ANNALS OF THE ACTM

A Journal of Tropical & Travel Medicine

ISBN 095787167 Official Journal of the Australasian College of Tropical Medicine - Volume 3 - December 2002

Official Journal of the Volume 3 - December 2002
Australasian College of Tropical Medicine

ANNALS OF THE ACTM
A Journal of Tropical & Travel Medicine

December, 2002

Official journal of the Australasian College of Tropical Medicine.

The Annals of the ACTM will be published once a year.

Secretariat

ACTM Secretariat,
P.O. Box 123 Red Hill QLD 4059 Australia
Tel. +61 (0)7 3872 2246
Fax. + 61 (0)7 3856 4727
Email: actm@tropmed.org
Design: AMAQ Design Services
Tel. +61 7 3872 2252 design@amaq.com.au

Instructions for authors:

The format of the Annals of the ACTM will, in general, follow the guidelines "Uniform requirements for manuscripts submitted to biomedical journals" and published by the International Committee of Medical Journal Editors (http://www.icmje.org/index.html).

The Annals will appear once a year and will consider for publication, papers on a wide range of topics relating to tropical and travel medicine. All papers will be refereed prior to acceptance for publication.

Papers will be included in one of the following categories:

a) **Invited/submitted reviews (5000-10,000 words).**
b) **Submitted research papers (up to 5000 words).**
c) **Case reports (1000 – 2000 words).**
d) **Research reports (1000-2000 words).**

Figures to be included: 1/4 page size = 250 words - 1/2 page size = 500 words etc. 1 page with image – 900 words; 2 pages with image-1800 words etc.

Manuscripts should be double spaced and a short summary should be included at the beginning of the paper after the title and author details.

Title page with contributor names and addresses should be on a separate page.

Each table and figure should be on a separate page together with appropriate caption, explanatory notes etc. Any acknowledgements should be included at the end of the paper before the references.

Where appropriate, authors must confirm in the paper that experimental procedures on humans and animals conformed to accepted international ethical guidelines.

References should be numbered consecutively in order of appearance in the text. For details of references, consult "Uniform requirements for manuscripts submitted to biomedical journals" at http://www.icmje.org/index.html

In the first instance, papers submitted for consideration should be sent to;
The Editor - Professor J.M. Goldsmid,
Discipline of Pathology,
University of Tasmania,
GPO Box 252-29
Hobart, Tas. 7001, Australia
Email: j.m.goldsmid@utas.edu.au
Fax + 61 (0)3 6226 4833

Final copy text files should be sent to design@amaq.com.au as an attachment (Microsoft Word) or provided on CD or Floppy. If photographs to be included need to be scanned, they can be posted to the ACTM Secretariat, P.O. Box 123, Red Hill, Qld 4059, Australia (Att. Trisha Curtis). These will be returned to the author if so requested.

Statements or opinions in papers published in the Annals of the ACTM are solely those of the authors and not necessarily those of the Editorial Board or the Australasian College of Tropical Medicine. The inclusion of commercial advertising material in the Annals of the ACTM does not constitute a guarantee or endorsement of the product on the part of the Annals or the College. The College disclaims any responsibility for any injury to persons or property resulting from published material or products referred to in articles or advertisements.

On acceptance of an article for publication in the Annals, copyright of the article is automatically transferred to the ACTM.

Editorial comment:

The Council of the Australasian College of Tropical Medicine has always been aware of the need to serve its members more fully and to provide them with value for money. Thus over the years, the College has worked for the betterment of Tropical Medicine through its secretariat services to members and through its regular publication, the ACTM Bulletin. The Bulletin has been expanded to publish College business, short scientific reports and other items of interest. To remain in touch with developments in the field of Tropical Medicine and in recognition of changing needs, about two years ago, the College established a Faculty of Travel Medicine. This created an important link between people working in the tropics and those interested in many aspects of Tropical Medicine but who were working in a non-tropical setting and in so doing it recognised the increasing importance of the health needs of travellers to and from tropical areas.

Earlier this year, Council took the decision to publish a journal, initially once a year but in time and as finances allowed, perhaps to increase the numbers of issues each year if the venture proved a success. It is with great pleasure that we present the first issue of that journal – the Annals of the ACTM – a journal of tropical and travel medicine.

We are privileged to launch the Annals with two invited reviews: The first paper is by Professor Ahmed Latif, Professor of Medicine and Dean of the Faculty of Medicine at the University of Zimbabwe. He writes with a depth of knowledge and recognised expertise to give a fascinating account of the interrelationship between HIV infection and the other common Sexually Transmitted Infections in southern Africa, together with a discussion on how this knowledge can be utilised in countries with limited resources, in dealing with the AIDS epidemic. A second review, by Dr Tim Inglis from Western Australia, discusses how technological developments are resulting in a new approach to the investigation of infections of public health significance.

The President of the ACTM, Assoc. Prof. Peter Leggat and the Editor of the Annals, Prof. John Goldsmid join in hoping that the Annals will provide all members with interesting and useful information which will help to further the role of the College in the advancement of knowledge in the fields of tropical and travel medicine and help attain the highest standards of practice in these disciplines. We invite members to submit reviews, research papers, case studies or research notes for consideration for inclusion in future issues of the Annals of the ACTM.

Assoc. Prof. P.A. Leggat, President, ACTM.

Prof J.M. Goldsmid, Editor, Annals of the ACTM.

HIV INFECTION AND SEXUALLY TRANSMITTED INFECTIONS IN SOUTHERN AFRICA

Ahmed S. Latif

SUMMARY

The highest prevalence rates of human immunodeficiency virus (HIV) infection and sexually transmitted infections (STIs) in the world are in sub-Saharan Africa. Of the 40 million persons estimated to be living with HIV infection and AIDS in 2001, 70% live in sub-Saharan Africa. Within sub-Saharan Africa the highest prevalence rates are found in the southern African countries. In some of these countries HIV prevalence rates of up to 36% have been recorded. The modes of transmission of both HIV and other STIs are the same; common modes of transmission in much of the developing world being heterosexual intercourse and vertical transmission from the infected mother to the foetus and neonate. Unsafe sexual behaviour and practices and high prevalence rates of STIs have been identified as the main causes of the spread of the HIV epidemic. A number of biological, economic, social and behavioural factors are responsible for driving the epidemic in southern Africa.

HIV infection and STIs are closely interrelated and each has an effect on the natural history of the other. HIV infection affects the natural history and response to therapy of genital herpes infection, human papilloma virus infection, syphilis, chancroid and possibly pelvic inflammatory disease.

The methods of prevention of both HIV infection and STIs are the same. Primary prevention of both may be achieved through behaviour change. In addition it has been shown that effective STI management leads to a reduction in HIV transmission. Therefore an essential component of HIV/AIDS control is the rapid and effective treatment of the treatable STIs.

INTRODUCTION

The United Nations Joint Programme on AIDS (UNAIDS) estimates that over 40 million adults and children were living with HIV infection and AIDS by the end of 2001[1]. Over 28 million of these live in Africa south of the Sahara desert. Sub-Saharan African countries are not uniformly affected by HIV infection. The prevalence rates of HIV infection in Senegal are less than 1%, while in Rwanda and Burundi the prevalence rates are thought to be around 11%. In Guinea-Bissau the prevalence of HIV infection is estimated by UNAIDS to be 2.5% and interestingly the prevalent virus type in Guinea-Bissau is HIV Type II. In the rest of Africa HIV infection is predominantly caused by HIV Type I [1]. The epicentre of the pandemic, previously thought to be central and eastern Africa, has shifted to southern Africa. The highest prevalence rates of HIV infection are reported in Botswana (36%),

Table 1 AIDS/HIV cases and adult HIV prevalence rates in some southern African countries

COUNTRY	CASES	RATE (%)
Malawi	800,000	16
Zambia	870,000	20
Zimbabwe	1,500,000	25
Mozambique	1,200,000	13
South Africa	4,200,000	20
Botswana	290,000	36
Lesotho	310,000	31
Swaziland	130,000	25
Namibia	160,000	20

HIV INFECTION AND SEXUALLY TRANSMITTED INFECTIONS IN SOUTHERN AFRICA

Ahmed S. Latif
MBChB, DipVen, FCP, MD, FACTM
Professor of Medicine and Dean,
College of Health Sciences,
University of Zimbabwe,
P. O. Box A 178,
Avondale, Harare, Zimbabwe
Email: aslatif2000@yahoo.com

Lesotho (31%), Swaziland (25%), Zimbabwe (25%) and South Africa (20%) [1]. Table 1 summarises the estimated number of cases and the prevalence rates of HIV in some southern African countries.

The pandemic of HIV infection has had devastating consequences on all sectors of society. Its effects are found not only in infected individuals and their family members but also on the community. In countries with a high HIV prevalence in Africa the epidemic has adversely affected the health system, the agriculture, education, transport, labour and mining sectors, and economic growth and development has slowed down or stopped. In a number African countries as a result of the pandemic, gains made in life expectancy rates at birth in the years before 1980 have been lost, and it is estimated that life expectancies in countries affected badly by HIV infection and AIDS may be less than 40 years [2]. Life expectancy data are shown in Figure 1.

HIV prevalence is thought to be decreasing in some central African countries. Studies carried out in Uganda have shown that prevalence of HIV infection amongst persons between the ages of 19 and 45 years has fallen from 24% in 1990 to less than 10% in 1999 [1].

The transmission of HIV in adults in sub-Saharan Africa is mainly through heterosexual intercourse [3]. Transmission is enhanced in the presence of other STIs [4-6]. Many of these STIs are highly prevalent in Africa, and have contributed significantly to the rapid spread of HIV in the region. The World Health Organization estimates that annually about 69 million new episodes of 4 treatable STIs occur each year in persons aged between 15 and 49 years in Sub-Saharan Africa [7]. The improved control of STIs has therefore been advocated as a strategy for the control of HIV transmission [8]. Table 2 summarises these data.

Figure 1: Projected changes in life expectancy in some Southern African countries 1955 to 2000 (UN Population Division)

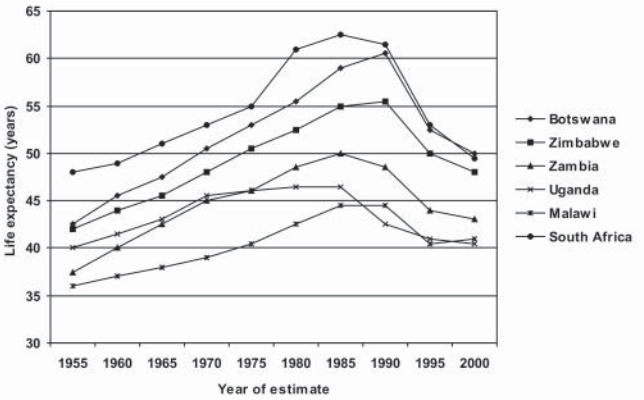


Table 2 Estimated annual incidence of selected STIs in Sub-Saharan Africa

	Incident cases per year (millions)		
	Men	Woman	Total
Syphilis	2.1	1.7	**3.8**
Chlamydial infection	7.6	8.2	**15.8**
Gonorrhoea	8.2	8.8	**17.0**
Trichomoniasis	16.2	15.9	**32.1**
Total	**34.1**	**34.6**	**68.7**

Factors driving the HIV epidemic in southern Africa

A number of social, behavioural and biological factors have been responsible for the perpetuation of the epidemic of HIV infection in southern Africa. The problem has been compounded by the weakening health-service delivery systems due to the poor economic climate prevailing in many countries in the region. These factors are summarised in Panel 1. Unsafe sexual behaviour and practices contribute to the transmission of STIs including HIV infection. Risky sexual behaviour is affected by social, economic, and cultural factors, and its effects are compounded by poor access to care and by poor health seeking behaviour.

Untreated, many STIs may remain asymptomatic for long periods of time, especially in women, and hence transmission of infection continues. Frequent sexual partner change and engaging in multiple concurrent relationships is a major factor in the transmission of HIV since such activities lead to infection and persons who have recently been infected have a high concentration of virus in secretions and are highly infectious to others [9]. Although condom use is known to protect against the acquisition and transmission of STIs there is a general reluctance amongst men to use them and women are not skilled to negotiate condom use with their partners. With the introduction the female condom women have, to some extent, been empowered to make an informed choice to protect themselves from infection. However women who depend on marriage for economic survival are unable to insist on condom

Panel 1: Factors driving the HIV epidemic in Southern Africa

1. Social and behavioural factors:
Social and behavioural factors implicated in enhancing the transmission of HIV infection:

- Frequent partner change amongst the adult population
- Overlapping sexual partnerships – as opposed to serial monogamous relationships
- Engaging in commercial sex
- Separation of marital partners - moving back and forth between home and distant workplaces
- Drinking alcohol in public places
- Sex across age groups; older men having sex with young women and girls
- Women's economic dependence on marriage
- Women's lack of empowerment in negotiating safe sex
- Poverty
- Unwillingness to use a condom

2. Biological factors:
Biological factors implicated in perpetuating the epidemic:

- High rates of sexually transmitted infections in communities where HIV is prevalent
- Low rates of male circumcision
- Prevalence of more virulent clades of HIV-1, e.g., clade C HIV-1 is more prevalent in southern Africa

use by their spouses. Studies have shown that with condom use, a substantial reduction in HIV incidence may be achieved [10].

The role of alcohol use in HIV acquisition has been demonstrated in studies carried out in southern Africa. In a cohort study carried out among HIV negative factory workers in Zimbabwe it was demonstrated that the drinking of alcohol in public places was an independent risk factor for HIV acquisition [11].

The role of the intact foreskin in men in the acquisition of HIV infection and other STIs has been suggested [12,13]. Studies carried out in two African cities with very high HIV prevalence (Kisumu, Kenya and Ndola, Zambia) and two with much lower prevalence (Cotonou, Benin and Yaoundé, Cameroon) have provided evidence that differences in HIV prevalence between the cities could not be accounted for by variation in sexual behaviour alone, since Yaoundé had the highest rate of partner change. Differences in biological cofactors such as male circumcision and ulcerative STIs, which affect the per-contact probability of HIV transmission, seemed more important than behaviour in driving the epidemic [14,15].

STIs are thought to enhance HIV transmission by increasing the infectiousness of HIV positive individuals and the susceptibility of HIV negative individuals by breaching mucosal integrity as a result of ulceration or inflammation, and by recruiting HIV infected or susceptible target cells to the genital tract. Evidence for STI cofactor effects comes from observational studies showing strong associations between HIV and STIs even after adjustment for confounding by risky sexual behaviour [16-18] and from biological studies of genital secretions from STI patients showing increased shedding of HIV that decreases after treatment [19-21]. The data suggest that ulcerative STDs, such as chancroid, syphilis, and herpes, have a stronger effect than non-ulcerative STDs, presumably because of greater disruption of the genital mucosa.

Burden of STIs

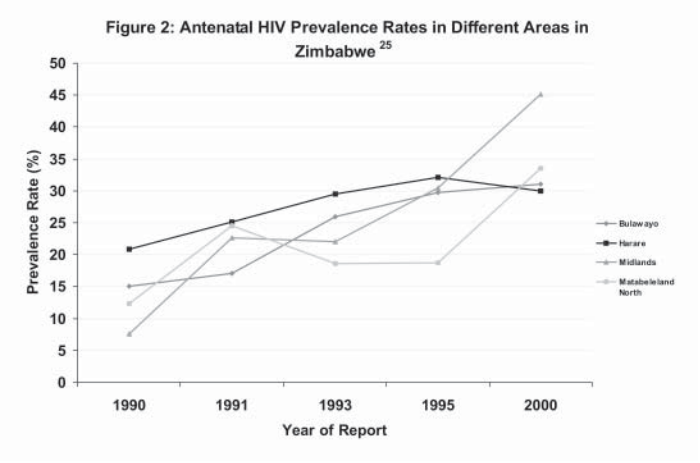
Table 2 shows WHO estimates of the annual incidence of curable STIs in sub-Saharan Africa. These estimates are based on extrapolation of prevalence data from various sources and may not reflect the true picture. STI rates are clearly high in many countries in Africa and are common reasons for adult outpatient attendances. The most reliable data are derived from antenatal clinics in which women are screened for syphilis. Reported rates of active syphilis range from 2·5% in Burkina Faso to 17·4% in Cameroon [22,23].

Prevalence of HIV infection and STIs in Zimbabwe

Since the first cases of AIDS were recognised in 1983 [24] there has been a massive exponential increase in the number of reported cases in Zimbabwe. Prevalence of HIV infection in the country has been monitored mainly through the periodic sentinel surveys carried out amongst antenatal clinic attendees [25]. In addition a number of studies have been carried out amongst targeted groups considered to be at high risk for infection [26-28].

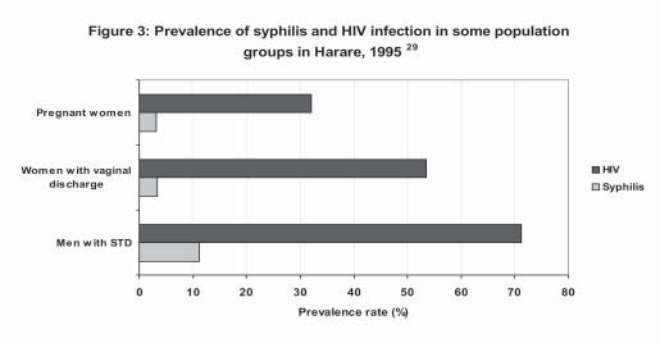
Figure 2 demonstrates the change in trend in HIV prevalence amongst pregnant women tested in the cities of Harare and Bulawayo, and in Midlands and Matabeleland North provinces. It may be noted that in some parts of the country the HIV prevalence rates amongst pregnant women have more than doubled over a period of ten years.

Persons seeking care for STIs including vaginal discharge demonstrate higher HIV-seropositivity rates than women attending for antenatal care. In a study carried out in Harare in 1995 [29], it was demonstrated that over 50% of women seeking care for vaginal discharge and over 70% of men seeking care for an STI were HIV positive. Figure 3 summarises these findings. It was noted that the prevalence of syphilis was much lower than that of HIV infection in these groups.



Age-specific prevalence of selected STIs in symptomatic and asymptomatic women in Zimbabwe

In a study carried out in Harare [29] the age-specific prevalence of syphilis, gonorrhoea, chlamydial infection, genital warts and trichomoniasis was determined in a group of asymptomatic antenatal clinic attendees and a group of women seeking care for vaginal discharge. Amongst 1189 pregnant women aged between 15 and 45 years evidence for syphilis was found in 4%, gonococcal infection in 1.7%, chlamydial infection in 4.3%, trichomoniasis in 10.7% and genital warts in 3.3%. The prevalence of HIV infection in the cohort of pregnant women studied was 38.3%.



Amongst the 467 non-pregnant women aged between 15 and 52 years with vaginal discharge, evidence for syphilis was found in 3.3%, gonococcal infection in 9.6%, chlamydial infection in 7.9%, trichomoniasis in 19.1% and genital warts in 10.1%. The prevalence of HIV infection in non-pregnant women seeking care for vaginal discharge was 53.6%.

Other than HIV infection, the commonest STI found in both pregnant and non-pregnant women was trichomoniasis (10.7% of pregnant women and 19.1% of non-pregnant women).

In the group of women studied the prevalence of any of these STIs was highest amongst those aged less than 18 years being 30.4% amongst pregnant women and 75% amongst non-pregnant women with vaginal discharge. Figures 4 and 5 summarise these data. The study also showed that HIV infection was commonest among women aged between 25 and 29 years. However HIV infection was also found in young women aged less than 20 years as well.

In another study carried out in 1998 among 1634 family clinic attenders in the two major cities in Zimbabwe, the prevalence of candidiasis was found to be 17.3%, the prevalence of bacterial vaginosis was 9%, trichomoniasis 4.1%, chlamydial cervicitis 2.9% and gonorrhoea 1.8%. The low prevalence of cervical gonococcal and chlamydial infection confirmed the low prevalence of these infections in antenatal carried attenders found in 1995 [29].

In a study carried out among 497 men attending for STI care in Zimbabwe [30], 244 (49.1%) presented with the syndrome of urethral discharge, 179 (36%) had the syndrome of genital ulcer disease, while 35 (7%) had both syndromes. *Neisseria gonorrhoeae* was isolated from 61% of men with urethral discharge. *Chlamydia trachomatis* was identified in 33 (22.1%) of men with urethral discharge. Mixed gonococcal and chlamydial infection occurred in 15.4% of men with urethral discharge. 10.7% of men had syphilis while HIV infection was found in 73.9%. Risk factors associated with HIV seropositivity included a past history of STI (p=0.001), and, drinking of alcohol (p=0.008).

Figure 4: Age-specific prevalence of selected STIs amongst pregnant women [29]

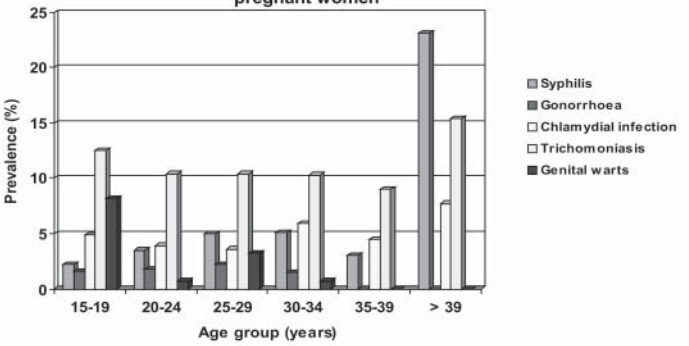
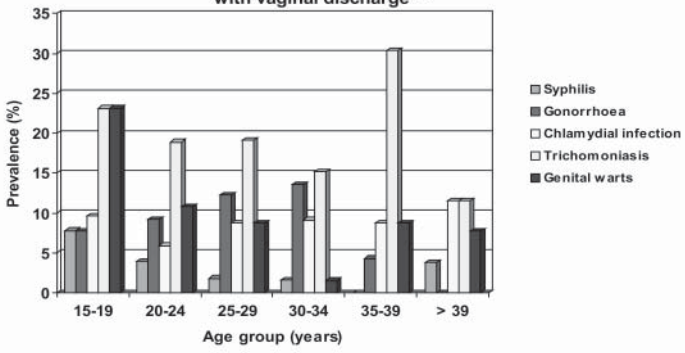


Figure 5: Age-specific prevalence of selected STIs amongst women with vaginal discharge [29]



STD control for HIV-1 prevention

HIV control measures include improved STI management, aiming at reducing the prevalence of STIs and hence the probability of HIV transmission. In an earlier study of HIV concordant and discordant couples carried out in Zimbabwe, it was demonstrated that HIV concordance between spouse pairs was associated with a history of genital ulcer disease in the male partner [5]. Studies have also demonstrated non-ulcerative STIs also facilitate the transmission of HIV [16]. The effect of STI control on HIV incidence is difficult to assess. Three trials have been conducted in East Africa in order to address this question:

1. In Mwanza, Tanzania, a study demonstrated that improved STI treatment services reduced HIV incidence in the general population by about 40% [31]. The incidence of new cases of active syphilis also fell sharply [32]. The syndromic management approach was used in treating symptomatic persons with STIs in the study.

2. In Rakai, Uganda, the effect of mass treatment of the population for common bacterial STIs was measured on rates of HIV infection. Disappointingly, although reductions were seen in some STIs, there was no significant effect on HIV incidence [33].

3. A third trial was carried out in Masaka, Uganda. In this study the effect of a community-based behavioural intervention with or without the provision of improved STI care through the syndromic management approach was assessed. Despite reductions in STIs and changes in reported behaviour, neither the behavioural nor the STD treatment intervention had a significant effect on HIV-1 incidence [34].

A number of reasons have been postulated for the contrasting findings [35,36]:

1. The interventions in the three studies were different; in Mwanza the intervention was mainly the rapid treatment of symptomatic STIs through the syndromic management approach while in Rakai the intervention was periodic mass treatment and in Masaka the intervention focused not only on syndromic management of symptomatic STIs but also on promoting behaviour change.

2. The epidemic of HIV infection in Uganda had already showed signs of being generalised rather than concentrated in high-risk groups, with new infections occurring between stable partners who are repeatedly exposed to HIV because of the high prevalence of infection in the general population.

3. At the time of the trials there was much less risky behaviour in Uganda than in Tanzania.

4. Repeated periodic mass treatment was not given frequently enough to have an effect on reducing STI prevalence in the community.

5. Information and education of the general public led to less risk-taking sexual behaviour and hence the low prevalence of STIs.

These findings have important implications for HIV and STI control programmes. The importance of early effective treatment of STIs has a beneficial effect on HIV control. Wherever STI prevalence rates are high the implementation of improved STI management is an important component of HIV control. Finally, the approach to STI and HIV control needs to be multi-pronged, and should address both biomedical and socio-behavioural variables.

A number of interventions have been shown to work in controlling STIs and the spread of HIV infection in different parts of the world [8]. For control programmes to be effective some or all of the interventions should be implemented. Interventions found to be effective include:

§ Mass media campaigns
§ Condom social marketing
§ Prevention of mother-to-child transmission
§ Programmes for out-of-school youth
§ Treatment of sexually transmitted infections;
§ Outreach to men who have sex with men
§ Public sector condom promotion and distribution
§ Voluntary counselling and testing programmes
§ School-based programmes
§ Workplace programmes
§ Peer counselling for sex workers
§ Harm reduction programmes for injecting drug users

Since HIV infection is an STI and since its transmission is facilitated by other STIs interventions should be developed to control STIs. Some of these activities are shown in Panel 2.

Panel 2: STI control for HIV prevention

- **Primary prevention**
STIs and HIV share common modes of transmission and hence the primary prevention activities for both are the same. Primary prevention activities should promote public information and education, safer sexual behaviour, safer sexual practices including abstaining from sex, having sex with only one lifelong mutually faithful partner delaying sexual debut, reducing frequent partner change, avoiding sex across large age gaps, using condoms
- **Rapid and effective treatment for treatable STIs**
Strategies for the rapid and effective treatment of STIs should be implemented and should include improved access to high quality care, providing STI care through the syndromic case management approach, promoting good health seeking behaviour
- **Case finding**
Partner notification and treatment, detecting infections, among attenders of reproductive health centres, detecting STIs in groups at high risk for infection
- **Targeted interventions**
Developing interventions to detect and treat STIs in groups engaged in high-risk behaviour, e.g., youth in- and out-of-school, sex workers, long-distance truckers
- **Voluntary counselling and testing for HIV**
Promoting voluntary testing for HIV in groups at risk for STIs and HIV infection, promoting self assessment of risk

HIV INFECTION AND THE NATURAL HISTORY OF STIs

HIV infection, by altering the host's immune response, may alter the natural history of other STIs [6]. Possible effects of HIV infection on STIs include: altered clinical features of other STIs, alteration in the accuracy of diagnostic tests, and an alteration in the response to treatment [37]. The frequency of occurrence of HIV effects on STIs is not clear. Also what is not clear is whether the effects are due to HIV itself or are due to the immune suppressed state that is associated with HIV infection. The HIV related effects on STIs have been reported in persons with syphilis, chancroid, herpes simplex virus infection, and human papilloma virus infection. These infections are discussed individually below.

1. Syphilis

HIV infected persons who become infected with *Treponema pallidum* were more likely to present with secondary syphilis, and that HIV infected subjects with secondary syphilis were more likely to have persistence of the primary chancre [38]. Neurological manifestations of syphilis have been reported to occur more frequently in patients co-infected with HIV [39]. Usually the neurological manifestations of syphilis in HIV infected patients are those that are usually associated with early syphilis, i.e., asymptomatic neurosyphilis, syphilitic meningitis, meningovascular syphilis and ocular manifestations. Involvement of the central nervous system, as evidenced by changes in the cerebrospinal fluid, occurs early in the course of syphilis in both HIV-infected and non-HIV-infected individuals. It has been reported that HIV infection may modify an individual's serologic response to infection with *T. pallidum*. Studies have reported that in persons with HIV infection false positive reactions to the non-specific tests for syphilis may occur and also more persistent and higher rapid plasma reagin (RPR) titres may occur. In addition, in persons with syphilis and more advanced HIV infection, false negative reactions in the specific tests for syphilis have been reported [40-43].

2. Chancroid

Studies have shown that HIV infection diminishes the response to treatment of chancroid, particularly when single dose treatment regimens are used [44]. Other studies have shown that the clinical features of chancroid differ in immunosuppressed persons, in such persons chancroid may present with multiple genital ulcers and are less likely to have inguinal bubo formation [45]. Genital ulcers caused by *Haemophilus ducreyi* may be quite persistent in persons immunosuppressed with HIV infection. A diagnostic dilemma that clinicians in Africa often face is that in persons with HIV infection and immune suppression it is often extremely difficult to differentiate clinically between the persistent genital ulcers of chancroid and those caused by herpes simplex virus particularly in the absence of a bubo.

3. Genital herpes infection

In persons with HIV infection recurrences of genital herpes simplex virus infection have been reported to occur more frequently and tend to be more severe and persistent [46,47]. Persistent primary lesions of genital herpes simplex virus occur and the frequency of recurrences increases as the cell mediated immunity declines.

In Africa, HIV and herpes simplex virus type-2 (HSV2) have a synergistic relationship. HSV2 infection is widespread, with seroprevalence rising to 70–80% by age 30 years in some parts of eastern and southern Africa [15,48,49]. HSV2 prevalence rates seem to be somewhat lower in West Africa, where HIV-1 spread is also less extensive [15]. The reasons for geographical variation in HSV2 prevalence are unclear, although male circumcision may be protective against HSV2 as well as HIV-1 infection, which might provide part of the explanation [12].

HIV transmission is enhanced by HSV2 infection and by other genital ulcerative conditions. In a meta-analysis of data from longitudinal studies, HIV risk was doubled in HSV2-seropositive individuals [50], and a strong association between HIV and HSV2 was found in a study of men in Zimbabwe [51].

4. Human papilloma virus infection

HIV infection alters the clinical presentation of genital human papilloma virus infection. Genital warts tend to be larger, are more extensive and more persistent, and recur more frequently after treatment in persons with HIV infection when compared to non-HIV-infected individuals. Genital warts in persons with HIV infection may be multifocal and the transition of warts to neoplasia has been reported. An increased prevalence of anal and cervical cancer has been reported in homosexual men and in heterosexual women [52-54]. Studies have shown that the rate of detection of human papilloma virus DNA is greater in persons with HIV infection and that multiple serotypes of the virus (Types 16 and 18) may be identified [55].

5. Other STIs

There are no published reports describing the effect of HIV infection on gonococcal, chlamydial and *Trichomonas* infection. However, it has been reported that gonococcal pelvic inflammatory disease occurs more commonly in HIV infected women when compared non-HIV-infected controls [56]. Candidial balanoposthitis and vulvovaginitis occur extremely commonly in immunosuppressed persons. The response to therapy of candidiasis with the standard topical or systemic therapy seems not to be adversely affected by HIV infection, though recurrences of thrush following successful initial therapy occur commonly.

Sexually transmitted infections and the natural history of HIV infection

Theoretically, STIs may affect the progression of HIV infection by inducing immunosuppression themselves, e.g., as happens during the course of early syphilis and in infection with the herpes simplex virus, or by chronic immune stimulation and even by direct viral interaction [40,57]. Studies have shown that in homosexual men, rectal gonorrhoea and cytomegalovirus infection are associated with faster development of AIDS [58].

There is laboratory evidence that HIV is activated by some regulatory genes of several DNA viruses including the herpes simplex virus, cytomegalovirus, Epstein Barr virus, the human herpes virus type 6, the hepatitis B virus and the papova virus [59]. Though studies are lacking there is a possibility that infection with other viruses may trigger HIV replication and further immune suppression.

Factors associated with STI and HIV acquisition

A case control study carried out among blood donors during the early period of the epidemic in Zimbabwe [60] identified a number of risk factors associated with HIV seropositivity including, multiple sexual partners, engaging in commercial sex, being in the habit of taking alcohol, having had STIs in the past and being married but living away from the spouse. In a cohort of HIV negative male factory workers in Zimbabwe, HIV seroconversion was associated with similar risk factors [11]. The role of STIs in the transmission and acquisition of HIV has also been demonstrated in the region [5, 16-18].

In a study among women in Zimbabwe [29] factors associated with HIV infection include having a partner who is HIV positive, having had STIs in the past and interestingly it was found that the absence of intravaginal lactobacilli was strongly associated with being HIV positive ($p<0.0001$; CI: -0.98 to –0.51 among 1189 pregnant women studied; and $p<0.0001$; CI: -1.4 to –0.6 among non-pregnant women with vaginal discharge). Lactobacilli form part of the normal vaginal flora and by their production of organic acids, and in some species hydrogen peroxide, form a natural chemical barrier against vaginal infections [61]. It is postulated that the use of herbal and chemical substances intravaginally to produce dryness and tightness of the vagina for the purpose of sexual gratification of partners results in alteration of vaginal flora [29]. This practice is commonly encountered in many countries in the southern African region.

The syndromic management of STIs

A large number of bacterial, viral, fungal and protozoal infections may be transmitted from person to person during sexual intercourse and result in STIs. In order to make a specific aetiologic diagnosis of STI, laboratory facilities are needed.

Syndromic management is one approach of treating STIs that is based on symptoms and signs rather than laboratory tests and can be undertaken by different cadres of health professionals. In resource-constrained settings laboratory services are not available at health facilities where most care-seekers attend.

Most pathogens that cause STIs produce a limited range of easily recognizable symptoms and signs. These symptoms and signs may be identified after taking a history and examining a patient and recognising the pattern of symptoms and signs as a syndrome. The STI-associated syndromes and their causes are shown in Panel 3. The common sexually transmissible pathogens present in symptomatic patients as a small number of syndromes. In the syndromic management approach care providers are encouraged to take a history from patients and then to examine them and a make a diagnosis of the STI syndrome. Once a diagnosis is made the patient is treated for all the common pathogens that cause the syndrome [62]. However the syndromic approach is only practical when symptoms and/or signs are present. In persons with STIs, who do not have symptoms or signs, the diagnosis can only be made by carrying out laboratory tests. Women with STIs, particularly gonococcal and chlamydial cervical infection, may have no symptoms, and may remain undiagnosed until complications occur or until a sexual partner becomes infected.

Panel 3: STI-associated syndromes and their causes

STI syndrome	STI-related causes	Treatment
Urethral discharge syndrome	*Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis*	Treat for gonococcal and chlamydial infection
Vaginal discharge syndrome	*Candida albicans, T. vaginalis*, bacterial vaginosis, *N. gonorrhoeae, C. trachomatis*	Treat according to STI risk and the clinical features of the discharge*
Syndrome of genital ulcers	*Treponema pallidum, Haemophilus ducreyi*, herpes simplex virus, *C. trachomatis, Calymmatobacterium granulomatis*	Treat for syphilis and depending on prevalence, for chancroid, LGV or donovanosis
Syndrome of lower abdominal pain/tenderness in women	Pelvic inflammatory disease (PID) caused by *N. gonorrhoeae, C. trachomatis*, anaerobic bacteria	Treat for gonococcal and chlamydial infection as well as for anaerobic bacterial infection
Syndrome of acute scrotal swelling	*N. gonorrhoeae, C. trachomatis*	Treat for gonococcal and chlamydial infection
Syndrome of acute inguinal lymphadenitis (bubo)	*H. ducreyi, C. trachomatis* (Types L1, 2 and 3)	Treat for chancroid and LGV
Syndrome of purulent neonatal conjunctivitis	*N. gonorrhoeae, C. trachomatis*	Treat for gonococcal and chlamydial infection

LGV = Lymphogranuloma venereum, which is caused by *C. trachomatis* Types L1, 2 or 3
* See text describing risk assessment and management of vaginal discharge syndrome

Once a syndromic diagnosis is made then patients are treated for the common causes of the syndrome (see Panel 3). It is necessary therefore to treat for more than one infection though the patient may have a single infection. The over-treatment associated with this approach has been found to acceptable and cost-effective. It is important that prior to developing standard treatment guidelines some studies are carried out to determine the common causes of STI syndromes locally and to determine the antimicrobial susceptibility pattern of STI pathogens.

Management of vaginal discharge syndrome

Most STI syndromes may be managed effectively and appropriately using the syndromic management approach. However, the syndromic management of vaginal discharge syndrome poses special problems:

§ vaginal discharge is a common symptom in women and may physiological;

§ it may indicate vaginitis or cervicitis;

§ cervicitis is usually caused by STI pathogens such as *N. gonorrhoeae* or *C. trachomatis*, and both these infections may lead to serious complications such as pelvic inflammatory disease;

§ vaginitis is by far the commonest cause of non-physiological vaginal discharge;

§ vaginal discharge may be caused by a larger range of pathogens

To treat vaginal discharge for both cervicitis as well as vaginitis requires that the patient receives treatment for 5 infections though she may only have a single infection. To treat all women with vaginal discharge for vaginitis initially, since that is the commoner cause, may lead to the delayed treatment of cervicitis with the possibility that serious complications may ensue. Conversely, if all women are treated for cervicitis initially, then the patient may not be relieved of her symptoms as she probably has vaginitis which is the commoner condition. It is therefore advisable to carry out an assessment of risk for cervicitis in all women who attend with vaginal discharge. The World Health Organization (WHO) advises that all women presenting with vaginal discharge should have an assessment for risk of cervicitis performed [63]. The risk assessment is based on demographic and behavioural characteristics and is applicable only in women who present with symptoms and signs of vaginal discharge. WHO advises that women with vaginal discharge should be considered risk assessment positive if:

§ The partner has STI

Or if any two of the following are found:

§ Patient is less than 21 years of age

§ The patient is an unmarried woman

§ The patient admits to having had sex with a new partner in the last 3 months

§ The patient admits to having had sex with more than one partner in the last 3 months.

WHO also advises that these risk factors may not be universally applicable and that wherever possible studies should be carried out locally to determine risk factors. The sensitivity and the specificity for the detection and treatment of cervicitis using this approach are quite low. Therefore WHO advises that all women with a vaginal discharge who have a positive risk assessment of cervicitis should be given treatment for gonococcal and chlamydial infection and if the discharge is suggestive of candidiasis clinically, then treatment for vaginal candidiasis should also be given. If the discharge is suggestive of trichomoniasis or bacterial vaginosis then appropriate treatment should be provided.

Risk factors for cervicitis in women with vaginal discharge have been identified in a number of African countries and vary considerably from place to place. In Zimbabwe we were able to demonstrate that in women with vaginal discharge the following risk factors were associated with cervical gonococcal and/or chlamydial infection [29]:

- The patient uses of intravaginal drying agents (p=0.04),
- The patient has had sex with more than 1 partner in the last 3 months (p=0.02),
- The patient has had sex with a new partner in the last 3 months (p=0.003),
- The patient states that her partner has an STI (p=0.01),
- The patient states that her partner is currently using a condom with the subject (p=0.03)

In this study the age, and marital status of the patient were not identified as risk factors. The fact that current use of condoms being identified as a positive risk factor for cervicitis is interesting and further investigations revealed that men often commence using condoms after realizing that they may have become infected through casual sex.

Finally in the syndromic management approach, comprehensive care is provided and the opportunity is taken to educate and counsel the patient on the risks of STIs and the association between STIs and HIV infection, the patient is counselled on risk reduction after discussing his/her risk taking behaviour and reasons for risk taking, the patient is advised on ways of preventing becoming infected, the patient is taught how to use a condom and is given a supply of condoms, and the patient is encouraged to arrange for his/her partner to be treated.

Management of genital ulcer syndrome

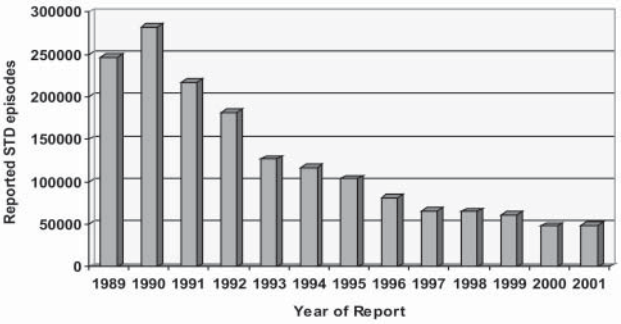
Genital ulcers may be caused by a number of sexually transmissible and non-sexually transmissible conditions. The common STI-related causes include, herpes simplex virus, *T. pallidum, H. ducreyi, Chlamydia trachomatis* (Types L1, L2 and L3), and *C. granulomatis.* As in the case of vaginal discharge, it would be inappropriate to treat for all the causes of in every patient. Herpes simplex virus infection is an incurable lifelong infection. Since the advent of HIV infection in Africa genital herpes simplex virus infection is probably the commonest cause of genital ulcerations [32,48,49]. The recommendations for the syndromic management of genital ulcers do not include treatment for herpes simplex virus; most countries in southern Africa recommend treatment for syphilis and for chancroid, LGV or granuloma inguinale (Donovanosis) depending on prevalence. WHO advises that in areas of high prevalence of genital herpes simplex virus infections (more than 10% of genital ulcers being caused by herpes simplex virus), the inclusion of acyclovir or a similar anti-herpes simplex virus agent in the syndromic management of genital ulcers may be considered [63].

The changing prevalence of STIs in Zimbabwe

A system of universal reporting of STI episodes according to syndromes is followed in Zimbabwe. However reporting is often incomplete and does not occur from the very large and well-utilized private sector. Countrywide it has been noted that there has been a slight decrease in the number of STI syndromes managed at public sector based health facilities. In 1994 7.4% of all outpatient attendances in the country were for STIs; in 1998 this figure dropped to 5.6% [64].

Within the City of Harare a dramatic decline in STI episodes has been reported [65]. Primary care clinics run by the Health Services Department of the City of Harare are obliged to report all episodes of all illnesses treated and STIs are reported syndromically. Figure 6 shows the annual episodes of STIs reported from Harare Health Services Department clinics from 1989 to 2001.

Figure 6: Annual episodes of STIs reported from Harare City Health Department Clinics, 1989-2001



The decrease in the annual reported episodes of STIs in Harare may be explained in a number of different ways:

- The decline may be the result of a true decrease in STI incidence,
- It may be the result of a change in health seeking behaviour, or
- It may be the result of under-reporting

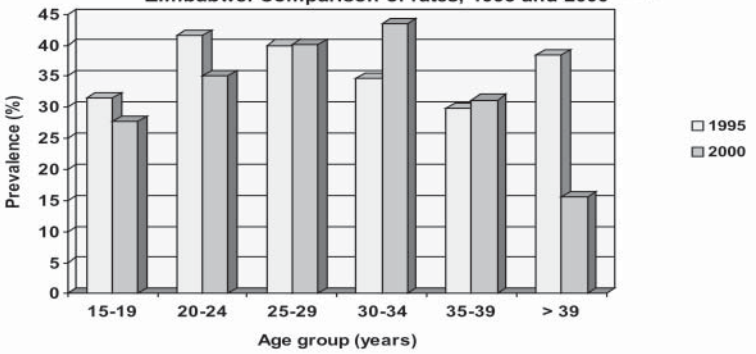
Under-reporting is an unlikely explanation for this pattern as reporting from Harare Health Services Department clinics is most complete and has the best coverage in the country. There may well have been a change in health seeking behaviour with more persons seeking care in the private sector. However, in a survey carried out in 1999 [66], it was shown that health facilities in the private and industrial sector also reported a decline in the numbers of patients attending for STI care. A true reduction in the incidence of STIs in Harare is likely, and possible reasons for this include:

- High level of knowledge and awareness of the nature and transmission of STIs and HIV infection in the country achieved through incorporation of health education programmes within school curricula, public health education and targeted education programmes for groups considered to be at greater risk for infection. In addition
- Widespread promotion and distribution of condoms
- Nationwide promotion of good health seeking behaviour
- Incorporation of high quality care for STIs within primary health care and reproductive health care services through the syndromic management approach making STI care accessible and acceptable
- Change in the sexual behaviour of the public as a result of the awareness of the high mortality rates among young people

The current STI care and prevention activities are fully integrated within primary health care and reproductive health care programmes throughout the country [66]. This has led to STI care being more accessible and less stigmatising, and as a result more acceptable. Through the syndromic STI management approach persons with STIs are treated effectively at the first point of contact with a health facility. This results in persons with STIs being rendered non-infectious quickly and being less likely to developing complications.

The syndromic management approach for the management of STIs has also contributed to the decrease in the prevalence of STIs in the country. In the syndromic approach to the management of genital ulcers symptomatic persons receive treatment for syphilis and chancroid. The treatment for syphilis comprises of an intramuscular dose of benzathine penicillin for persons not allergic to penicillin. This has been a nationwide practice for almost 20 years now [67], and one of the effects of this approach has been the reduction in the prevalence of syphilis. This reduction is evidenced amongst pregnant women attending for antenatal care in the two major cities in the country. In Harare syphilis prevalence rates fell from 5.1% in 1988 to 1.1% in 1999, while in Bulawayo the rates fell from 10.3% in 1988 to 5.8% in 1999.

Figure 7: Age-specific HIV prevalence rates in pregnant women in Zimbabwe: Comparison of rates, 1995 and 2000 [25,30]



Periodic surveys of HIV prevalence among antenatal clinic attenders have shown HIV seropositivity of around 35% in 2000. This rate is similar to the rate of 32% found in 1995. However when HIV prevalence rates are examined according to age groups it is noted that whereas in 1995 the highest HIV prevalence rates were in the 20 to 24 year olds, in 2000 the highest rates were found in the 30 to 34 year olds (Figure 7). Also it is noted that HIV prevalence in the age groups 15 to 19 years and 20 to 24 years was lower in 2000 than it was in 1995.

The differences observed in the younger age groups are encouraging and may be indicative of the reduction in incidence of HIV infection in the country.

CONCLUSION

The highest prevalence rates of HIV infection in the world are found in southern Africa. Most countries, already suffering from the effects of economic recession, have to contend with the high morbidity and mortality attributed to the pandemic. The effects of the epidemic are seen at the individual, community and the national levels and all sectors of society are affected. The high costs of drugs have precluded the large-scale use of antiretroviral therapy which forms the standard of care in the developed world. With the pandemic of HIV infection the burden of disease has increased to such levels that in many countries health services have become overwhelmed. The high STI prevalence rates in many countries in southern Africa have been partly responsible for the rapid spread of HIV infection. HIV infection and other STIs are closely linked and there is evidence that with effective control of STIs, HIV incidence may be reduced. The delivery of high quality STI care may be made accessible and acceptable by integrated services within primary health care and reproductive health care facilities. Effective STI care may be provided through the syndromic case management approach. Some countries in east and central Africa have demonstrated a slow but measurable decline in HIV prevalence possibly through behaviour change, effective STI service provision and condom promotion and use. In countries with high STI prevalence rates, improved STI treatment remains an important component of HIV control programmes.

REFERENCES

1. UNAIDS. Report on the global HIV/AIDS epidemic. Geneva, Switzerland. June 2002.
2. United Nations Population Division. World Population Prospects: The 2000 Revision. New York. 2001.
3. Aral S. Heterosexual transmission of HIV: the role of other sexually transmitted infections and behavior and its epidemiology, prevention and control. *Annu Rev Public Health.* 993;14:451-467.
4. Kamali A, Nunn AJ, Mulder DW, Van Dyck E, Dobbins JG, Whitworth JA. Seroprevalence and incidence of genital ulcer infections in a rural Ugandan population. *Sex Transm Infect* 1999; 75: 98–102.
5. Latif AS, Katzenstein DA, Bassett MT, Houston S, Emmanuel JC, Marowa E. Genital ulcers and transmission of HIV among couples in Zimbabwe. AIDS. 1989;3:519-23.
6. Wasserheit JN. Epidemiological synergy: interrelationships between human immunodeficiency virus infection and other sexually transmitted diseases. *Sex Transm Dis* 1992; 19: 61-77.
7. WHO. Global prevalence and incidence of selected curable sexually transmitted infections: overview and estimates. Geneva: WHO, 2001.
8. Stover J, Walker N, Garnett GP, Salomon JA, Stanecki KA, Ghys PD, Grassly NC, Anderson RM, Schwartländer B. Can we reverse the HIV/AIDS pandemic with an expanded response? Lancet 2002; 360: 73-77.
9. Moss GB, Overbaugh J, Welch M, et al. Human immunodeficiency virus DNA in urethral secretions in men: association with gonococcal urethritis and CD4 cell depletion. *J Infect Dis* 1995; 172: 1469–74.
10. Rojanapithayakorn W., Hanenberg RS. The 100% Condom Program in Thailand. *AIDS* 2002;10:1-7.
11. Mbizvo MT, Latif AS, Machekano R, MacFarland W, Bassett MT, Ray S, Katzenstein D. HIV seroconversion among factory workers in Harare: who is getting newly infected? Centr Afr J Med. 1997;43:135-139.
12. Moses S, Bailey RC, Ronald AR. Male circumcision: assessment of health benefits and risks. *Sex Transm Infect* 1998; 74: 368–73.
13. Moses S, Bradley JE, Nagelkerke NJD, et al. Geographic patterns of male circumcision practices in Africa: An association with HIV seroprevalence. Int J Epidemiol. 1990;19:693-697.

14. Buve A, Carael M, Hayes RJ, et al. The multicentre study on factors determining the differential spread of HIV in four African cities: summary and conclusions. *AIDS* 2001; 15 (suppl 4): S127-S131.
15. Weiss HA, Buve A, Robinson NJ, et al. The epidemiology of HSV-2 infection and its association with HIV infection in four urban African populations. *AIDS* 2001; 15 (suppl 4): S97-S108.
16. Laga M, Manoka A, Kivuvu M, et al. Non-ulcerative sexually transmitted diseases as risk factors for HIV-1 transmission in women: results from a cohort study. *AIDS* 1993; **7**: 95–102.
17. Plummer FA, Simonsen JN, Cameron DW, et al. Cofactors in male female sexual transmission of human immunodeficiency virus type 1. *J Infect Dis* 1991; 163: 233–39.
18. Cameron DW, Simonsen JN, D'Costa LJ, et al. Female to male transmission of human immunodeficiency virus type 1: risk factors for seroconversion in men. Lancet 1989; **2**: 403–07.
19. Ghys PD, Fransen K, Diallo MO, et al. The associations between cervicovaginal HIV shedding, sexually transmitted diseases and immunosuppression in female sex workers in Abidjan, Cote d'Ivoire. *AIDS* 1997; **11**: F85-F93.
20. Cohen MS, Hoffman IF, Royce RA, et al. Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. *Lancet* 1997; 349: 1868–73.
21. Moss GB, Overbaugh J, Welch M, et al. Human immunodeficiency virus DNA in urethral secretions in men: association with gonococcal urethritis and CD4 cell depletion. *J Infect Dis* 1995; 172: 1469–74.
22. Meda N, Sangare L, Lankoande S, et al. The HIV epidemic in Burkina Faso: current status and the knowledge level of the population about AIDS, 1994–1995. *Rev Epidemiol Sante Publique* 1998;46:14–23.
23. Mbopi Keou FX, Mbu R, Mauclere P, et al. Antenatal HIV prevalence in Yaounde, Cameroon. *Int J STD AIDS* 1998; 9: 400–02.
24. National AIDS Coordination Programme. Report on HIV/AIDS in Zimbabwe: Background, projections, impact, interventions. Ministry of Health and Child Welfare. Harare, Zimbabwe. July 1998.
25. National survey of HIV and syphilis prevalence among women attending antenatal clinics in Zimbabwe, 2000. Health Information and Surveillance Unit, Department of Disease Prevention and Control, Ministry of Health and Child Welfare. Harare, Zimbabwe. 2000.
26. Bassett MT, Latif AS, Katzenstein DA, Emmanuel JC. Sexual behavior and risk factors for HIV infection in a group of male factory workers who donated blood in Harare, Zimbabwe. J Acquired Immune Deficiency Syndromes. 1992;5:556-559.
27. McFarland W, Gwanzura L, Bassett MT, Machekano R, Latif AS, Ley C, Parsonnet J, Burke RL, Katzenstein DA. Prevalence and incidence of herpes simplex virus type 2 infection among male Zimbabwean factory workers. J Infect Dis. 1999;180:1459-1465.
28. Machekano RN, Bassett MT, Zhou PS, Mbizvo MT, Latif AS, Katzenstein DA. Report of sexually transmitted diseases by HIV infected men during follow up: time to target the HIV infected? Sex Transm Inf. 2000;76.
29. Latif AS, Mason PR, Marowa E, Gwanzura L, Chingono A, Mbengeranwa OL. Risk factors for gonococcal and chlamydial cervical infection in pregnant and non-pregnant women in Zimbabwe. Centr Afr J Med. 1999; 45:252 – 258.
30. Latif AS, Marowa E, Mason PR, Gwanzura L, Chingono A, Mbengeranwa OL. A report on a study to determine the aetiology and pattern of STD amongst men and women presenting to health centres in Harare, Zimbabwe, and to determine risk factors for cervicitis among symptomatic and asymptomatic women. Ministry of Health and Child Welfare, Harare, Zimbabwe. 1995.
31. Grosskurth H, Mosha F, Todd J, et al. Impact of improved treatment of sexually transmitted diseases on HIV infection in rural Tanzania: randomised controlled trial. *Lancet* 1995; 346: 530–36.
32. Mayaud P, Mosha F, Todd J, et al. Improved treatment services significantly reduce the prevalence of sexually transmitted diseases in rural Tanzania: results of a randomized controlled trial. *AIDS* 1997; 11:1873–80.
33. Wawer MJ, Sewankambo NK, Serwadda D, et al. Control of sexually transmitted diseases for AIDS prevention in Uganda: a randomized community trial. *Lancet* 1999; 353: 525–35.
34. Elizabeth L Corbett, Richard W Steketee, Feiko O ter Kuile, Ahmed S Latif, Anatoli Kamali, Richard J Hayes. HIV-1/AIDS and the control of other infectious diseases in Africa. *Lancet* 2002; 359: 2177–87
35. Grosskurth H, Gray R, Hayes R, Mabey D, Wawer M. Control of sexually transmitted diseases for HIV-1 prevention: understanding the implications of the Mwanza and Rakai trials. *Lancet* 2000; 355: 1981–87.
36. Boily MC, Lowndes CM, Alary M. Complementary hypothesis concerning the community sexually transmitted disease mass treatment puzzle in Rakai, Uganda. *AIDS* 2000; 14: 2583–92.
37. Laga M, Nzila N, Goeman J. The interrelationships of sexually transmitted diseases and HIV infection: Implications for the control of both epidemics in Africa. AIDS. 1991;5(suppl):S55-S63.
38. Clottey C, Dallabetta G. Sexually transmitted diseases and human immunodeficiency virus: Epidemiologic synergy? Infectious diseases clinics of North America. 1993;7:753-770.
39. Muscher DM, Manill RJ, Baughn RE. Effect of human immunodeficiency virus (HIV) infection on the course of syphilis and on the response to treatment. Ann Intern Med. 1990;113:872-881.
40. Haas JS, Bolan G, Larsen SA, et al. Sensitivity of treponemal tests for detecting prior treated syphilis during human immunodeficiency virus infection. J Infect Dis. 1990;162:862-866.
41. Hutchinson CM, Rompalo AM, Rechart CA, Hook EW II Characteristics of patients with syphilis attending Baltimore STD clinics: Multiple, high risk subgroups and interactions with human immunodeficiency virus infection. Arch Int Med. 1991;151:511-516.
42. Johnson PDR, Graves SR, Stewart L, et al. Specific syphilis serological tests may become negative in HIV infection. AIDS. 1991;5:419-423.
43. Rompalo AM, Cannon RO, Quinn TC, Hook EW III. Association of biologic false-positive reactions for syphilis with human immunodeficiency virus infection. J Infect Dis. 1992;165:1124-1126.
44. Tyndall M, Malisa M, Plummer FA, et al. Ceftriaxone no longer predictably cures chancroid in Kenya. J Infect Dis. 1993;167:469-471.
45. Latif AS. Sexually transmitted diseases in Africa. Genitourin Med. 1990;66:235-237.
46. Maier JA, Bergman A, Ross MG. Acquired immune deficiency syndrome manifested by chronic primary genital herpes. Am J Obstet Gynecol. 1986;155:756-758.
47. Norris SA, Kessler HA, Fife KH. Severe, progressive herpetic whitlow caused by an acyclovir-resistant virus in a patient with AIDS. J Infect Dis. 1988;157:209-210.
48. Kamali A, Nunn AJ, Mulder DW, Van Dyck E, Dobbins JG, Whitworth JA. Seroprevalence and incidence of genital ulcer infections in a rural Ugandan population. *Sex Transm Infect* 1999; 75: 98–102.
49. Obasi A, Mosha F, Quigley M, et al. Antibody to herpes simplex virus type 2 as a marker of sexual risk behavior in rural Tanzania. *J Infect Dis* 1999; 179:16–24.
50. Wald A, Link K. Risk of human immunodeficiency virus infection in herpes simplex virus type 2-seropositive persons: a meta-analysis. *J Infect Dis* 2002; 185: 45–52.
51. Gwanzura L, McFarland W, Alexander D, Burke RL, Katzenstein D. Association between human immunodeficiency virus and herpes simplex virus type 2 seropositivity among male factory workers in Zimbabwe. *J Infect Dis* 1998; 177: 481–84.
52. Mandelblatt JS, Fahs M, Garibaldi K, et al. Association between HIV infection and cervical neoplasia: Implications for clinical care of women at risk for both conditions. AIDS. 1992;6:173-178.
53. McMillan A, Bishop PE. Clinical course of anogenital warts in men infected with human immunodeficiency virus. Genitourin Med. 1989;65:225-228.
54. Rudlinger R, Grob R, Buchmann P, et al. Anogenital warts of the condyloma acuminatum type in HIV-positive patients. Dermatologica. 1988;176:277-288.
55. Feingold AR, Vermund SH, Burk RD, et al. Cervical cytologic abnormalities and papillomavirus in women infected with human immunodeficiency virus. J Acquir Immune Def Syndr. 1990;3:896-903.
56. Plummer FA, Simonsen JN, Chubb H, et al. Epidemiological evidence for the development of serovar specific immunity after gonocccal infection. J Clin Invest. 1989;83:1472-1476.
57. Hirsch MS, Schooley RT, Ho DD, Kaplan JC. Possible viral interactions in the acquired immune deficiency syndrome (AIDS). Rev Infect Dis. 1984;6:726-731.
58. Phair J, Jacobson L, Detels R, et al. Acquired immune deficiency syndrome occurring within 5 years of infection with human immunodeficiency virus type-1: The multi-center AIDS cohort study. J Acquir Immune Defic Syndr. 1992;5:490-496.
59. Zack JA, Arrigo SJ, Chen ISY. Control of expression and cell tropism of human immunodeficiency virus type 1. Adv Virus Res. 1990;38:125-146.
60. Bassett MT, Latif AS, Katzenstein DA, Emmanuel JC. Sexual behavior and risk factors for HIV infection in a group of male factory workers who donated blood in Harare, Zimbabwe. J Acquired Immune Deficiency Syndromes. 1992; 5:556-559.
61. Gray RH, Wawer MJ, Sewankambo N, Serwadda D. HIV-1 infection associated with abnormal vaginal flora morphology and bacterial vaginosis. Lancet. 1997;350:1780.
62. Latif AS. Syndromic Management of Sexually Transmitted Diseases – Part I: Overview. Centr Afr J Med. 1998; 44:210-213.
63. World Health Organization/Global Programme on AIDS. Management of Sexually Transmitted Diseases. Geneva. World Health Organization. 1992.
64. Ministry of Health and Child Welfare. Report of the Epidemiology Unit. Ministry of Health and Child Welfare, Harare, Zimbabwe. 2000.
65. City Health Department. Annual reports of the Director of Health Services. Harare City Health Department, Harare, Zimbabwe. 1990 to 2001.
66. Latif AS, Marowa E, Mbengeranwa OL, Siziya S. Evaluation of integration of prevention and care of STDs into primary health and reproductive health services in Zimbabwe. A Report of a UNAIDS funded project. 2000.
67. Lush L, Walt G, Ogden J. Transferring policies for sexually transmitted infections: What's wrong with global guidelines? Journal of Health Policy and Planning. Accepted for publication. 2003.

Invited review

REAL-TIME MOLECULAR EPIDEMIOLOGY

Timothy J J Inglis

SUMMARY

Molecular epidemiology is a collection of laboratory methods that are being used with increasing frequency to support infection control, communicable disease control and environmental health investigations. The methods used rely on the analysis of microbial nucleic acids and usually attempt to demonstrate the existence of a cluster of microbial isolates from distinct cases that are indistinguishable or closely related. Recognition of a group of indistinguishable isolates against a background of unrelated isolates can advance an epidemiological investigation by helping to define incidental sporadic infections caused by the same pathogen from the case cluster. Recent development in molecular typing methods have shortened the time taken to process microbial isolates to the point of an interpretable result. The automated version of ribotyping is now sufficiently fast to generate genetic typing data while the outbreak investigation is still under way. Experiences with melioidosis and listeriosis outbreak analysis are compared, indicating that rapid, real-time genetic typing can have a significant effect on the course of the outbreak. A collaborative network of typing laboratories is the most effective way to build up the requisite skills and to support public health authorities in less advantaged communities.

What is molecular epidemiology?

'Molecular epidemiology' is a term that has come to describe a critical contribution the microbiology laboratory can make to public health. Molecular epidemiology differs from the time- place- person analysis that forms an essential component of conventional descriptive epidemiology, though in some respects it may be complementary to a conventional analysis.

The basis of molecular epidemiology is the use of molecular taxonomic markers to identify potential epidemiological connections between clinical cases of a given infection by the comparison of microbial isolates. Molecular epidemiology therefore presents a box of tools for developing and refining inferences about the source and propagation of an outbreak. Though these tools might be powerful in the right hands, they are not cheap or easy to use. Nor are they a substitute for a good working hypothesis, a proof of source, or incontrovertible evidence of so-called 'clonality'.

Determinative bacteriology

The processes that comprise molecular epidemiology are a continuation of the methods used to attribute a given genus and species name to a specific clinical isolate. If we stay with clinical bacteriology, the dilemma facing the diagnostic laboratory can be understood in terms of how far we should go to attribute a specific bacterial name. Sometimes the genus name is all that may be required e.g. *Staphylococcus* or *Pseudomonas*. But usually the identification process gains a momentum of its own and the species name is added e.g. *Staphylococcus aureus* or *Pseudomonas aeruginosa*. Identification past this stage is rarely undertaken for purely diagnostic purposes, unless a specific serotype or other subtype of the species is more pathogenic. However, the determination of a subtype, especially by molecular methods, can be extraordinarily useful to distinguish a cluster belonging to the same subtype. Molecular methods that analyse bacterial DNA are regarded as more reliable than non-molecular methods that assess potentially variable phenotypic features. Nevertheless, there are some phenotypic methods that are sufficiently stable to be useful for subtyping (e.g. sero- and phage typing of salmonellae). The further the laboratory goes towards a detailed description of a given bacterial isolate, the more is known about its taxonomic relationship to other closely related bacteria. Laboratories equipped to perform this level of what is known as determinative bacteriology employ more highly discriminating methods with greater taxonomic depth, but will do so sparingly.

Speed

The speed of a given molecular epidemiological method is analogous to laboratory turnaround time, though the time taken to complete a given process may run on a more elastic time scale. Speed has been a neglected aspect of molecular epidemiology until recently when rapid, automated methods became available. As in the case of a diagnostic test, the time to completion of a molecular epidemiological analysis has a direct bearing on whether or not the results will affect an outbreak investigation in time to affect decisions about control measures. Advocates of more labour-intensive methods must address issues such as how quickly their chosen method(s) can influence decisions on how to investigate an outbreak, generate a hypothesis, or introduce disease control and environmental health measures.

The ideal typing method

Much of the drive to develop molecular epidemiology has come from clinical microbiology research groups that have had access to well-staffed research laboratories and have been able to fine tune a given method for months or even years. In some cases completion of a molecular epidemiological analysis has taken so long that it can have little relevance to disease management and control decisions[1]. Nevertheless, a short list of comparative performance features has been advanced [2]. This includes typability, discrimination, epidemiological concordance and reproducibility. Service providers would add to this short list, speed, cost, data storage and transfer.

WA melioidosis outbreak

The cause of the small cluster of acute melioidosis cases that occurred in WA late in the 1997dry season was not immediately apparent. Preliminary environmental studies highlighted the possible role of the potable water supply[3]. An

REAL-TIME MOLECULAR EPIDEMIOLOGY

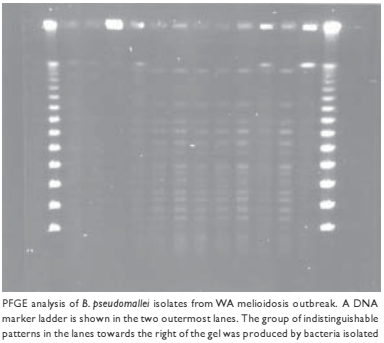
Timothy J J Inglis, BM, DM, FRCPath, DTM&H, FRCPA,

Division of Microbiology & Infectious Diseases, PathCentre, Locked Bag 2009, Nedlands, WA 6909, AUSTRALIA.

Fax: (08) 9381 7139

tim.inglis@health.wa.gov.au

isolate of the causal pathogen, *Burkholderia pseudomallei*, from a domestic water outlet was indistinguishable from the outbreak strain by pulsed-field gel electrophoresis (PFGE) analysis. This form of molecular typing had to be performed outside WA, until the skills had been acquired here. The delays caused by transfer of *B. pseudomallei* isolates interstate contributed to the slow rate of progress with the investigation. The upstream source of contamination in a water treatment plant was only discovered around a year later when further environmental isolates had been recovered and typed by PFGE[4].



PFGE analysis of *B. pseudomallei* isolates from WA melioidosis outbreak. A DNA marker ladder is shown in the two outermost lanes. The group of indistinguishable patterns in the lanes towards the right of the gel was produced by bacteria isolated from patients in the outbreak cluster.

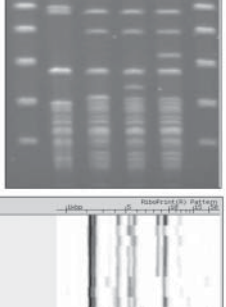
In contrast, a small cluster of listeriosis cases occurred in WA during late May and early June, 2000. The use of an automated ribotyping protocol in conjunction with rapid molecular detection and confirmation allowed a link to be established between clinical infections and cooked chicken pieces in 48hr[5]. By six days a likely source had been identified and control measures put into place. The effectiveness of those measures was confirmed within a month. The startling efficiency of the investigation and its seamless progression to disease control reflected the speed of a molecular typing method that could produce an interpretable result in around 8hr, which could in turn be compared against all previously analysed patterns in the digital archive. PFGE was nevertheless used to confirm the preliminary results obtained by automated ribotyping. There were no further cases of listeriosis in WA for the next six months, and only two cases in the following year.

What was different?

The difference in the way the laboratory responded to the two outbreaks reflected a fundamental change in our approach to molecular epidemiology. In the thirty months that separated the two events, a molecular epidemiology laboratory was established at PathCentre with a service focus. This required quality control and validation of molecular typing procedures that are probably not needed in a research laboratory. As new typing protocols were introduced, comparisons were made with established methods. Also during this period, an automated ribotyping device (RiboPrinter, Dupont-Qualicon) was installed. Preliminary ribotyping work generated a digital archive of ribotyping patterns based on analyses of local bacterial isolates, giving the laboratory a ready-to-use library of previously encountered ribotypes. Initially, this archive was principally *Listeria monocytogenes* ribotypes. The collection of *Listeria* ribotypes was sufficiently comprehensive to begin to assess the local population structure of *L. monocytogenes*. This, in turn, gave the laboratory a uniquely relevant resource with which to assess alternative or complementary molecular typing methods. The slower PFGE method was shown to be more discriminating than *Eco*R I ribotyping and thus to provide useful additional typing data. The listeriosis outbreak was therefore investigated initially by ribotyping. PFGE was then used to provide confirmatory evidence of the existence of a cluster belonging to a distinct single type.

Where next?

Comparison of gel patterns formed by digested microbial DNA has often been made by naked eye examination of agarose gels. Gels can be recorded by scanner and then analysed using software such as GelCompar. The intuitive assessment made by naked eye is surprisingly consistent. Recently a new type of software was introduced that enables a more sophisticated analysis of agarose gel patterns. The new analytical system (Bionumerics) allows comparison of different molecular typing systems and creation of composite image-based data sets.



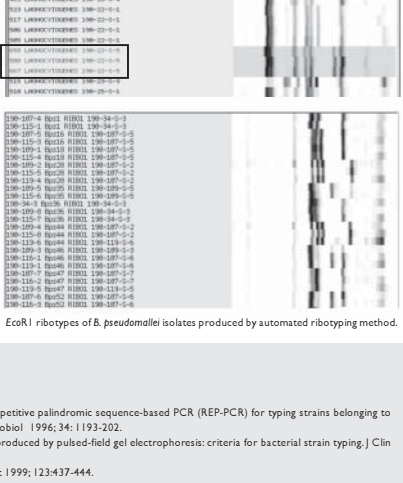
Listeria monocytogenes analysis by pulsed-field gel electrophoretic (left) and automated ribotyping (right). The two centre lanes are indistinguishable *L. monocytogenes* isolates, and the two outer lanes are the molecular size markers. On the automated EcoR1 ribotype comparison, three closely related isolates are indicated.

The application of molecular typing methods to other bacteria of public health significance is already well under way, and rapid methods such as automated ribotyping have been applied to a variety of bacterial genera. The food-borne pathogens were amongst the first major group on the to do list. This laboratory obviously gave *B. pseudomallei* a high priority rating and recently completed a comparison of the two principal methods used here [6]. In view of its global significance, tuberculosis is on the list. Current methods such as IS6110 typing by Southern blot are slow and cumbersome. Newer methods such as variable number tandem repeats and spoligotyping have provided useful alternatives, though no single method has been entirely satisfactory[7]. These methods have been used in combination to construct a phylogenetic analysis of *Mycobacterium tuberculosis* isolates from a wide range of locations, from which preliminary inferences have been drawn about the likely origins of the disease and their putative relationship to population migrations and cattle domestication[8]. A rapid version of the internationally standardised IS6110 method would be a useful contribution to public health on a world scale.

Also high on the priority list is the growing catalogue of antibiotic resistant hospital pathogens responsible for nosocomial infections.

CONCLUSION

To conclude, real-time molecular epidemiology can have a significant impact on outbreak response. Rapid molecular typing methods can speed up the identification of a point source of infection, its route of transmission and the efficacy of control measures. From our own recent experience, it is clear that the integration of a molecular typing service with other components of public health response will improve the impact of future public health interventions. It is hardly surprising, then that most of the major Australian public health laboratories have a molecular epidemiology laboratory in some shape or form. An Australia-wide real-time molecular epidemiology service would make a huge difference in our capacity to identify and respond to a major public health threat.



*Eco*R1 ribotypes of *B. pseudomallei* isolates produced by automated ribotyping method.

Acknowledgment. I thank Lyn O'Reilly of the Molecular Epidemiology Laboratory, PathCentre for figures 2 and 3.

REFERENCES

1. Snelling A, Gerner-Smidt P, Hawkey PM, Heritage J, Parnell P, Porter C, Bodenham AR, Inglis TJJ. Validation of use of whole-cell repetitive palindromic sequence-based PCR (REP-PCR) for typing strains belonging to the *Acinetobacter calcoaceticus-Acinetobacter baumannii* complex and application of method during a hospital outbreak. J Clin Microbiol 1996; 34: 1193-202.
2. Tenover FC, Arbeit RD, Goering RV, PA Mickelsen, Murray BE, Persing DH, Swaminathan B. Interpreting DNA restriction patterns produced by pulsed-field gel electrophoresis: criteria for bacterial strain typing. J Clin Microbiol 1995; 2233-39.
3. Inglis TJJ, Garrow SC, Adams C, Henderson M, Mayo M, Currie B. Acute melioidosis outbreak in Western Australia. Epidemiol Infect 1999; 123:437-444.
4. Inglis TJJ, Garrow SC, Henderson M, Claire A, O'Reilly L, Sampson J, Cameron B. Source of *Burkholderia pseudomallei* traced to water treatment plant. Emerg Infect Dis 2000; 6: 56-9. [http://www.cdc.gov/ncidod/eid/vol6no1/inglis.htm]
5. Inglis TJJ, Clair A, Sampson J, O'Reilly L, Vandenberg S, Leighton K, Watson A. Real-time application of automated ribotyping and DNA macrorestriction analysis in the setting of a Listeriosis outbreak. Epid Infect (in press).
6. Inglis TJJ, O'Reilly L, Foster N, Clair A, Sampson J. Comparison of rapid, automated ribotyping and DNA macrorestriction analysis of *Burkholderia pseudomallei*. J Clin Microbiol 2002; 40: 3198-3203.
7. Cowan LS, Mosher L, Diem L, Massey JP, Crawford JT. Variable-number tandem repeat typing of *Mycobacterium tuberculosis* isolates with low copy numbers of IS6110 by using mycobacterial interspersed repetitive units. J Clin Microbiol 2002; 40: 1592-602.
8. Sola C, Filliol I, Legrand E, Mokrousov I, Rastogi N. *Mycobacterium tuberculosis* phylogeny reconstruction based on combined numerical analysis with IS1081, IS6110, VNTR, and DR-based spoligotyping suggests the existence of two new phylogenetic clades. J Mol Evol 2001; 53: 680-9.

A PROBABLE CASE OF SUBCUTANEOUS DIROFILARIASIS ACQUIRED IN ZIMBABWE

J.M.Goldsmid & S.S. Bettiol

The patient, a young male parks ranger in Tasmania, presented to his GP with a lump on his back a few months after a rafting trip on the Zambezi River in Zimbabwe. A provisional diagnosis of a sarcoma was made and a biopsy taken and sent to the local pathology laboratory for examination.

Microscopic examination revealed that the lump was due to a helminth infection with sections of nematodes being clearly visible (Fig. 1). Initially, it was suspected that the helminth was *Onchocerca volvulus* as the clinical presentation and the appearance of the sections fitted that of onchocerciasis. However, *O. volvulus* is not endemic in Zimbabwe and no other filarial skin infections of humans have been recorded endemically from that country[1]. The section was that of a non-fertile female worm (Fig. 2) which was identified as a probable animal filarial species – either an animal *Onchocerca* or, due to the prominent cuticular ridges (Fig. 3), a *Dirofilaria* species. The only other case of a possible zoonotic filarial infection ever recorded from Zimbabwe, was a case of cerebral filariasis, identified at the time as being due to *Acanthocheilonema* (= *Mansonella*) *perstans* [2]. Subsequently, in retrospect, it was suggested that this latter infection might have been a human case of infection with *Meningonema peruzzi* [3], a filarial infection which had recently been described from the central nervous system of non-human primates in Africa[4].

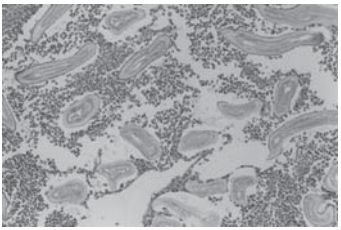


Fig. 1. Section of biopsy showing sections of nematode worms

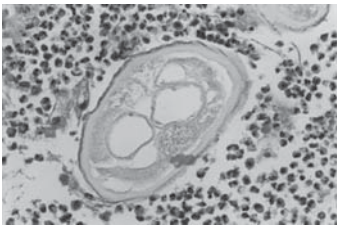


Fig. 2 High power magnification of transverse section of infertile female worm. Diameter of worm 144 x 88 mu.

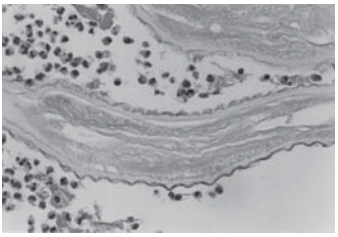


Fig. 3 High power magnification of worm to show prominent cuticular folds.

What makes the present case particularly interesting is that in 1970, Condy[5] had written, in a paper on filariasis in Rhodesian wildlife: "The subject of human filariasis is therefore not at all clear. Microfilariae of animal origin could well play a significant part in filarial infestations of humans in Rhodesia".

Is the present case one such infection? Certainly the time frame and history indicates that the infection was acquired while in Zimbabwe and the section itself suggests a zoonotic filarial infection, probably a *Dirofilaria*.

REFERENCES:

1. Goldsmid JM. A review of the importance of human parasitic diseases in Rhodesia. C Afr J Med 1978; 24: 181-187.
2. Dukes D, Gelfand M, Gadd K G, Clarke V de V, Goldsmid JM. Cerebral filariasis caused by *Acanthocheilonema perstans*. C Afr J Med 1968; 14: 21-27.
3. Orihel TC. Cerebral filariasis in Rhodesia – a zoonotic infection? Amer J Trop Med Hyg. 1973; 22: 596-599.
4. Orihel TC, Esslinger JH .*Meningonema peruzzi* gen et sp n (Nematoda: Filaroidea) from the central nervous system of African monkeys. J Parasitol 1973; 59: 437- 441
5. Condy JB, Hill RR . Filariasis in Rhodesian wildlife. C Afr J Med. 1970; 16: 249-251

A PROBABLE CASE OF SUBCUTANEOUS DIROFILARIASIS ACQUIRED IN ZIMBABWE

J.M.Goldsmid

PhD, FRCPath, FASM, FACTM, FIBiol, FAIBiol., Hon. FRCPA

S.S. Bettiol

PhD, MACTM, MASM

Discipline of Pathology, University of Tasmania

RESPONSE TO THE ANTHRAX BIOTERRORISM THREAT IN SOUTH AFRICA

John Frean and Lorraine Arntzen

SUMMARY

Together with many other countries, South Africa faced an epidemic of bioterrorism threats in the months following the first anthrax attacks in the United States in October 2001. A uniform threat assessment algorithm was drawn up for emergency service first responders. Centralised laboratory services for human samples and for environmental and powder samples were provided. The Special Bacterial Pathogens Laboratory of the National Health Laboratory Service, which dealt with most of the clinical samples, screened 846 specimens resulting from nearly 140 incidents. No anthrax bacilli were isolated from any specimen, human or otherwise. There was generally good cooperation between the public health, laboratory, and emergency services, and while none of the threats were genuine, it was a useful 'dry run' for dealing with future bioterrorism incidents. However, the capacity of the country's already overstressed public health sector to adequately manage a real biological threat must be questioned.

Introduction

Immediately following the reports of anthrax terrorism in the United States in October 2001[1], many countries, including South Africa and Australia, experienced a spate of bioterrorism threats[2,3]. Although these 'white powder incidents' invariably turned out to be deliberate hoaxes or mistaken innocent materials such as chemical or cosmetic products, emergency and medical services were obliged to handle them as potentially genuine threats, and they caused major public disruption and put emergency and medical services under strain. Although the incidence of bioterrorism hoaxes has dwindled, the potential for a real attack has not[4], and we thought it useful to briefly review the response and outcome of the incidents over the year October 2001 to October 2002 in South Africa, from the viewpoint of a public medical microbiology laboratory service.

Public Health Sector Response

When it became clear that public alarm and disruption of public health services were likely to continue, the South African National Department of Health convened a meeting of the services that were responsible for handling bioterrorism threats, namely, military, communicable diseases, emergency and disaster management, and laboratory services. Information and advice on anthrax and bioterrorism for the general public and medical practitioners was compiled, and a uniform plan for dealing with threats anywhere in the country was quickly drawn up. In summary, the first responder was the SA Police Service, in its capacity as primary manager of all suspicious package investigations; substances or articles suspected of being of biological hazard were secured, then passed to the Chemical and Biological Unit of the Military Health Services, who were responsible, after rendering items safe to transport, for delivering the material to the Onderstepoort Veterinary Research Institute (OVRI) for identification of any anthrax spores or bacilli. As far as human contacts were concerned, a simple algorithm was developed which could be applied in the majority of incidents (Figure 1), based loosely on Centers for Disease Control and Prevention (CDC) guidelines[5]. Specimens from humans were referred to medical diagnostic laboratories, mainly those of the National Health Laboratory Service (NHLS), which has a network of over a hundred branches serving public hospitals over most of the country (excluding KwaZulu-Natal Province); some private

RESPONSE TO THE ANTHRAX BIOTERRORISM THREAT IN SOUTH AFRICA

John Frean
MB, ChB, Med (Path), DTMH, FACTM

and Lorraine Arntzen
Dip Med Tech, MSc

Special Bacterial Pathogens Laboratory

National Institute for Communicable Diseases

National Health Laboratory Service

Johannesburg, South Africa

Correspondence: Dr JA Frean, NHLS Central Laboratories, PO Box 1038, Johannesburg 2000, South Africa.
E-mail: johnf@mail.saimr.wits.ac.za

medical laboratories also screened specimens. Most laboratories, both public and private, because they lacked equipment and expertise to identify *B. anthracis*, referred suspected anthrax exposure-related specimens to the Special Bacterial Pathogens (SBP) Laboratory. This is a high security (BSL3) facility that deals mainly with plague and anthrax diagnosis and is located at the NHLS headquarters in Johannesburg.

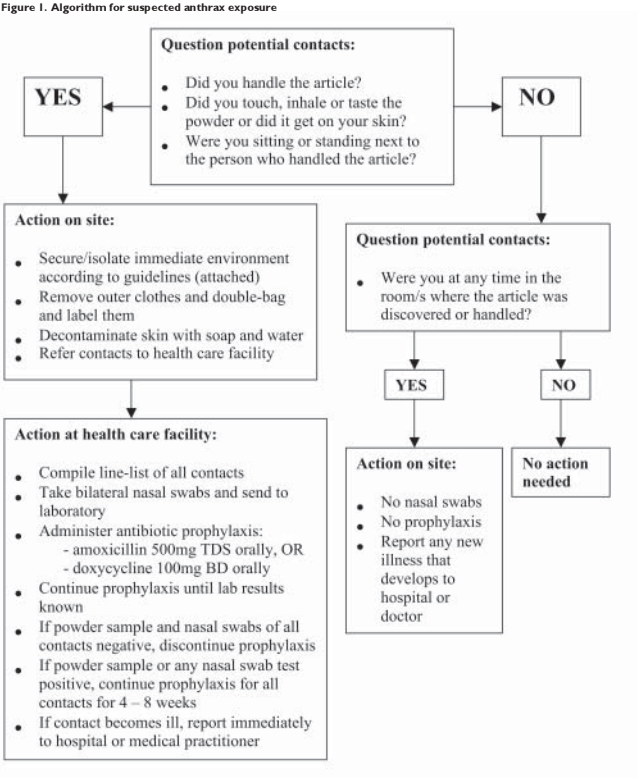
Laboratory Methods

Specimens, usually nasal swabs, were primarily screened for the presence of *B. anthracis* by plating onto 5% horse blood agar, incubated at 37 °C for 12 to 24 hours. In a class 2 biological hazard cabinet in the high-security laboratory, plates were inspected for colonies with characteristics of *B. anthracis*, namely: medium size (3-5 mm diameter), non- haemolytic (or only slightly so), flat, matt greyish-white colonies with an irregular edge and a tacky texture when teased with a microbiological loop[6]. Any suspicious colonies were plated out on 5% horse blood agar and tested for susceptibility to penicillin (10 µg disk) and to lysis with gamma phage (the gift of Peter Turnbull, UK). A few specimens for anthrax serology were submitted; the method used was a conventional sandwich ELISA with *B. anthracis* protective antigen used to capture IgM and IgG antibodies.

Data Review Methods

Incident demographics were obtained from the specimen data logged on the laboratory computer system. Large private pathology practices in Johannesburg and Pretoria were requested telephonically for information related to anthrax bioterrorism over the past year; not all were able to supply accurate information about the numbers or origin of specimens they had processed.

Figure 1. Algorithm for suspected anthrax exposure



RESULTS

The SBP Laboratory screened a total of 846 specimens of human origin, arising from 137 incidents. Smaller numbers of specimens were processed elsewhere (Table 1). Excessive delays often occurred before specimens reached the Laboratory; once received, however, a preliminary result was usually available within 18 to 24 hours. No specimen yielded *B. anthracis*, although several suspicious cultures were further investigated as described above.

South Africa is divided into 9 provinces (Figure 2), and Table 2 shows the geographic origin of incidents resulting in referral of specimens, mainly to the SBP Laboratory in Johannesburg. Private laboratory data were incomplete so the table represents the minimum incidence. Gauteng, the most urbanised province, had the highest rate of bioterrorism incidents (Table 2). One specimen was received from a neighboring country, Botswana (not shown in table).

Table 1. Number of specimens of human origin screened for presence of *B. anthracis*, South Africa, 2001-2002

Laboratory	No. specimens processed	No. with suspicious colonies on screening	No. of *B. anthracis* isolated
NHLS SBP Lab, Jhb	846	10	0
NHLS Cape Town	80	1	0
Private Laboratory, Johannesburg	112	Not known	0
Private Laboratory, Pretoria	Data incomplete	Not known	0
Private Laboratory,Durban	30	Not known	0
Total	>1068	>11	0

DISCUSSION

Anthrax is endemic to parts of South Africa, particularly the region that forms the North West Province and the adjoining areas of Botswana and Lesotho (Figure 2). The incidence in humans is very low, with 0 to 5 cases notified annually for the last two decades[7]. Exposure is typically related to the informal butchering and consumption of cattle that have died from anthrax. Periodic epizootics of anthrax in wildlife occur in the Kruger National Park on the eastern border of the country[8] but humans are not normally exposed in this situation. The rarity of human disease means that most clinical laboratories do not have experience in identifying *B. anthracis* and offering central diagnostic

services for the human samples (at NHLS) and the powders or other material (at OVRI) was a logical step. The CDC guidelines for handling exposure to items or environments suspected of being contaminated with *B. anthracis* called for prolonged prophylaxis/presumptive treatment, regardless of laboratory test results[5]; however, this was on the basis of proven cases of anthrax, including fatal cases, resulting from exposure to mailed items in the United States[9]. In the absence of a credible threat (ie no suspected infections, no isolation of *B. anthracis*), the limited antibiotic regimen and screening policy adopted in South Africa was practical and economical. Fortunately its sensitivity in detecting real anthrax threats was not put to the test, but it is acknowledged that circumstances in the future may be different and require a modified approach. A valid criticism is that the current focus is on anthrax to the exclusion of other agents.

Despite the fact that the bioterrorism attack in the US was small (22 human cases) and simple (only one agent, one mode of transmission, a non-drug-resistant agent, no transmission to animals)[10], the cost in monetary and manpower terms was enormous; more than 121 000 specimens were tested for *B. anthracis*, and 3.75 million antibiotic tablets were delivered[9], which illustrates the potential for disaster that a large-scale attack would hold. For a developing country like South Africa, which has overwhelming problems with natural epidemics like AIDS and tuberculosis, and a public health infrastructure already under severe stress, bioterrorism preparedness is a daunting prospect, but one which must be faced. Expert information and advice, such as provided by the CDC[3], and international support, such as the World Health Organization's moves to establish a worldwide bioterrorism response laboratory network[11], will be essential for South Africa to develop and maintain the capacity to respond adequately to bioterrorism.

Figure 2. Provincial boundaries of South Africa.

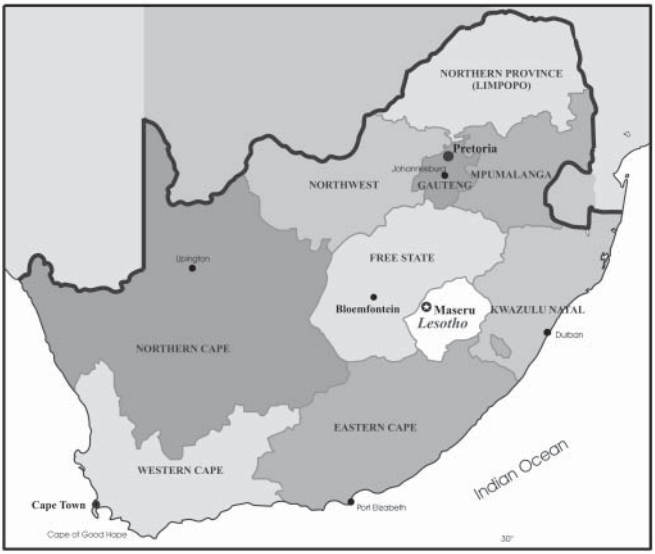


Table 2. Number and geographic-related rates of suspected bioterrorism incidents, South Africa, 2001-2002. *Mid-2002, source: Statistics South Africa, Pretoria.

Province	No. of incidents	Population*	Rate (per million population) of bioterrorism incidents
Gauteng	105	8,106,190	12.9
Mpumalanga	6	3,156,272	1.9
North West	5	3,659,902	1.4
Eastern Cape	8	7,132,141	1.1
Northern Cape	1	888,390	1.1
KwaZulu-Natal	7	9,212,123	0.7
Limpopo	4	5,843,851	0.7
Western Cape	3	4,313,959	0.7
Free State	1	2,859,081	0.3
Total	**140**	**45,171,909**	**3.1**

Acknowledgements: Jan van den Ende for non-NHLS data; Tersia Kruger for technical help; Peter Turnbull for expert advice.

REFERENCES

1. Centers for Disease Control and Prevention. Update: investigation of anthrax associated with intentional exposure and interim public health guidelines, October 2001. MMWR Morb Mortal Wkly Rep 2001; 50: 889-97.
2. Bates J. Anthrax: an update for Australia. Austr J Med Sci 2002; 23: 92-101.
3. Polyak CS, Macy JT, Irizarry-De La Cruz M, Lai JE, McAuliffe JF, Popovic C, et al. Bioterrorism-related anthrax: international response by the Centers for Disease Control and Prevention. Emerg Infect Dis [serial online] 2002; 8. URL: http://www.cdc.gov/ncidod/EID/vol8no10/02-0345.htm
4. Spencer RC, Lightfoot NF. Preparedness and response to bioterrorism. J Infection 2001; 43: 104-110.
5. Centers for Disease Control and Prevention. Update: investigation of bioterrorism-related anthrax and interim guidelines for exposure management and antimicrobial therapy, October 2001. MMWR Morb Mortal Wkly Rep 2001; 50: 909-919.
6. World Health Organization. Guidelines for the surveillance and control of anthrax in humans and animals 2002. URL: http://www.who.int/emc-documents/zoonoses/docs/whoemczdi986.html
7. National Department of Health. Anthrax in South Africa, 1980-1989. Epidemiological Comments 1990; 17: 3-10.
8. De Vos V. The ecology of anthrax in the Kruger National Park, South Africa. Salisbury Med Bull 1990; No. 68 (Suppl.): 19-23.
9. Perkins BA, Popovic T, Yeskey K. Public Health in the time of bioterrorism. Emerg Infect Dis [serial online] 2002; 8. URL: http://www.cdc.gov/ncidod/EID/vol8no10/02-0444.htm
10. Hughes JM, Gerberding JL. Anthrax bioterrorism: lessons learned and future directions. Emerg Infect Dis [serial online] 2002; 8. URL: http://www.cdc.gov/ncidod/EID/vol8no10/02-0466.htm
11. World Health Organization. WHO's response to the threat of the deliberate use of biological and chemical agents to cause harm. Wkly Epidem Rec 2002; 34: 281-287.

Contents: