC sentinel surveillance or population-based surveys with higher prevalence rates largely due to sicker patients seeking diagnosis.

Historically, HIV incidence was estimated from back calculation models derived from AIDS incidence, cohort studies or measurement of seroconversion rates among persons serially tested for HIV. However,
the widespread availability of successful therapy has decoupled the link between incident HIV infection and incident AIDS, severely limiting the utility of AIDS incidence data for modeling. Newer methods, including special studies using CDC’s serologic testing algorithm for recent HIV seroconversion (STARHS or “detuned” assay) in 1998,3 have been used to estimate HIV incidence in limited settings. A key strength of STARHS is that incidence can be calculated from a single specimen. There is hope that the assay will be used to establish incidence estimates, detect foci of ongoing HIV transmission and identify the leading edge of the epidemic. Efforts are underway in the United States to link HIV reporting with STARHS to calculate a national HIV incidence estimate. However, there are technical problems with the detuned assay, including the lack of validation on non-subtype B HIV-1 infections, making it unsuitable at this time for use on a large scale in all parts of the world.

Several recommendations were made:

- Avoid collection of unnecessary data
- Focus on data quality and communication of results
- Use multiple approaches (“triangulation”)
- Focus at multiple levels – on HIV infection, advanced HIV disease, death, impact and orphans
- Collect data on HIV testing and care and begin surveillance for ARV resistance
- Use focused behavioral surveillance, for instance, on youth

With regard to seroprevalence surveys:

- Strengthen ANC-based sentinel surveillance
- Invest in population-based HIV surveys
- Develop methods to compare and reconcile the data between the two
- Continue unlinked anonymous testing and explore how high participation in PMTCT programs needs to be for the data to be representatives

With regard to measuring incident infections:

- Conduct serial seroprevalence surveys in young people to get insight on HIV incidence
- Continue efforts to conduct cohort analyses

With regard to measuring burden of disease:

- Use WHO expanded case definition consistently
- Conduct immunologic testing of persons with HIV infection
- Calculate the minimum AIDS incidence and prevalence
- Doing better tuberculosis cases reporting in concert with routine diagnostic HIV testing to provide a method for achieving AIDS case reporting. This is particularly appealing as tuberculosis registries have greater completeness than AIDS registries in Africa and are therefore easier to strengthen.

With regard to mortality surveillance:

- Undertake special studies should to assess the rates and proportions of HIV-related deaths. These should include sentinel testing of cadavers for HIV and following cohorts of HIV-treated patients, such as the CDC HIV Outpatient Study (HOPS) in the United States.
- Make additional efforts to monitor pediatric surveillance as a measure of the success of the efforts to prevent mother-to-child transmission.
Although better surveillance data are needed, there is a wealth of data currently that has, unfortunately, not been translated into action. It is important that as HIV surveillance improves to keep in mind the interface between data and policy, particularly prevention policy, and the obligation to use fully the data collected.

Dr. Timothy Brown of the University of Hawai‘i East-West Center discussed surveillance in low-level and concentrated epidemics. Surveillance in low-level and concentrated epidemic situations began with the publication of WHO’s field guidelines for first-generation surveillance in 1989 and emphasized early warning by measuring the prevalence of HIV infection in key groups and by monitoring trends over time. Second-generation surveillance, begun in 1997, seeks to combine several data streams, including AIDS case surveillance, HIV seroprevalence surveillance, STI surveillance and behavioral surveillance, into a comprehensive data stream (Figure 1). The fundamental idea of second-generation surveillance in low-level and concentrated epidemics is to tailor surveillance to meet the local situation, focusing on locally relevant groups and on new infections and risk behaviors. It stresses the use behavioral data as markers of the future direction of the HIV epidemic that could theoretically allow pre-emptive action to be taken prior to increases in infection. Underpinning the theory of second-generation surveillance is the idea that existing and new epidemiologic and behavioral data will be analyzed in an integrated fashion and lead to a better understanding of the epidemic.

Figure 1. Second-generation surveillance.
However, the reality of how well the goals of second-generation surveillance in low-level and concentrated epidemics have been met is less than ideal. An evaluation team from UNAIDS and WHO in 2000 examined HIV serosurveillance systems in terms of the frequency and timeliness of data collection, the appropriateness of the populations surveyed, the consistency in sites and groups studied and the extent to which relevant adult populations were covered and representative of the risk populations. The evaluation found that serosurveillance systems were fully implemented in 47 of 167 countries, partially implemented in 51, and poorly implemented or not implemented at all in 69.

Similar problems exist with regard to collecting appropriate behavioral data. UNAIDS and WHO are in the process of evaluating behavioral surveillance systems, and preliminary results with reveal serious data gaps in our knowledge of HIV risk behaviors in countries with low-level and concentrated epidemics. While two-thirds of Asian countries have begun behavioral surveillance, only half conduct surveys in MSM or IDU. This is a notable lack given the continuing transmission among IDU and a growing body of evidence of high HIV infection levels among MSM. In Latin America and the Caribbean, where MSM have been heavily affected by HIV, only one-fourth of countries conduct behavioral surveillance in female CSWs, MSM or IDUs. In East Europe and Central Asia, one half of the countries conduct surveillance in CSW and MSM. In North Africa and the Middle East, one half conduct behavioral surveillance in female CSW but only one-quarter in MSM and IDU.

Several notable issues have arisen in behavioral surveillance in low-level and concentrated epidemics. First, access to key populations is limited. One of the most common reasons for a data gap is difficulty inherent in accessing key stigmatized or extra-legal populations such as, MSM, IDU and CSW. In many places the national surveillance system simply does not have access to these populations. Moreover, the representativeness of the current samples, especially when sampled using convenience methods, is questionable. A third major gap is that in virtually every country the size of the key populations — MSM, IDU and CSW — involved in HIV transmission in low-level and concentrated epidemics is unknown. The current numbers have huge errors that lead to substantial uncertainties about estimates, although capture-recapture and multiplier methods have been used effectively in some situations. A related problem is the lack of information on levels of risk in the population at-large. The frequency and extent to which the general adult population comes into contact with these high-risk populations, such as male clients of female CSWs, is unmeasured and unknown even where good behavioral surveillance data exist. Finally, the extent to which these key populations have been reached by prevention programs and what percentage of at-risk persons have been exposed to these programs remain unknown. These data will become increasingly essential.

With regard to integrated analysis of epidemiologic and behavioral data, questions arise regarding the systematic study of new infections, analysis of epidemiologic and behavioral data together, understanding the extent to which behavior is influencing national epidemics and how well we can predict the future of low-level and concentrated epidemics. Integrated analysis is not occurring routinely and is not generally a part national programs in developing countries. Furthermore, data analysis to help understand how behavior is influencing national epidemics and to predict the future of low-level and concentrated epidemics is missing. Measures of the extent to which second-generation surveillance has contributed to appropriate changes in responses suggest that responses in key populations are not improving.

There are a number of reasons for this poor performance and failure to motivate a response in low-level and concentrated epidemics. First, surveillance data which show low levels of HIV infection are unconvincing to decision makers. Also, efforts to demonstrate that there are links between surveillance
and prevention have been inadequate. There are political costs and stigma associated with discussing marginalized populations making it difficult for policymakers to act. There is a general lack of understanding of the epidemiology of HIV in these populations and a sense of waiting for generalized spread before needing to act. Old problems in data quality remain — defining the right populations, sampling in a consistent manner and reporting findings to the central level. Data gaps are significant, and there are still critically important populations with high HIV prevalence that remain outside of surveillance systems.

Although there are serious gaps in current HIV surveillance and continued need for better data analysis, there are new approaches that merit consideration. New tools for measuring HIV incidence, which, once operationalized, will be of value. Use of HAART will affect surveillance, and surveillance will affect the use of HAART. HAART may affect risk behaviors as well. VCT and PMTCT programs are expanding, and techniques for integrating data from these sources should be explored. Finally, as surveillance data are used for purposes beyond what they were designed for, such as for estimations, projections and integrated analyses, gaps in knowledge will be identified that will need to be addressed. So far, there has so far been a general failure to implement surveillance in low-level and concentrated epidemics in the right populations. New approaches and data sources will help, but the fundamental issue remains building the capacity to do better with what data that are already available.


The Ethiopian surveillance system is based on ANC sentinel surveillance, surveys including the Behavioral Surveillance System (BSS) and military recruits, universal AIDS case reporting and universal STI reporting. The ANC sentinel surveillance system, which started with a few sites in Addis Ababa in 1989, is now up to 67 sites in 2003. In urban areas the prevalence is between 6% and 23%, and in rural areas it is 5% or less. Prevalence is highest among women 15 to 24 years old (12.1%) and declines to 11% among 25-34 year olds and 7.3% among 35-49 year olds. From 2001 data the national prevalence estimate is 6.6% (13.7% urban and 3.7% rural); among military recruits prevalence rates are 7.2% among those from urban areas and 3.8% among those from rural areas with peak prevalence among 25 to 29 year olds.

Overall, there are an estimated 2.2 million people in Ethiopia living with HIV infection, an estimated 219,400 AIDS cases and 1.2 million orphans. Nationally 15,202 AIDS cases have been reported; this represents only 6.9% of the total estimated number of AIDS cases. The peak age of AIDS is among 25-29 year olds, and there have been increases in both HIV-related tuberculosis and non-HIV-related tuberculosis; 51% of all tuberculosis cases are now estimated to be due to HIV infection. An estimated 2.1 million Ethiopians will have died from HIV by the end of 2004 and 3.5 million by 2009. By 2009 the annual number of deaths among 15 to 49 year olds, which would have been 214,000 without HIV, will be 405,000. This will lead to a decrease in life expectancy at birth from 54 years to 45.2 years and 1.7 million orphans.
Discussion

With regard to the general population-based HIV surveys and their relationship to ANC sentinel surveillance, cautions were voiced about how to communicate changing estimates and how results from general population-based surveys still need to be analyzed carefully both by themselves and in an integrated fashion with other data.

Questions were raised about the epidemiologic construct of low-level epidemics (<1% prevalence in ANC populations) implying a relatively minor problem or even a non-problem, and the potential need for a new classification system. The 1% cutoff was felt to be problematic and, since low-level and concentrated epidemics typically involve only a few socially stigmatized groups, make the epidemic easy to ignore politically. Discussants suggested that bringing the high-risk communities themselves into the equation and helping them to “own” the problem is one step. Others are improving communications with the media and policymakers, particularly around the potential for the epidemic to bridge to the general population, and the fact that low-level epidemics do not necessarily stay at low levels. The availability of ARV therapy (ART) will force governments to address these populations, and their decisions will be aided by arguments about the cost-effectiveness of prevention programs. Additionally the importance of detailed epidemiologic analysis of what was happening in high-risk groups was emphasized.

A point was raised about the challenges of pediatric surveillance. Historically the AIDS case definition in children in generalized epidemics has not been sensitive with a lot of overlap between HIV-related and HIV-unrelated clinical syndromes, and for this reason HIV testing will need to be central to any surveillance effort in children.

With regard to the specific case of Ethiopia, the vast underreporting of AIDS cases was discussed. Various reasons were given for underreporting, including patients not accessing health-care institutions, reporting delays and lack of capacity in hospitals for testing needed for diagnosis. Additionally, in response to a specific question, Dr. Asseged responded that there is no evidence of an IDU epidemic in Ethiopia; modes of transmission are predominantly heterosexual intercourse, vertical transmission and parenteral transmission through blood.
Update 2. Ethical Issues in Surveillance

**Dr. Michael St. Louis of CDC GAP opened the session with an overview of ethical issues in surveillance for HIV in resource-constrained settings.** The context of the HIV surveillance has changed. In this era of increased resources, there is an effort to make HIV testing more routine primarily through “opt-out” consent processes as well as ARV drugs; there is, accordingly, substantially increased political oversight and media interest. There is a general lack of societal consensus on the ethics of unlinked anonymous testing and a shift toward using data obtained from facility-based services (e.g., VCT, PMTCT data). In addition, newer population-based sampling approaches will presumably provide more accurate data than ANC sentinel surveillance. These circumstances lead to four key ethical questions:

- Should ANC sentinel serosurveillance be continued?
- How should we approach HIV testing in general population-based surveys?
- What approaches should be used for outreach for surveillance?
- How should human subjects committees figure into these decisions?

The first issue is whether or not ANC sentinel surveillance should be continued in the era of vastly expanded PMTCT programs and HAART. Since ANC sentinel surveys utilize unlinked anonymous testing, there is no consent and no opportunity for results to be used clinically. Historically the need to understand the epidemiology of HIV infection in countries with generalized epidemics has overshadowed the inability of this ANC-based sentinel surveillance to benefit individual patients. Methodologically, as PMTCT testing coverage increases, there should be a convergence at some point between ANC sentinel surveillance data and PMTCT program data, which would obviate the need for unlinked anonymous testing. However, how much coverage is needed is not yet clear from empirical evidence, and, as PMTCT and VCT become more widespread, it is unclear whether the increased availability of testing will increase or decrease societal concerns regarding the value of unlinked anonymous testing.

Adding HIV testing to general population-based behavioral surveys is another option for obtaining estimates of the prevalence of HIV infection in a country. There are both methodological and ethical issues surrounding this approach as well. For instance, should participants be required to get their test results, and, if they are, how will this affect non-participation bias? If it is an ethical requirement that VCT should be immediately available in areas where the household surveys are being conducted, there is a possibility that resources would have to be redirected posing its own ethical concerns regarding the beneficence of using limited resources to conduct such surveys.

If there is outreach for surveillance, should protocols for the use of the data generated be reviewed by a human subjects committee and should informed consent of those tested be obtained? Standards will need to be developed for referring individuals found to be HIV-infected through these outreach programs to prevention and care services, which in turn will report these patients in their own monitoring data. In the end, this sort of surveillance may be an even more ethical approach than that represented by the research model with informed consent and human subjects committee approval.

With respect to appropriate institutional responses, the role of human subjects committees in approving surveillance activities in general is evolving. CDC’s model of “research determination”, which classifies public health surveillance activities as either constituting research or public health practice based on a number of criteria, is one model that may be applicable. A basic distinction is that research is designed to produce generalizable knowledge whereas surveillance describes the current status of a disease in a
population. CDC’s process of research determination both divides research from public health practice and provides a documentable process to demonstrate that potential ethical concerns in surveillance projects have been addressed; this model may also be appropriate for Africa.

In conclusion the expansion of the global response to AIDS and the expanded surveillance repertoire will prompt new ethical concerns, rekindle old ones and bring new attention to these issues. Attention needs to be paid to emerging ethical concerns proactively, and a documented, institutionalized approach should be used to encourage the development of well-designed, defensible surveillance strategies. In addition, it is important to pay attention to public opinion on ethical issues of research and other interventions at both the national and international levels. Finally some true ethical problems that are usually not discussed and omitted in ethics reviews. These include not publishing data or delaying publication excessively, using data known to be flawed without full disclosure of their limitations, such as poor lab quality or incorrect sampling procedures, allowing or supporting interpretations of data that are known not to be correct and conducting surveillance or surveys that are not really needed.

Professor Ronald Baer of the Columbia University Mailman School of Public Health provided a framework for discussion of surveillance ethics. There is little systematic knowledge of the ethics of surveillance, and there is a false dichotomy between public health research and public health practice, including surveillance. Research, whose goal it is to obtain generalizable information, has an institutional system in place for ethical oversight. However, public health practice does not have an institutional mechanism to assure ethical conduct of surveillance. Although both activities require ethical oversight, the research model is specifically not applicable to surveillance.

The principles of research ethics favor the individual over society by setting guidelines for informed consent and confidentiality. This presumption cannot serve as the ethical foundation for surveillance. The public health practice model has two basic assumptions: that individuals forego or undergo certain things for society’s good and that paternalism is a defining value. There is an affirmative duty for health agencies to conduct surveillance as a societal good. The role of ethics in surveillance is to provide shape to the duty to monitor the incidence and prevalence of diseases, to facilitate its control and to place bounds on such efforts. Importantly, social good alone cannot justify violation of human rights.

There are several questions that should be considered in developing ethical standards for surveillance (Table 2). Mandatory case reporting has been an aspect of surveillance in many countries and has served as the primary source of information on the incidence and prevalence of diseases. Case reporting usually requires that health care providers report individually identifying information about their patients to public health registries. The mandatory aspect of reporting means that neither the patient nor health care provider has a choice in reporting. The lack of consent raises questions about the limits of privacy in public health practice. In fact, at times physicians have felt that reporting intrudes on the privacy of their patients, and this has contributed to incomplete reporting.

There are no definitive answers that are universally applicable. Factors that must be considered are the state of the epidemic, the infrastructure, the public health and medical capacity, the availability of resources to manage and secure a disease registry and the political culture. A relevant example comes from the experience in the United States when unlinked anonymous HIV seroprevalence surveys were first implemented. There was an initial consensus that it was ethical because there was a lack of effective treatment for HIV infection and VCT was available so that persons tested through the unlinked surveys could choose to be screened for HIV.
Privacy was also assured, and the knowledge gained was beneficial. WHO subsequently approved unlinked anonymous surveys in developing countries. Even then, these surveys provoked some controversy, and several developed countries delayed instituting unlinked anonymous surveys. This paradigm changed with the availability of effective treatment. In 1994 zidovudine was found to reduce the risk of perinatal transmission and, as a result, there was increasing discomfort over testing women and not providing results and treatment that could reduce the risk of acquiring disease. Based on growing ethical concerns, the United States discontinued its survey of childbearing women. Although the United States no longer conducts the survey of childbearing women, funds from the U.S. are used and U.S. agencies have collaborated with developing countries in designing and conducting ANC surveillance. Are ethical standards being applied differently in these situations?

A goal of surveillance is to gather information for public health benefit. When this link is not present, the ethical foundation of surveillance is subverted. Although one cannot always ensure that public health data will lead to increases in services or other direct benefits, there must be, at a minimum, a commitment to use the information to benefit the populations under surveillance including advocacy for vulnerable populations. It must also be noted that release of public health information may cause harm to marginalized populations. This risk should always be considered and balanced against the possible benefits of communicating surveillance findings. Surveillance activities must be done within the context of ethics and standards, and the ethical practice of surveillance must be institutionalized and applied systematically as it has been for research.

Dr. Shabbir Ismail of CDC GAP-Ethiopia discussed the Ethiopian experience with ANC sentinel surveillance and the attendant ethical issues. Ethiopia uses ANC sentinel surveillance, universal AIDS case reporting and routine syphilis screening among pregnant women as its three sources of HIV/AIDS surveillance information. The backbone of the system is ANC sentinel surveillance, which is conducted at 77 sites through the nation and utilizes unlinked anonymous testing of serum samples left over from prenatal syphilis screening. Specimens in most ANC sites are tested at locations other than where they are drawn, and ANC staff does not receive information on the HIV test results.
Ethical concerns have focused around operational issues including anonymity, lack of linking results and patients and confidentiality. National guidelines for ANC surveillance have been developed and these address ethical issues. Training of regional staff has been done, and after they completed the training, they then trained the onsite staff on the appropriate procedures and ethics of ANC surveillance. Field observations have noted some areas of ethical concern. For example, most site staff consider ANC surveillance to be research and, therefore, think that consent should be obtained. In some areas syphilis screening is done only during the months when HIV sentinel surveillance is carried out and has caused anxiety in women at some of the sites. ANC codes have been found on both specimen tubes, which indicates that the specimens were linked, and at some centers there were backlogs of data to be entered.

Suggestions to improve the ethical conduct of unlinked anonymous testing included:

- Developing clear national operational guidelines that address ethical issues
- Ensuring strict adherence to the guidelines
- Well designed training for federal and regional coordinators and for surveillance site staff
- Providing close supervision at all levels
- Monitoring of client and data flow by site coordinators to identify and prevent break downs in procedures that protect anonymity
- Separating sample collection and testing geographically
- Regular and frequent review of all procedures at each site
- Orienting of other non-surveillance health care workers at the site
- Maximizing efforts to maintain confidentiality
- Offering confidential VCT and PMTCT services available on site
Discussion

The subsequent discussion focused on the evolving ethical standards for unlinked anonymous testing of pregnant women in ANC sentinel serosurveillance systems. There was a general consensus for strongly articulating the centrality of the ANC sentinel surveillance system to HIV surveillance and the clearer linking of surveillance activities to intervention activities. One point of discussion was that efforts to offer VCT and/or PMTCT at ANC surveillance sites may create a situation in which surveillance needs are driving programs. In resource-constrained areas, should the presence of an ANC surveillance site be the sole justification for offering VCT or PMTCT programs, or should other criteria be used to determine where these program services should be instituted?

The extent to which these issues represented American standards (the term “ethical imperialism” was used in a subsequent summary) and how much of it represented a problem perceived by African nations was also discussed. The consensus was that there was an affirmative duty to conduct surveillance. One discussant suggested that data are becoming available from PMTCT sites that can be compared with ANC sentinel surveillance data to provide an empirical basis for weighing the necessity of unlinked anonymous testing. He also suggested that we have underestimated the importance of ANC sentinel surveillance data, as evidenced by the role of these data in decisions leading up to the U.S. Presidential Emergency Plan for AIDS Relief (PEPFAR).

A separate point of discussion was the failure to use data collected for surveillance purposes. This failure was viewed in the words of one discussant as a “rupture of the ethical underpinnings of surveillance”, and there was general consensus that it was unethical to conduct surveillance and not use the data.
Update 3. Quality Assurance with HIV Testing Technologies

Dr. Robert Martin of CDC provided an overview of quality assurance (QA) and HIV testing and suggested recommendations for the implementation of QA especially with regard to GAP. The opportunity to focus on quality exists because of the need for credible results and because funding QA is no longer viewed as a cost but as an investment in building a lasting infrastructure for all laboratories to respond to new health threats. Examples of lab quality initiatives in several countries were provided. At the Government Hospital for Thoracic Medicine in Tamil Nadu, India, steps have been taken to institute a number of improvements in patient care and surveillance, build a new laboratory facility, identify a QA officer and conduct a week-long QA workshop at the hospital. In Cambodia the first QA assessment was conducted in April 2003, and a national meeting of laboratory directors in all Cambodian provinces was subsequently held to develop a national laboratory network and a national QA program and to address communication issues among laboratories. In Ethiopia steps are being taken to develop a laboratory at the Ethiopian Health and Nutrition Research Institute, identify a QA officer for the laboratory and implement QA activities. The first national conference for all laboratories in Ethiopia was recently held to discuss a national QA program.

One of the first steps to assure quality in laboratory practice is to conduct an assessment of laboratory systems within each country. Within the CDC GAP country support system, there is an ongoing joint program of CDC, the United States Association of Public Health Laboratories, the Australian National Reference Laboratory and ministries of health to assess the laboratory system in each country. Following the assessment, steps typically involve the determination of three or four initiatives that will begin the process of improvement and outlining discrete and practical next steps. Under the systems approach to quality, the goals are to ensure the quality of the overall process, to detect and reduce errors, to improve consistency within and between laboratories and to contain costs.

QA is part of a larger quality systems approach that includes both quality control (QC) and QA. The overall quality system involves 12 components (information management, organization, personnel, equipment, purchasing and inventory, process control, documents and records, occurrence management, assessment, process improvement, customer service and facilities and safety). Process control includes validation and QC. Quality management incorporates all activities in an overall management function that determine quality policy objectives and implementation through activities such as quality planning, QC, QA and quality improvement within the system. QA refers to planned and systematic activities to provide adequate confidence that requirements of quality will be met and includes internal QC, proficiency testing, test standardization, training, competency evaluation, equipment maintenance, pre-post analytic phase, management and organization. QC is the set of procedures for continually assessing laboratory work and the emergent results. The key steps in developing a quality systems initiative are to develop a framework for common approach, develop training materials and conduct workshops that present the framework, provide information and training and encourage the development and implementation of a national quality systems plan.

Barriers to quality often include a lack of understanding of and commitment to QA, inappropriate staff, lack of training programs and the absence of appropriate leadership at each management or control level. Embracing the quality system concept, providing assistance in the development of national quality systems, providing training and training materials for local use and providing long-term technical support for quality system development and implementation are CDC GAP priorities.
Dr. Mark Rayfield, also of CDC, provided an overview of QA with various HIV testing technologies, and how to integrate them in algorithms that provide good testing data for surveillance.  Key elements to designing a testing strategy to support surveillance in country include an assessment of tests currently used in country, choosing the right tool and recognizing that specimens are central to the entire process. The testing environment used thus far in most surveillance approaches employs centralized testing, which has the advantages of ease of management, QA, ability to apply advanced technologies, efficiency of scale and ease of data management. However, this approach limits the dissemination of technologies within country and tends to overemphasize the logistics of getting an optimal-quality specimen to a central lab in a limited time frame. Decentralized testing, on the other hand, offers the opportunity to disseminate technologies across countries, allows for local involvement and consensus building around methods being used by laboratories and allows for improved, integrated surveillance systems. However, decentralized testing requires an expanded QA effort, and there is a need for improved data management and logistical support and heightened concerns for confidentiality (Table 3). Most GAP countries rely on central laboratories, which often have the disadvantage of a weak national reference laboratory, poor resources, an aging professional staff, weak QA at the national level, poorly integrated services and limited data exchange. QA and QC issues that still need to be considered include developing a standardized method of specimen collection and transport, establishing standard operation procedures, deciding personnel qualifications, designing proficiency testing programs, procurement and management of instruments and reagents, record keeping and reporting and conducting pre- and post-analytic checks.

While QA and QC are being standardized throughout GAP countries, expansion of testing has created the possibility for increased decentralized testing. With the expansion of decentralized testing, there needs to be an assessment of needs and capabilities at each site, development of site-specific protocols and consideration of alternative testing formats, such as rapid tests and the use of dried blood spots.

Table 3. Issues in centralized and decentralized testing.

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<td>Limited dissemination of technologies</td>
<td>Confidentiality with positive tests</td>
</tr>
<tr>
<td>Huge premium on specimen transport</td>
<td></td>
</tr>
</tbody>
</table>
Table 4. Rapid test formats and commercially available products.

<table>
<thead>
<tr>
<th>Format</th>
<th>Commercial test kit</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agglutination device</td>
<td>Capillus HIV 1/2®</td>
<td>98.9%</td>
<td>99.7%</td>
<td>99.4%</td>
<td>99.4%</td>
</tr>
<tr>
<td>Lateral flow (dip stick)</td>
<td>Determine®</td>
<td>99.4%-100%</td>
<td>99.6%-99.8%</td>
<td>97.9%-99.7%</td>
<td>99.7%-100%</td>
</tr>
<tr>
<td></td>
<td>HemaStrip®</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>Determine® and HemaStrip® combined</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

There are several different algorithms that can be employed in surveillance. The first is either single or multiple enzyme immunosorbent assays (EIA), which provide for optimal sensitivity and specificity. The need for and choice of a confirmatory test is dependent on prevalence of disease and sensitivity and specificity of screening tests. A second option involves multiple simple or rapid tests, which have the disadvantage of losing the efficiency of scale provided by a centralized laboratory but have the distinct advantage of being able to expand access to VCT and PMTCT programs. Third is a combination of EIAs and rapid tests, either using rapid tests as the first test and EIAs as the confirmatory test in decentralized settings or using EIAs as the first test and rapid tests as the confirmatory tests in centralized settings. Examination of these algorithms is ongoing and results are expected within one year. An important consideration is that time needs to be allotted for establishing the quality of the tests in country, development of algorithms incorporating the test, pilot testing the algorithms and then nationalizing the process.

With regard to simple rapid tests, there are three formats — flow-through devices, agglutination devices and lateral flow devices (Table 4). Agglutination devices include Recombigen®, Serodia®, Capillus® and Simpli-Red®. Commercially available lateral flow devices include Unigold®, HemaStrip®, Determine® and OraQuick®. All perform reasonably well in the field with high sensitivities, specificities and predictive values.

Dried blood spots can be used as a specimen collection format. They have been integrated into a number of countries in the context of external QA of test performance at remote sites. The samples are stable, and there is substantial interesting in pursuing dried blood spot methodology. However, several steps are needed before considering implementation at the national level, including standardized training, standardized elution protocols, development of transport controls and internal assay controls and optimization of standard EIAs using dried blood spots. Future directions in alternative technologies include incidence assays with both dried blood spots and rapid tests, oral fluids and using dried blood spots for infant polymerase chain reaction (PCR) assays, ARV resistance testing and HIV genotyping.
Two speakers, Dr. Achara Teeraratkul from CDC GAP-Thailand and the Thai Ministry of Public Health, and Dr. Eugénie Kayirangwa of the Rwandan Treatment and Research AIDS Center and Family Health International (FHI)/IMPACT, provided updates from the field regarding HIV testing.\textsuperscript{12,13} In Thailand surveillance systems include AIDS and symptomatic HIV surveillance, HIV serosurveillance, behavioral surveillance and perinatal HIV outcome monitoring. The development of laboratory QA for HIV testing has included guidelines and training, test kit evaluation and external and internal QA. HIV test kits in Thailand are required to have a sensitivity greater than 99.5% and a specificity greater than 98% for licensure. Additional steps for licensure include reviewing manufacturers’ documents, laboratory evaluation and clinical evaluation.

Routine external quality assessments involve 994 laboratories, 80% of which are government laboratories. The network for external quality begins with four regional reference centers, which conduct assessment of local laboratories. The Thai National Institute of Health conducts assessment of the four regional reference centers and provides technical support to improve laboratory performance. External QA methods also include proficiency testing using serum specimens from blood donors, HIV-infected and non-infected persons. Each reference center receives and tests the samples, assesses the ability of blood samples and reports results to the Thai National Institute of Health laboratories. Internal QC involves the national reference centers providing well-identified samples and daily testing assessment.

The success of the Thai program was attributed to having guidelines for testing and standard operating procedures, adequate financial resources, appropriate facilities, adequate human resources, educational and supervisory support and linkage to international organizations. The national laboratory QA program has benefited patients by providing them with reliable diagnoses and has benefitted diagnostic laboratories through improvement of overall laboratory performance. The national QA program has improved public health programs by supporting reliable nationwide surveillance. Manufacturers have benefitted from the program by being able to use the information from laboratories to determine batch-to-batch variation. Challenges to the program include increasing knowledge and understanding of lab QA among participants, increasing coverage of participants, expanding follow-up activities to identify ways to correct for errors, obtaining more government financial support and commitment for sustainability and government reform. Government reform includes improvement in such issues as decentralization of administration, government freeze on manpower and a limited number of qualified supervisory personnel. In summary, reliable and reproducible HIV testing is an important component of HIV serosurveillance. Thus, laboratory QA is similarly important, and sustainability of the program requires strong support from local authorities and international alliances.

In Rwanda, external and internal QC is conducted through the coordination of the Treatment and Research AIDS Center, the National Reference Laboratory, district level centers and sentinel sites at the local level. Parameters of good quality include coordination, supervision, data management and laboratory QA. The Treatment and Research AIDS Center is generally responsible for coordination and supervision of district level centers and for data management. The National Reference Laboratory coordinates the sentinel sites to record and store the samples and to test for HIV. Each of the sentinel sites is responsible for collecting, labeling, storing and sending samples to National Reference Laboratory to be tested for HIV.

Internal QC in Rwanda is achieved through several mechanisms: samples of known serostatus in addition to the manufacturer’s controls are incorporated onto each plate, 10% of samples negative on screening with the Vironostika EIA are tested with a confirmatory test (Murex) and maintenance of the equipment
and calibration of pipettes are regularly performed. For external QA, 5% of the negative sera and 50% of the positive sera are sent to the external accredited CDC-Ugandan Viral Research Institute in Entebbe, Uganda, 10% of negative and all positive syphilis serologies are retested at the National Reference Laboratory and the National Reference Laboratory receives lyophilized samples of WHO external QA serology three times per year. When discrepancies occur, they are usually due to bacterial contamination, poor storage of sera and reagents, poor distribution of antigens and late reading of results; however, resolving discrepancies is usually accomplished through formative supervision, training and rotating the personnel. These QA methods in Rwanda have accounted for the 100% concordance with the WHO external QC serology.

Update 4. Informatics

Dr. Meade Morgan of CDC-Atlanta discussed the use of information systems to support HIV surveillance. Information systems are defined as the organizational framework and technical infrastructure for collecting and managing data and for turning data into information that is used productively. Several examples of information systems that support HIV programs can be found in Table 5.

The key issue for HIV information systems is to build national health informatics infrastructure balancing the need to meet short-term data and reporting requirements with the long-term need to build sustainable health management systems. At least for now the primary emphasis is on short-term solutions. The types of data that need to be reported are threefold:

- In the short term, aggregate monthly or quarterly statistics on adverse health outcomes with paper-based systems at the clinic level and computerization at the district, regional hospital or national level
- In the medium term, yearly or less frequent surveys with computerization capacity resting with the implementing organization
- In the long term, clinical records that are needed immediately to weekly and involve simple forms or computerization at the clinic level

The bottom line is that the HIV pandemic demands a rapid response. Short-term solutions should be implemented first but, to the extent possible, should strengthen the national health information system.

There are several potential strategies to meet both short and longer needs at the same time. First, information technology capacity can use existing health informatics systems, such as WHO Regional Office for Africa’s (AFRO) integrated disease surveillance system. Secondly, human resources should be strengthened by building a culture, through training, that understands and appreciates the utility of health information. To the greatest extent possible the emphasis should be on building a general-purpose, rather than vertical, infrastructure. Using, for example, cellular networks or the Internet for communication and standardized tools, such as EpiInfo or Health Mapper, whenever possible makes the information technology system more adaptable to other diseases and other situations. Finally, applying standards in data collection and analysis is key. This includes integrating logbooks, reporting forms, software and security across the entire surveillance system. A number of other key issues must be borne in mind as well. The design and construction of a health information system should be able to support longitudinal care records, such as electronic medical records, facilitate inter- and intrasite program
There are a series of principles for information systems. First there is a need to identify stakeholders’ needs and to build their buy in. Once identified their needs must be understood, and throughout the design phase their input and that of the end-users need to be obtained because the quality of the data in the system will in the end be a function of how useful the users think the data are. Finally the design team needs to be sure that adequate staff is allocated for data systems from data collection all the way through to analysis and use. There are similar needs for adequate training and human resources. A central tenet of his design principles is the data retrieval and analysis should drive data entry, that is, using the data regularly should reinforce the need for careful data entry rather than careful data entry being a disembodied activity for its own sake. Standards should be incorporated where feasible, and building out existing solutions rather than creating them de novo should be considered. Maintainability and extendibility are key principles when designing information systems.

There are three noteworthy existing systems that are being used – the Routine Health Information Network (RHINO), the WHO’s Health Metrics Network and UNAIDS’ Country Response Information System (CRIS)* -- which are ongoing efforts to improve the quality of data gathered in resource-constrained settings. Among efforts to improve HIV surveillance data specifically were the Epidemic Projections Package (EPP) for generalized epidemics from WHO, UNAIDS’ Workbooks for estimating prevalence in concentrated and low-level epidemics, Tulane University’s SPECTRUM for demographic projections and GOALS for resource allocation and the U.S. Bureau of the Census’s data base on HIV surveillance data. There are also other valuable adjuncts, such as WHO’s Health Mapper and CDC’s EpiInfo.

Table 5. Examples of information systems supporting HIV programs.

| Pharmacy management |
| Laboratory management information |
| Logistics/supply chain management |
| Program monitoring |
| Targeted program evaluation |
| Facility-based patient information systems ✓ |
| National notifiable disease reporting systems ✓ |
| Vital Statistics registries ✓ |
| Facility-based surveys (e.g. ANC clinics) ✓ |
| Population-based surveys ✓ |

✓ Indicates part of surveillance system or used by surveillance system

communication thus ensuring referral linkages from the facility to the field and back and to transmit the data needed for the monitoring and evaluation system once there is consensus on indicators. Throughout these efforts the emphasis should be on practical use of innovative technology.

* RHINO: [http://www.cpc.unc.edu/measure/rhino](http://www.cpc.unc.edu/measure/rhino)
Several informatics activities will be supported by PEPFAR. USAID, CDC, the Health Resources and Services Administration (HRSA) and John Snow International have written a concept paper on strengthening national health information systems. Site teams will be visiting PEPFAR countries to review existing information technology strategies and to recommend future directions and activities.

Within CDC GAP there are an informatics team consisting of systems analysts, programmers and statisticians and a handful of in-country informatics units in Botswana, Thailand, Uganda and Zimbabwe. There are several information system resources that GAP has supported, including a concept paper on facility-based patient information system, an inventory of HIV care and treatment information systems, a list of core data elements for patient and clinic management of ARV programs and databases built in EpiInfo to support PMTCT programs, ARV care and general program management. CDC has also developed software packages, including EpiInfo, which is for database management and analysis of epidemiologic data; EZ-Text, which allows analysis of structured qualitative data; AnSWR, which allows analysis of unstructured qualitative data; and patient-flow analysis, which provides time-process analysis to improve clinic management of patient flow. EpiInfo is the jewel in the crown. It is free-ware and downloadable; is designed for health information; allows form creation, data entry, analysis and report generation including mapping; has training materials and user support; has a large user population and existing applications for problem solving; involves low effort and fast start-up and is consistent with WHO AFRO’s integrated disease surveillance system.

Ms. Elizabeth Pisani of Family Health International described the Indonesian experience with health informatics. In Indonesia, the development of a new data management system was driven by the chaotic decentralization of public health functions, including HIV control programs. There was no secure funding for surveillance, a poor understanding of data quality, poor interpretation of data, no data transfer, no institutional memory leading to loss of data trends, no use of data at any level and no training at the district level where all decisions had to be made. To meet this challenge a group from the Ministry of Health, AusAID, the Macfarlane Burnet Institute and Family Health International developed the SSHIV software to both control and drive data quality. Its purposes were to increase data reporting from both HIV serosurveillance and behavioral surveillance, impose limits on data (e.g., sites, populations, sample sizes), encourage compliance with existing testing protocols, identify a minimal national system and to provide opportunities for widespread training on fundamental principles of surveillance to those who were actually doing the surveillance activities. SSHIV has a number of important design features, such as automatic back up, extensive help files, logic checks and warnings and exportability to Excel and .dbf formats, and reporting-generating capacities including reports in nationally standardized formats, reports on international indicators such as the United Nations General Assembly Special Session (UNGASS) indicators and reports in Indonesian and English. An example of an SSHIV screen is shown in Figure 2. SSHIV allows some flexibility to meet local district-level needs but is not so flexible that central control of core data elements can be lost.

Ms. Kimberly Marsh of CDC described CDC’s new training module on electronic data management and analysis for HIV sentinel surveillance. WHO and CDC guidelines have both recommended specific approaches for collecting, managing and analyzing data, but there is a limited capacity at country level for implementing best practices and using computing tools and a critical need for high quality HIV sentinel surveillance data. To meet this need, CDC developed a computer-based course in 2002 and 2003. The course objectives were to introduce best practices for systemically collecting, managing, processing and reporting survey data and to use EpiInfo for Windows 2002 for forms, analysis, statistics, maps and graphics. The course is intended for epidemiologists and statisticians, last 3.5 to 5
days, utilizes a case-based approach and focuses at least initially on HIV sentinel surveillance in generalized epidemics using three years of ANC data from a fictitious country. The course content is shown in Table 6. Future plans include modifying the course to a train-the-trainers format and to develop modules for concentrated epidemics, behavioral data and other circumstances.

Dr. Shabbir Ismail of CDC GAP-Ethiopia spoke about piloting the CDC training course in Ethiopia. The objectives of the course were to teach students to design data collection and entry forms, design entry screens, develop check codes, conduct basic descriptive analyses and generate regional and national reports. Potential participants were selected from the Ministry of Health and regions and then chosen on the basis of basic computing skills, prior training in epidemiology and statistics, work with HIV/AIDS-related data and willingness and readiness to process local surveillance data and on a recommendation from the regional health bureaus. The 30 participants included regional surveillance coordinators (physicians, health officers and nurses) and statisticians and came from the Ministry of Health, regional health bureaus, Addis Ababa University and CDC GAP-Ethiopia.

The training extended over five days and emphasized hands-on training; each participant had a personal computer. Course elements included an orientation to EpiInfo 2002, developing data collection forms, creating data entry screens with Make View, writing check codes, single and double data entry, simple

Figure 2. SSHIV spreadsheet screen, Indonesia.
data analysis, reporting writing and mapping. Future plans will involve providing students personal computers with EpiInfo 2002 already installed to take back home with them, to encourage the use of the system to process local data for the 2003 sentinel surveillance round and routine morbidity data, to provide training courses to other regions, to provide refresher courses and to initiate electronic data processing, transfer and feedback at the local level.


Dr. Tobi Saidel provided an overview of the limitations of conventional probability sampling methods for hidden populations, described two main alternative strategies (time-location sampling [TLS] and respondent-driven sampling [RDS]) and answered questions. Methods exist for conducting high-quality surveys with high-risk and hidden populations; however, there is insufficient capacity to conduct these surveys on a consistent basis. “Hidden” populations are populations with high-risk behaviors for whom no sampling frame exists and who, because their behaviors may not be socially sanctioned, are often reluctant to have their identities known. The most common examples of hidden populations include CSWs, IDUs, MSM and migrants. For these populations, conventional household cluster sampling methods are typically inadequate because of the small sample size of the “hidden” populations, respondents’ potential reluctance to reveal non-sanctioned behavior and the lack of stable presence of relevant populations in households. Additionally institutional settings, such as schools and factories, where conventional cluster sampling can be done, are unlikely to have sufficient representation from these populations to make sampling in these types of venues a feasible option. To address these problems, TLS and RDS have recently been developed for probability sampling of “hidden” populations.

Methodologically, TLS relies on clusters of potential participants defined by a time and location dimension, for instance, areas where CSW congregate during evening hours. A random sample of potential clusters (e.g., two-hour time intervals from 7:00 PM to 11 P.M. in each of the areas for seven nights per week) is chosen, and all or a part of the sample in that time-location cluster is interviewed. Since in most cases the absolute size of the population being sampled is not fixed, selecting samples with probability-proportion-to-size methods should be avoided. The first-stage sample consists of a simple random sample or a systematic random sample of the time-location clusters. The second-stage sample consists of all potential respondents or simple random sample of eligible participants who are physically in the location during the time interval chosen. The length of the time interval depends on the expected volume of contacts at the site. These should be the same in all locations; if different time intervals are chosen for different sites, the data need to be weighted to create a composite estimate.
The strength of TLS is that it extends probability-sampling methods to “hidden” populations that congregate in accessible places. However, its limitations are that it reaches only the most visible subset of these high-risk populations, it requires high quality mapping, it can be difficult to ensure the randomness of the second-stage sample and repeat attendees at the same or multiple sites may interfere with the randomness of the method. This method has been used in Bangladesh to sample IDUs, MSM, male and female CSW, long-distance truck drivers and rickshaw drivers; in Cambodia to sample MSM; in India to sample MSM, female CSW and taxi drivers; and in Laos to sample female CSW and truck drivers.

RDS, the other strategy discussed, in principle improves on TLS. RDS is essentially chain-referral sampling that starts with a set of “seeds” or members of a “hidden” population purposely chosen based on an understanding of the target population’s network. It attempts to overcome lack of a sampling frame by using these seeds to recruit no more than three new participants from his or her network. A system of dual incentives is used to encourage participation, and recruitment waves continue until the sample size is reached. This method produces asymptotically unbiased population estimates, as measured by the ratio of Horvitz-Thompson estimators, and its primary strength is ease of access to hidden populations.

The most commonly used form of chain-referral sampling is snowball sampling. Although this method can be used to access hidden populations and is easily implemented, it has several limitations. These are that the final sample depends heavily on the set of seeds chosen (since seeds with large personal networks can dominate the sample), parts of the chain can be masked if seeds are reluctant to reveal the identity of their contacts, contact information of new participants may be of poor quality and, in essence, this method results in a non-probability convenience sample. RDS, although similar to snowball sampling, has several mechanisms built in to overcome the limitations of regular snowball sampling. RDS limits the number of recruits per recruiter to a maximum of three, which encourages a longer referral chain by minimizing the ability of a person with large personal networks to dominate the sample. Given a long referral chain, usually three to six waves of recruitment, the composition of the sample will stabilize regardless of the initial seeds. That is, composition of the sample will not change significantly after a certain number of waves of recruitment. In general, the greater the homophily – the likelihood of a participant recruiting others similar to himself or herself – the greater the number of waves that will be needed to reach equilibrium. This convergence around the population parameters is consistent with Markov chain theory. RDS utilizes several population parameter estimates to compensate for undue influence of the initial seeds and dampens the effect of the size of personal networks.

There are also several unanswered questions about RDS as it applies to HIV/AIDS surveys. First, how do we view the epidemiological importance of different subgroups within a “hidden” population? Is the more visible subset, for instance, MSM who congregate in bars, at higher risk of transmitting and acquiring infection than those who are more hidden? Secondly, can RDS produce a nationally representative sample, or is it only useful in smaller geographical settings? Thirdly, there are a series of questions that involve field operations. How well will RDS work outside the United States? Although formative research is not theoretically necessary, it will likely be necessary in some situations to pick the best initial seeds. If formative research becomes necessary, will RDS actually be less expensive than TLS? How well will it work in situations where the behavior in question is highly stigmatized or socially repressed? There is some experience with RDS outside the United States, for instance, in sampling IDU in Nepal, attempting implementation among female CSW in East Timor and among IDU in Georgia, and a number of other studies are being planned.
Discussion

The discussion session provided clarification of some of the methodological issues raised. In response to a question of how RDS is used to estimate population sizes, RDS by itself does not give population size estimates; however, it could either be used as a multiplier or as one arm of a capture-recapture study. Regarding monetary incentives in areas where exchange of money is considered culturally inappropriate, there has not been a lot of experience to date but using non-monetary gifts as incentives may work, although more research is necessary to determine appropriate incentives. Another question asked about the need to conduct separate, intensive studies that define hidden populations in order to describe the homophily of the population; experience and prior knowledge of the population are necessary and that data can be analyzed along the way.

Where and when are these newer methods necessary? They are, after all, difficult to implement in the field, and getting the incentives right is thorny. How much prevention should be delivered along with surveillance, and, if these methods are used to uncover hidden populations for service delivery, how useful will the surveillance data be? RDS adapted for prevention should probably be used only when no other methods are available, and initial prevention efforts should concentrate on the most visible segments of the “hidden” population where most of the risk likely occurs, although there is no empirical basis for this assumption. The experience in Indonesia when using RDS for delivering prevention messages was that the investigators were overwhelmed with participants, which caused a strain on minimally available resources, services, and staff.

Another possibility is a hybrid methodology, using RDS for initial assessment and epidemiologic mapping and then switching to TLS or venue-based methods for repeated measures. However, creating a distinction between the use of these methods for surveillance and the use of them for delivering prevention services is artificial and may be short sighted. Capture-recapture has been used successfully in Brazil to estimate size of HIV-infected population and size of population of persons living with AIDS, and there are plans to use this method for estimating the population sizes of MSM and IDU. RDS had also been used in Brazil for estimating HIV prevalence among IDU and for understanding their counseling, testing, care and treatment needs.

Do national AIDS control programs have the methodological expertise and funding necessary to undertake and analyze these complex behavioral methods? This type of expertise often exists in national statistical bureaus rather than in ministries of health. Another option, Priorities for Local AIDS Control Efforts or PLACE methodology, was also brought up. This five-step methodology focuses on places rather than individuals and more specifically on high-priority areas for local HIV control efforts. Areas of high transmission are identified, and key informants are asked to provide information regarding venues where new partnerships are formed. Investigators then confirm the sites and interview patrons at the sites. This method can be used both for surveillance and targeted prevention activities; there is experience with its use in Africa, Asia, Latin America and the Caribbean.
Update 6. Estimation and Projection Tools

*Dr. Timothy Brown of the University of Hawai’i East-West Center discussed UNAIDS’ EPP and recent developments and future changes in its use.* The goal of EPP is to improve national capacity to develop estimates and projections. It was developed to fit trends in surveillance, provide short-term (i.e., five-year) projections, reproduce real-world epidemiologic trends and be useful to the national program without a lot of additional training. Twelve training workshops on EPP were held in 2003. An example of a projections page from EPP is shown in Figure 3.

Changes are currently being considered in EPP, and the strategy is one of incremental improvement rather than complete rewriting in order to minimize training requirements. Two issues that will be addressed in the newer version of EPP are turnover in high-risk populations and adjustment for the addition of new surveillance sites. In concentrated epidemics, there is a lot of mobility into and out of high-risk populations, and the base EPP assumption of a closed population does not hold. For example, female CSW are generally engaged in sex work for about 10 years and then re-enter the general population. Also certain high-risk populations may have higher mortality than others, for instance, IDU, and former HIV-infected members of high-risk populations may show up in general population surveys, such as former CSW in ANC surveys. To address these concerns, a new parameter that assumes persons are in high-risk populations for a period of time (1/d) has been introduced to model turnover. This is shown schematically in Figure 4. This provides better fits to several actual epidemics.

**Figure 3. EPP projections page, Botswana.**
The addition of new surveillance sites often will bring down the overall prevalence estimates because sites with lower-risk populations are generally added after sites that represent higher-risk populations. For example, Ethiopia added rural sites where prevalence rates were lower than those in urban areas. A leveling parameter will be introduced into EPP to deal with this, which fits trends for each site independently while assuming that the trajectories of the fitted curves for each site are the same. Future parameters that will be considered include ARV treatment effects, a shift to maximum likelihood instead of least squares optimization, allowing for demographic parameter changes over time and exploring programmatic impacts on transmission rates.

Three additional points were raised by the audience. The first concerned how to determine a duration parameter for MSM since this is not likely to be a behavior that one exits. The way to deal with this is to identify the period during which high-risk sexual behavior occurs rather than to focus on any male-male sex. The current difficulty in determining this duration is lack of data. The second issue concerned the effect of adding lower risk sites and the change in effect based on the size of the additional populations. This can be dealt with two ways in EPP. Each site can be fit independently and then assigned the proportion of the population that the site represents (this is done in some countries) or the population associated with each site can be specified and the overall national impact can then be calculated. The final topic of discussion was the importance of allowing the model to vary by parameters other than the ones discussed, such as educational level. The intent of EPP is to remain a simple model (it has five parameters including duration). However, additional parameters can be added in countries where such data exist. The method involves stratifying the data by that variable, such as educational level.
Ms. Karen Stanecki of UNAIDS spoke on two other tools used for estimates and projections, Workbook and Spectrum. Workbook and Spectrum are both software packages that can estimate a variety of epidemiologic parameters. Workbook is the simpler tool and gives adult point prevalence estimates in low-level and concentrated epidemics. It takes inputs from biological and behavioral surveillance data, including size estimates for high- and low-risk populations, and uses curve-fitting techniques. It essentially performs the same function that EPP does in generalized epidemics.

Spectrum is the more complex tool; its inputs include adult HIV prevalence (from Workbook or EPP), population size estimates from the UN Population Division and a variety of epidemiologic assumptions. Its outputs include the numbers of persons living with HIV and AIDS, the number of new infection and the number of deaths due to AIDS. Figure 5 gives an overview of Workbook and Spectrum in low-level and concentrated epidemics, and Figures 6 and 7 are actual spreadsheets from Workbook. Spectrum software is available on the Futures Group web site (http://www.futuresgroup.org).

Figure 5. Overview for low-level and concentrated epidemics.
Figures 6 and 7. Workbook spreadsheets.

![Workbook spreadsheets image]

### Table 1: Population Sizes Estimates

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<tr>
<th>Regional Name</th>
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<tbody>
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<tr>
<td>High Population</td>
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#### Sub-Total Populations

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### Table 2: Estimates of People Living with HIV/AIDS

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#### Sub-Total Populations

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### Table 3: Partner Tests

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### Table 4: ANC Data Applied to Low Risk Women

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### Table 5: National Estimates

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### Table 6: Consistency Checks

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Please select one:

- Select
- ANC data
- ANL data

Notes:

- While the extent of missing data is valued in low-risk countries, it will have more of a滝7% of the adult (65-44) population of 4565 people who input drug day.
- Less than 0.2% of the adult (65-44) population of 4565 people who input drug day.
- Less than 0.2% of the adult (65-44) population of 4565 people who input drug day.
- Less than 0.2% of the adult (65-44) population of 4565 people who input drug day.
For generalized epidemics ANC data are the sole input, and EPP is used instead of Workbooks to produce adult point prevalence estimates (Figure 8). The epidemiologic assumptions are:

- The female-to-male ratio increases up to 1.3:1 in generalized epidemics
- Fertility is 50% higher in 15-to-19-year-old women and 20% lower in all other age groups
- The mother-to-child transmission rate is 32%; this can be modified based on country-specific estimates
- Median adult mortality is 9.0 years overall, 8.6 years for males and 9.4 years for females because of the earlier age at which females are infected

Recently, Spectrum has been updated in a variety of ways. It has an updated child survival curve. It directly calculates the percentage of children born to HIV-infected mothers from adult ANC data and perinatal transmission rates. Its life tables have been updated based on the 2002 United Nations Population Division’s revisions. Finally, the female-to-male ratio has been increased from 1.2 to 1.3 in generalized epidemics. New indicators that are now estimated by Spectrum include the number of new infections, the number of HIV-infected women, the number of persons needing ARV drugs, the numbers of persons on ARV drugs and the numbers of new orphans, both in total and by age.

**Dr. Neff Walker of UNICEF discussed errors, ranges, uncertainty, bounds and plausibility bounds in HIV estimates.** Potential errors exist at several levels when using ANC data to estimate HIV prevalence in the general population. These include the ANC estimate itself, the ANC to general population adjustment, the adult survival estimates due to AIDS and other causes, curve fitting and epidemiologic trajectory modeling, population estimates, sex ratios, vertical transmission probability and child survival estimates due to AIDS and other causes. In order to deal with error, it is necessary to

**Figure 8. Overview for generalized epidemic.**
identify the steps and assumptions used in making the estimates, to develop an estimate of error for each step and assumption and then to combine individual errors into an overall estimate of error using a parametric bootstrap approach. Assumptions and errors inherent in using ANC prevalence data to estimate adult HIV prevalence are shown in Table 7. There are additional multiplicative errors in estimates of incidence, prevalence and mortality in children to be cognizant of. Future work will include running bootstrap programs on a series of countries that vary in prevalence levels and amounts of data, completing analyses for additional sources of variance for estimates for children and investigating plausibility bounds by comparing them to independent data sources.

Dr. Peter Ghys of UNAIDS discussed comparing sentinel surveillance based on estimates to survey-based results in constructing national estimates for HIV prevalence and building on work published in 2003. In 2001 methods for estimating HIV prevalence in generalized epidemics included:

- Curve-fitting approaches using all available data over time to develop an estimate of prevalence for pregnant women in urban and non-urban areas
- Adjusting median HIV-1 prevalence in non-urban areas down by 20% because of under-representation of remote rural clinics
- Assuming HIV-1 prevalence in pregnant women is a good proxy for prevalence in all adults aged 15 to 49 years
- Calculating the national estimate of HIV-1 prevalence by weighting urban and rural areas
- Assuming the female-to-male ratio of HIV-1 prevalence grows to 1.2:1
- Calculating the number of people living with HIV and AIDS (both men and women) and other statistics from the national prevalence estimate

While ANC prevalence corresponds to the prevalence among males and females in the community, ANC sentinel surveillance typically underestimates the community prevalence among women and overestimates it in men. For example, in Yaoundé, Cameroon, HIV prevalence among ANC attendees was 5.5%, while in population-based surveys it was 7.8% in women and 4.1% in men. Similarly in Ndola, Zambia, HIV prevalence among ANC attendees was 27.3%, while in population-based surveys it was 31.9% in women and 23.2% in men.

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Table 7. Assumptions and errors in adult HIV prevalence estimates in generalized epidemics.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Base estimate</th>
<th>Error</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC prevalence</td>
<td>±2%</td>
<td></td>
</tr>
<tr>
<td>ANC: general population prevalence</td>
<td>1:1</td>
<td>SD 0.28</td>
</tr>
<tr>
<td>Adult survival</td>
<td>Median 9 years</td>
<td>SD 1 year with Weibull</td>
</tr>
<tr>
<td>Population size</td>
<td>UN population estimates</td>
<td></td>
</tr>
<tr>
<td>Sex ratio</td>
<td>1.3 female:1 male</td>
<td>SD 0.25</td>
</tr>
<tr>
<td>Mother-to-child transmission probability</td>
<td>32%</td>
<td>SD 5%</td>
</tr>
<tr>
<td>Child survival</td>
<td>39% at 5 years</td>
<td>SD = double Weibull</td>
</tr>
</tbody>
</table>

SD, standard deviation

---
The basic limitations of estimates derived from ANC sentinel surveillance data are threefold. First, the prevalence equivalence of ANC and general populations may not apply equally well in all countries, but, on the other hand, there is a growing body of studies that support this assumption, including the Zambian DHS (ANC prevalence was 19.5% while the DHS estimate was 18.9% in an analysis of DHS clusters situated near ANC sites) and a cohort study in Kisesa, Tanzania. Secondly, with the exception of South Africa, ANC-based estimates suffer from the insufficient inclusion of rural sites in the surveillance system in most countries; however, many countries have recently expanded their sentinel surveillance systems to include more rural sites. Finally, any adjustments that aim to account for the under-representation of smaller rural sites are necessarily crude.

In recent years national surveys have become available in a number of countries, including the DHS in Mali, the Dominican Republic, Zambia and Kenya and the Young Adult Survey in Zimbabwe and other surveys in Burundi and Niger. These types of surveys are of most value in high-prevalence epidemics and are definitely not useful for measuring HIV prevalence in low-level and concentrated epidemics.

Compared to the HIV prevalence estimates in these surveys, prevalence estimates based on ANC surveillance data have been higher in most countries. A limitation of national surveys is that non-response rates may be high, including a combination of refusal and not at home, averaging 24% in Zambia, 38% in South Africa and 26% in Kenya. Rates differ with women more likely to participate than men and rural populations more likely to participate than urban populations (Table 8). In addition participation rates vary widely between provinces, and in serial prevalence studies, such as in Kisesa, participation rates in rural males and urban males and females have fallen. Travel is an especially important issue to consider in non-response rates. Data from Yaoundé, Cameroon, suggest that prevalence of HIV in men is directly associated with duration of travel in the past 12 months. Finally, reasons for non-response vary and can be either more pronounced among persons with higher risk of HIV or those with lower rate of HIV (Table 9).

Table 8. Response rates and seroprevalence by sex and region of residency, Zambia, Kenya and South Africa.

<table>
<thead>
<tr>
<th>Country</th>
<th>Coverage rates (%)</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td></td>
<td>Urban</td>
<td>Rural</td>
</tr>
<tr>
<td>Zambia</td>
<td>67</td>
<td>80</td>
</tr>
<tr>
<td>Kenya</td>
<td>58.1</td>
<td>76.4</td>
</tr>
<tr>
<td>South Africa</td>
<td>58</td>
<td></td>
</tr>
</tbody>
</table>
Recommendations for research include examining non-responders who are able to be interviewed in the next round of cohort studies and responders from prior rounds who are unable to be interviewed in future rounds. In DHS a possible solution is also a specific repeat of surveys among those who were absent during the regular data collection period. Additionally, the characteristics of those who decline HIV testing are being explored in the Kenya DHS and should be explored in future surveys, as should the characteristics of those absent during data collection. Finally, comparing the female-to-male ratios for HIV prevalence, AIDS cases and excess mortality may help explore non-participation bias.

Seven steps were recommended for reconciling antenatal-clinic based prevalence estimates and those derived from national population-based samples:

- Compare HIV prevalence among pregnant women in ANCs and in surveys
- Compare HIV prevalence between urban survey areas and urban ANCs
- Compare HIV prevalence between rural survey areas and rural ANCs
- Compare HIV prevalence between ANCs and for both sexes combined for nearby clusters in the population-based survey
- Compare rankings of HIV prevalence by geographic areas (e.g., provinces or regions) for survey and ANC data
- Assess the level of non-response in the surveys data by selected key variables that have a strong association with HIV prevalence: by sex and age groups and by urban/rural residence
- Analyze and adjust for the effect of survey non-response bias on the prevalence estimate by assuming that non-responders have the same prevalence as survey participants or, if there are good reasons to assume that the relative risk of HIV infection is higher among non-responders (e.g., urban males), adjust using higher rates of infection.

The relationship between non-response rates and underestimation of HIV prevalence is shown in Figure 9.

Table 9. Possible relationship between HIV prevalence and non-response.

<table>
<thead>
<tr>
<th>HIV higher in non-responders</th>
<th>HIV lower in non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single person household</td>
<td>Young people away at school</td>
</tr>
<tr>
<td>Traveling associated with higher HIV risk</td>
<td>High risk perception and HIV fear</td>
</tr>
<tr>
<td>Absence due to HIV-related morbidity and mortality</td>
<td>At home secondary to HIV morbidity</td>
</tr>
<tr>
<td>Fear of learning HIV-positive serostatus</td>
<td></td>
</tr>
<tr>
<td>Prior knowledge of serostatus</td>
<td></td>
</tr>
</tbody>
</table>
In the media the question has been raised whether UNAIDS and WHO should lower their estimates by some 15%, as suggested by comparisons of previous ANC-based estimates with estimates from national surveys. This is already happening to some extent with downward revision of adult prevalence estimates in many countries. In the regional EPP workshops held in 2003, among the most important clarifications was the reclassification of ANC sites that had previously been considered as rural to urban. The surveillance system is also expanding, bringing more rural sites into the system. Additionally, the new national surveys provide new information on HIV prevalence, including in rural areas and among men, although the HIV prevalence from these surveys needs to be given appropriate weight following careful consideration of non-response and any bias it may introduce. The net effect of the above factors was the reduction of the UNAIDS/WHO 2003 estimate of the number of HIV infections in sub-Saharan Africa from 29.4 million in 2002 to 26.6 million in 2003.

Figure 9. Effect of relative risk of non-response by underestimation of HIV prevalence at different prevalence levels.