Foresight

Infectious Diseases: preparing for the future

OFFICE OF SCIENCE AND INNOVATION

T5.2: Review on HIV and AIDS as a Case Study

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Abstract:

HIV/AIDS, like SARS and influenza, is a novel pandemic arising from an animal source, but unlike the latter, the AIDS pandemic is likely to last 80-100 years. AIDS was not recognised until HIV had already spread internationally, owing to the long incubation period between infection and disease. The social drivers are sexual freedom, poverty, denial and stigma. Africa is worst affected, but currently the epidemic is growing most rapidly in Russia and Asia. India has overtaken South Africa as harbouring the highest number of HIV-infected people although the prevalence is lower. In the UK, about 58,000 people (diagnosed and undiagnosed) are estimated to be living with HIV, of those diagnosed about 50% are resident in London. Heterosexual HIV has overtaken homosexual transmission, but a high proportion of heterosexual infections are acquired outside the UK. Anti-retroviral drugs are effective in preventing or delaying progression to AIDS but do not cure infection. There is a threat of the emergence of multi-drug resistant HIV strains within 10 years. No efficacious vaccine is available and is unlikely to be by 2015. Because mortality is greatest among young adults, AIDS exerts a disproportionate impact compared to diseases of infancy or the elderly and is causing social and economic implosion in the worst affected regions. The catastrophe is growing and spreading.

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Introduction

The emergence of human immunodeficiency virus type 1 (HIV-1) in the human population is one of nature's more recent and highly successful adaptive radiations. This virus illustrates Darwinian natural selection at a fast-forward pace. In the west, HIV has readily exploited various niches of our late 20th century lifestyles, including air travel, narcotics dependence and bathhouses where promiscuous behaviour is the norm. Yet HIV is wreaking most havoc among the world's poorest and underprivileged communities. HIV/AIDS presents a frightening though fascinating danse macabre of sex, drugs and death, with no end in sight to the burgeoning pandemic.

In this review of HIV and AIDS as a case study, it may be helpful to contrast what is unique or peculiar to HIV with the factors that are common to other emerging infections. The risk analysis and risk estimate of HIV is derived from our virological knowledge of the infection (which is my area of expertise), and the social and political aspects of infection control (on which I am a non-expert).

Although the Foresight project requests a review and summary views on ‘HIV in Humans within the UK’, I shall treat HIV/AIDS as a global phenomenon. The reason for providing an international perspective is because non-UK drivers, sources and pathways have been of crucial importance in the emergence of AIDS in the UK, and the worldwide situation is likely to remain important to the projected UK outcomes and risks. Besides, the Government has declared its concern for, and engagement with Africa, where AIDS has exerted its most devastating effects to date.

HIV and AIDS: A short history of nearly everything

When a novel infectious disease comes to light, it is important to establish pivotal objectives and milestones in order to gain control over its spread. These include:

- Recognition of symptoms as a distinct disease entity
- Recognition of modes of transmission
- Identification of the infectious agent
- Development of laboratory diagnostic reagents and tests
- Development of therapeutic drugs if appropriate
- Development of a prophylactic vaccine

In the case of AIDS, the first four items proceeded apace, though not as quickly as with SARS which appeared 21 years later when more advanced techniques were available. Moreover the SARS coronavirus was much easier to isolate and propagate *in vitro*.

AIDS was first recognised in May 1981 when small clusters of young homosexual men in American cities were reported to suffer rare opportunistic infections (OIs) (*Pneumocystis carinii* pneumonia, cytomegalovirus retinitis) and Kaposi's sarcoma. The underlying immune deficiency was soon shown to involve a selective depletion of CD4-positive, T-helper lymphocytes. Initially, it was not clear whether 'gay compromise syndrome' as it was then named was transmissible or was related to non-infectious lifestyle factors. By early 1982, however, reports of AIDS in recipients of blood transfusions and pooled clotting factors, as well as among injecting drug users, indicated that an infectious agent was to blame. The appearance of AIDS in African countries and in Haiti suggested that the unknown pathogen was already widespread. Thus the disease was characterised and the main pathways of transmission were delineated before the causative agent, HIV, was first isolated in 1983 by Barré-Sinoussi and her colleagues in Paris.

Although HIV-1 was first isolated in primary T-lymphocytes in 1983, it did not become possible to propagate in bulk in T-cell lines until 1984. That technique led to the production of viral antigen for use in serological tests and to the molecular cloning and sequencing of the viral genome. Serological tests were soon commercialised and by October 1985 industrialised countries had instituted mass screening of blood donors. Since then the iatrogenic transmission of HIV via blood and blood products ceased to be a serious hazard in Western countries, particularly when genome testing covered the time gap between infection and seroconversion.

However, not all countries have adhered to the universal sensitive and specific diagnostic tests available, either due to their cost or due to sloppy practices. One driver of iatrogenic blood transmission of HIV is the commercialisation of blood donation. For instance the spread of HIV in rural China was greatly exacerbated by newly privatised, commercial collection of blood without rigorous regulation or application of sterile needles and syringes.

Human immunodeficiency viruses comprise two distinct viruses, HIV-1 and HIV-2, which differ in origin and gene sequence. Both viruses belong to the *Lentivirus* genus of *Retroviridae*, and our understanding of the molecular biology of their replication cycle has been crucial for the development of anti-retroviral therapy (ART).

It is estimated from phylogenetic molecular clock analyses that HIV-1 group M (the pandemic strain) stems from a point source or single person infected around 1931, and that HIV-2 arose about 10 years later. However, retrospective serological studies indicate that HIV-1 did not become epidemic in Africa until the 1970s, from where it also spread to Europe and the Americas. HIV-1 and HIV-2 have both taken root in India, while HIV-1 became

epidemic in Thailand in the 1980s and has spread to neighbouring East Asian and South-East Asian countries.

There has been debate why HIV-1 Group M took so long to take off epidemically, and also why other HIV types and groups have not followed suit. It is likely that HIV initially was ill adapted to reach high viral load and transmissibility in humans. Mutations in the *gag* gene were required to overcome species-specific viral restriction factors such as Trim5α which have only very recently been identified. Whether sexual transmission or injecting equipment was the main driver of the early epidemic in Africa has been hotly disputed. While I agree with the WHO (World Health Organisation) that sexual transmission is the major route today, contaminated needles and syringes may have been an important early pathway, as with the spread of hepatitis C virus in Egypt at the time of the bilharzia eradication campaign.

Figure 1 shows how the number of syringes and needles rose during the 20th century as the cost of production fell. But there was a period in the 1950s and 1960s when injection use in Africa rocketed through immunisation and (overuse) of injected antibiotics, while injecting equipment was relatively expensive, non-disposable and required re-sterilisation. Overall conditions were no more sterile than among injecting drug users today.

The current status of the HIV pandemic

Details of the estimates of HIV prevalence and AIDS mortality are available from UNAIDS. Currently ~40 million people are infected with HIV (Figure 2), not counting the 28 million who have died as a result of HIV infection in the past 25 years. Approximately 67% of HIV-infected people reside in sub-Saharan Africa, yet the most rapidly increasing rates of infection are currently in Eastern Europe and East Asia.

Some 14,000 persons become infected by HIV nightly, and the majority of untreated people will die from AIDS, with a mean incubation period of 8.7 years. In the meantime, infected persons are infectious to others. Although HIV is not highly contagious, and transmission depends on exchange of body fluids or secretions, clearly the reproductive rate, R_0, of HIV-1 Group M is greater than unity, so the total number of infected people continues to grow (Figure 3). In contrast, prevalence of HIV-1 Group O is not increasing, and cases of HIV-1 Group N remain anecdotal. HIV-2 is more prevalent than HIV-1 Groups N and O, particularly in west Africa where it first arose. However, its prevalence appears to be static, though more accurate data are needed.

HIV prevalence has reached alarming proportions in southern Africa. In regions such as KwaZulu-Natal, Botswana and Lesotho, prevalence rates among antenatal women are approximately 40%. Such a high rate of disease and death among young adults has reversed life expectancy, which in general has increased over the millennia (Figure 4). Only the Black Death in 14th century Europe has been so devastating.

We do not understand all the factors that determine the explosion of HIV transmission in sub-Saharan Africa. In fact, it is quite heterogeneous. For instance, prevalence rates have only risen from approximately 5% to 8% in Kinshasa over a 20-year period, whereas in Durban, HIV was virtually unknown in 1985 and prevalence is now more than 25%. Therefore it is simplistic to lay the whole blame for the spread of HIV on poverty, war, social conflict or famine since Kinshasa has suffered these blights more than Durban.

Neither is it clear whether the subtype C strains of HIV-1 prevalent in South Africa are more virulent or more transmissible than those (all subtypes) prevalent in the Democratic Republic of Congo. Subtype C has emerged in southern Africa and the horn of Africa during the 1990s and currently accounts for ~55% of new infections worldwide. A rapidly spreading genetically recombinant strain, HIV-1 A/G has recently emerged in west Africa with an epicentre in Nigeria.

Even in regions where the overall prevalence of HIV infection has remained relatively low compared with sub-Saharan Africa, AIDS has had a major impact on mortality among young adults, and to costs of healthcare. Figure 3 shows how the death toll due to AIDS became the highest single cause of death in the USA for men and women between the ages of 25 and 45 years. The dramatic fall in AIDS mortality in 1996 was due to the introduction of combination anti-retroviral therapy, not to a change in transmission dynamics of HIV.

To gain a sense of proportion of some current causes of global mortality, selected infectious pathogens and non-infectious causes are shown on a 'Richter' scale (Figure 5). AIDS is second only to cigarette smoking. This scale represents a snapshot in time. Both tobacco consumption and HIV infection are late 20th century manifestations and in 1980, HIV was near the bottom of the scale.

A major purpose of this Foresight project is to predict which infections might appear like HIV and SARS from previously unknown sources, and to predict which will shoot to the top of the scale like HIV, or make a transient peak and disappear again like SARS. Global mortality is not the only important factor in emerging infectious disease, however. The economic and psychological aspects of the SARS outbreak far outweighed the significance of its death toll.

HIV and AIDS in the UK

The first reported case of AIDS in the UK was in 1982. When we developed the first serological test for HIV antibodies in 1984, and tested some 2000 blood samples in London, we revealed an HIV prevalence of 34% among men and boys with haemophilia, 1.5% among injecting drug users and among 17% of gay men attending STI clinics, but <0.1% among healthy blood donors (Cheingsong-Popov et al Lancet ii, 477-483, 1984).

The year 2004 is the most recent for which the Communicable Disease Surveillance Centre of the Health Protection Agency (HPA) has accurate estimates of HIV and AIDS. The cumulative number of HIV infections actually diagnosed from 1984 to the end of 2004 is 70,000, but the estimated number significantly exceeds this figure. In 2004, the number of diagnosed HIV-infected patients seen for care was ~45,000, but the estimated number of adults living with HIV infection was 58,000, of whom 24,500 were men who have sex with men, and 26,000 heterosexually active persons of both sexes. Approximately 50% of HIV positive persons in the UK live in or near London.

The proportion of HIV infected people in different risk groups for exposure has changed markedly in the UK over the past 10 years. The number of infected heterosexual men and women has risen sharply, whereas the number of infected men who have sex with men has remained essentially constant (Figure 6). While the total number of infected people has risen year by year, the mortality rate has dropped since the introduction of combination ART in 1996. Almost 75% of HIV infections acquired through heterosexual intercourse were acquired in Africa or from recent African immigrants to the UK (Figure 7), and 62% of heterosexual infections were in women.

The trend in HIV infection in the UK is for an increasing number of heterosexual transmissions, a static number of new homosexual transmissions, a recent rise among injecting drug users, and essentially zero transmissions via blood transfusion and tissue transplantation thanks to effective screening measures. Anonymous antenatal testing through Guthrie cards indicates that 0.5% women in Central London are HIV positive (mainly of African origin or contact) with much lower rates elsewhere. Thus the HIV prevalence endemic in the UK is likely to increase, and we are now seeing the introduction of many HIV-1 subtypes, reflecting the international movement of the virus. The rapid rise in HIV infections in Eastern Europe and the Far East may exacerbate the situation.

Risk factors and protective factors

A number of host genetic factors affect either the risk of acquiring HIV infection when exposed, or the rate of progression to AIDS after infection. These include genes encoding major histocompatibility antigens, chemokines, chemokine receptors, and intracellular proteins such as Trim5 and APOBECG3.

A number of environmental factors also affect HIV transmission. Other sexually transmitted infections that cause genital lesions or inflammation increase the risk of sexual transmission. An intervention trial in Tanzania indicated that antibiotic prophylaxis may reduce HIV transmission, but this effect was not confirmed in Uganda. Intervention that also includes aciclovir to prevent genital herpes is being considered. On the other hand, pre-infection with GBV-C, a non-pathogenic virus related to hepatitis C virus, appears to reduce HIV infection and progression to AIDS, by raising protective plasma chemokine levels.

Male circumcision reduces female to male transmission in Africa by two thirds. Of three randomised controlled trials of circumcision as a protective factor, one stopped randomisation before enrolment was complete because of the strong protective effect of circumcision. The high density of dendritic cells and CD4+ lymphocytes targets of HIV infection in the foreskin may explain why removing it is protective.

HIV transmission and dynamics

Although there is a long asymptomatic period between primary infection and AIDS, the virus is not latent. A turnover of up to 10^8 new HIV particles may be produced daily, allowing for genetic and antigenic change (Figure 8). It also means that an infected person may be infectious to others at any time during the course of the infection and disease.

Nonetheless, it is becoming increasingly apparent that transmission during primary infection, when viral load is high, is a major pathway to the onward spread of HIV. Thus the overall pandemic, which may not peak for another 50 to 80 years, comprises an integral of 1000s of mini-outbreaks and local epidemics. This was seen, for example, in 1985 in Edinburgh when HIV rapidly spread among the injecting drug users, yet did not gain a serious foothold in IDUs in Glasgow. The discrepancy was probably related to social rather than virological factors. Edinburgh had a citywide system of illicit drug access and dealers, whereas Glasgow was divided into gangs by drug barons, so that inter-gang spread was impeded. Another mini-outbreak occurred in 1998 in Doncaster with multi-partner heterosexual behaviour among the unemployed, seeded by a single HIV carrier. In North America, ‘Patient D’, a gay airline steward set off outbreaks in dozens of cities from Montreal to San Diego; one could track the movements of this HIV carrier across airlines routes. I have already alluded to large discrepancies of HIV prevalence in cities in sub-Saharan Africa.

Heterogeneity in the pandemic will continue, and we are currently seeing an upsurge in HIV transmission in London. Local alertness and surveillance could be utilised to help to curb the size of such local outbreaks. More modelling is required on the dynamics of infectiousness during primary viraemia and on the heterogeneity of HIV transmission.

Anti-retroviral therapy and drug resistance

The recognition that HIV is a retrovirus led rapidly to the development of anti-retroviral therapy (ART), first targeted to blocking reverse transcription early in the viral replication cycle, and subsequently to protease inhibitors acting on virus particle maturation. Initial trials of azidothymidine (Zidovudine) in 1986 showed a marked drop in viral load, and increased survival of patients with advanced disease. However, the benefit was short-lived because of the rapid emergence of drug-resistant HIV in the treated patients. It took 10 years before the introduction of combination ART in 1996 showed a dramatic reduction in AIDS mortality.

This drop in mortality due to ART has been maintained for several years (Figure 3), but most virologists are worried that multi-drug resistant (MDR) variants of HIV will eventually arise, and will spread as new strains to the community at large. This risk needs careful analysis. Some studies indicate that MDR HIV is less fit, and that HIV reverts to wild-type by mutation once the drug selection pressure is removed. Nonetheless, a repeat of the story of antibiotic resistance to bacteria seems likely for HIV and AIDS. Novel drugs directed at old and new targets in the viral replication cycle will be required, and are feasible within the next 10 years.

There was concern raised by the New York Commissioner for Health in early 2005 that a ‘killer strain’ of HIV had arisen, that caused AIDS within months (rather than years) of acquiring infection, and that was also multi-drug resistant. To my mind, this high profile media announcement represents scaremongering. It is actually based on virus isolation from a single patient who did indeed develop the disease rapidly, but an anecdote does not make an epidemic. Nonetheless, the situation will require close surveillance and a similar rapidly progressing MDR case has been reported in Brazil.

It is surprising that during 25 years of pandemic diversification (Figure 7), there is little evidence that HIV-1 has changed its virulence, or that different virus subtypes have different mean incubation periods before AIDS. This is all the more odd because even in a single infected person, viral variants late in the course of infection tend to be more aggressive than early ones. Thus one would expect such substrains to start off with a more rapid course of infection when transmitted to the next individual. However, there appears to be a resetting of virulence clock upon transmission. Many virologists and modellers assume that late ‘X4’ strains are less transmissible, but I consider that they are actually less fit to evade immunity, i.e. they can be readily transmitted but only take systemically and flourish in someone who already has a partially compromised immune system. In other words, X4 variants of HIV-1 are opportunistic infections.

Prospects for an HIV vaccine

In 1984, not long after HIV was confirmed as the cause of AIDS, two eminent retrovirologists (Bob Gallo at NIH, Bill Jarrett in Glasgow) told the media that there would be an AIDS vaccine within 5 years. Sadly these predictions were incorrect. Twenty years later there is still no safe, efficacious vaccine in sight. Neither is there an effective vaccine for any of the lentivirus infections of animals (horses, sheep, cats and monkeys) as a model on which to design an HIV vaccine.

It is possible to immunise monkeys with candidate vaccines that protect them from challenge with the same precise isolate of SIV, but given the genetic and antigenic variability of HIV worldwide (Figure 8), that result is hardly promising. It is also possible to protect monkeys more broadly from SIV challenge by pre-infection with a live, attenuated strain of SIV. However, it is doubtful whether a live attenuated HIV vaccine could be safely administered. Such viruses established persistent infections, can be pathogenic in neonates,

and have a tendency to revert to virulence. Moreover, it would be difficult to evaluate their safety in phase I/II human trials when the virulent form of the virus takes almost 9 years on average to elicit disease. There could be a 40-year wait before declaring a live vaccine safe.

The most burning need for the prevention of HIV infection and AIDS is the development of an efficacious vaccine. Safe sex and vaginal microbicides are mere stopgaps that might slow the spread of HIV, whereas a vaccine could protect future generations. Thus any risk estimate of the future course of the AIDS pandemic must factor in a vaccine although it would be foolhardy to state when one will be available.

Syphilis as a model for AIDS

Like AIDS, syphilis is a sexually acquired infection that develops into a systemic, generalised disease. Like AIDS, syphilis appeared quite suddenly as a novel affliction and soon spread rampantly across the 'civilised' world. Some think that Columbus's sailors brought it home from Hispaniola, where its close relative, pinta, was endemic. Others think the Portuguese imported yaws from Africa, which then adopted a sexual route as its preferred means of transmission. Syphilis, was first noted in Catalonia in 1493, and became epidemic during the Siege of Naples in 1495. Whatever its origin, syphilis spread from Naples to Warsaw within five months, and by the new trade routes to reach Japan within 10 years. Similarly, HIV was probably introduced into south west Uganda by Tanzanian infantry during Milton Obote's invasion to overthrow Idi Amin. 'Slim' disease in Rakai district was noted a few years later. The subsequent spread of HIV along trucking routes has been well documented.

Syphilis is also a convenient surrogate marker of unsafe sex in epidemiological studies. The fact that syphilis became a much more frequent infection in the UK among men who have sex with men than among heterosexuals helps to explain the prevalence of HIV in the former group. Explanations of HIV being more readily transmitted via anal sex than vaginal sex should probably be regarded as of secondary importance to the correlation with the number of sexual partners during short time spans.

The time-line may be different, but the parallels between syphilis and AIDS are striking. What is sobering, perhaps, is that 500 years later we have not eliminated syphilis even though it is treatable by antibiotics. However, writing in 1546, Girolamo Frascotoro (*De Contagione*) noted that syphilis had become less virulent in the 40 years since the Siege of Naples. He had no access to laboratory tests or to computers for his modelling, and he was writing 300 years before germ theory of disease. Frascotoro had a message relevant to the Foresight project today, writing, ‘There will come yet other new and unusual ailments in the course of time. And this disease will pass away, but later it will be born again and be seen by our descendants.’

HIV stigma and prevention

Early on in the HIV epidemic the UK the DoH sensibly accepted advice not to make HIV a notifiable infection because it would have driven the infection underground at a time when there was no benefit to the individual to seek medical care. A remarkable partnership between Norman Fowler as Secretary of State for Health and Donald Acheson as Chief Medical Officer led to public health measures and safe sex campaigns that probably helped to keep UK's HIV+ population well below the estimates of mathematical modellers.
The stigma of being HIV positive can be harsh. For some women in Africa and Asia, reporting her status to her partner can all too frequently result in abandonment and/or brutal beating. Bottle-feeding an infant is commonly taken as a sign that the mother is infected. So there are many reasons not to 'come out', but this hinders HIV prevention. In contrast, the US gay community came together to fight AIDS and advocate HIV prevention and research.

AIDS and the Web

In the 24 years since AIDS was first recognised as a new disease, the development of our understanding of HIV and AIDS has broadly paralleled the development of the worldwide web and electronic means of communication. AIDS was the first disease about which patients frequently possessed or acquired considerably more knowledge than their doctors. The relative coherence and high level of education in the gay community in the USA led to the rapid exchange of information. Community advocacy groups emerged as drivers of an agenda that would otherwise have been largely left in the hands of professionals, e.g. on public health, clinical trials, funding, and even research objectives.

Today, many patients with other chronic or debilitating afflictions such as cancer, rheumatoid arthritis or heart disease download the latest information form the net. This non-deferential attitude to health professionals was pioneered with HIV/AIDS.

The net has also, of course, spawned non-peer reviewed, non-edited websites and bulletin boards that encourage the promulgation of all sorts of urban and rural myths and conspiracy theories and the fear and impact of HIV/AIDS has engendered more than its share of these two. Such non-orthodox views merit consideration, even if they are scientifically incorrect, when they influence public health policy or public attitudes to risk. In other words, misinformation can be a driver of infectious disease, be it MMR vaccine or AIDS.

AIDS and Denial

To be told that you are infected with a virus that has a 90% chance of slowly killing you is a terrifying prospect. Not surprisingly, some individuals react with denial. And if you are a political leader, to be told that in your country, recently emerged from minority rule, some 15-30% of young adults are infected with HIV is equally terrifying. One might react, as the presidents of Uganda and

Botswana have done, by initiating preventive public health campaigns and by enjoining the WHO, international health charities and pharmaceutical companies to seek every means of reducing the load of disease. In Uganda, HIV prevalence has fallen from 15% to 8% as those already infected died and the prevention campaign began to bite. But it is difficult to maintain this level of awareness and ‘good’ behaviour.

The alternative temptation is to ignore HIV or to deny its role in AIDS. In South Africa, the authorities questioned whether there is a genuine link between HIV and AIDS, criticised the international pharmaceutical companies for supporting the link only to sell their drugs, and were reluctant to accept epidemiological data that HIV transmission is related to sexual behaviour.

The problem of politicising AIDS is that HIV, like other infectious pathogens, does not heed national politics or respect national boundaries. However, a small number of maverick scientists who had challenged the role of HIV in AIDS on websites were appointed to the South African Government's AIDS Advisory Committee in the late 1990s. Two American molecular biologists, with little understanding of epidemiology, or indeed of Koch's postulates, claimed that HIV is a harmless virus, while an Australian claimed that HIV does not exist at all. This converted what many saw as an academic joke into a public health disaster. They argued that antiretroviral drugs were the cause of AIDS not the therapy. A reasoned response from the scientific and medical community (Durban Declaration, 2000) has only partially mollified the situation. Five years later the South African health minister, was reported in The Guardian (15 May 2005) as continuing to query the superior benefits of anti-retroviral therapy (despite the evidence in Figure 3) over taking vitamin supplements.

Such views are not the exclusive preserve of denialist websites or embattled presidents. For two years during the 1990s, the Sunday Times in the UK ran a series of articles by Neville Hodgkinson, accompanied by campaigning editorials, purporting that HIV had never been isolated and that the presence of AIDS in Africa was a myth; AIDS was simply a collection of relabelled age-old diseases. Part of preparedness for future epidemics will be to bring influential newspapers on board with scientific evidence, or at least encourage them to be neutral.

AIDS and Blame

For those who do admit that HIV has indeed caused an AIDS epidemic with huge mortality, it is tempting to cast blame for this tragedy on convenient scapegoats. This is reminiscent of frequent reactions to former pestilence as ‘acts of God’. For instance in 1348, the citizens of Strasbourg decided to slaughter all infidel residents (Jews) in the hope that the city would be spared from the approaching Black Death - a preventive method which proved to be ineffective. I shall cite two anecdotes concerning HIV.

Quite early in the course of the epidemic, rumours circulated that HIV was deliberately constructed in USA as a genetic recombinant between two other

retroviruses, human T-cell leukaemia virus and ovine maedi-visna virus. When this recombinant virus was tested on prisoners, so the story went, the virus escaped into the community via injecting drug use and gay sex. Although analysis of the full sequences of all three viruses (published in 1984 and 1985) made this notion scientifically absurd, the idea has taken root, not only among 'greens' against any form of recombinant DNA technology but also in several countries in Africa. It seems easier to accept the origin of AIDS as malevolent, ethnically targeted germ warfare from USA than as a cross-species infection that occurred in Africa itself.

The second blame theory is that HIV originated from tainted oral polio virus vaccines (OPV). In this case, the conspiracy theorists hold that no malevolence was originally intended, but that HIV's subsequent escape was subsequently covered up by denial, obfuscation and falsification of the records. This story first appeared in a beautifully crafted article by Tom Curtis published in 1992 in that well-known 'scientific' journal *Rolling Stone*. Live attenuated polio vaccine virus strains were initially propagated in cultures of kidney cells derived from Asian macaques such as Rhesus and Cynomolgus monkeys. After 1960, with the discovery of SV40 virus as a contaminant, production switched to kidneys from African green monkeys, which 25 years later were found naturally to harbour a strain of simian immunodeficiency virus (SIVagm). This theory was rapidly discredited among scientists because (a) SIVagm is not closely related to HIV-1 or HIV-2 phylogenetically, as are SIVcpz and SIVsm respectively; (b) the first authenticated HIV positive blood sample taken in Kinshasa in 1959 predates the introduction of the use of African green monkey kidney cells for polio vaccine production. To rescue the oral polio vaccine hypothesis, investigative writer Ed Hooper invoked two new claims in his 1999 book *The River*, namely that chimpanzee kidneys were used to prepare certain vaccine batches, and that this occurred during vaccine trials in the Belgian Congo in 1957/58. Despite overwhelming evidence from its genetic diversity that HIV-1 came into humans long before that date and retrospective analysis from the NIBSC in the UK demonstrating that the vaccine lots incriminated by Hooper were prepared in Rhesus cells, the polio vaccine theory continues to be promulgated on websites and in prize-winning television documentaries.

In our eagerness to deride this theory because of contradictory evidence, we are in danger of overlooking the general hazards of biologicals as medicines, since it is not possible to screen for the unknown. SV40 really did contaminate millions of polio vaccine doses; and lentivirus must have been present in African green monkey kidney cell substrates, so we should consider its failure to infect humans as a lucky escape, since SIVsgm cannot overcome human cell restriction factors. Moreover HIV did infect more than 1 in 3 British patients with haemophilia in 1981-1984 via blood products, before we were aware of HIV or had developed screening tests. We still require a proper risk analysis of xenotransplantation.

Myth, Risk and Trust

An odd outcome for public health risk arising from the polio vaccine theory of HIV's origin nearly 50 years ago is that it has affected the current polio eradication campaign more than HIV and AIDS. In 2003, a religious leader in northern Nigeria claimed that modern polio vaccines made in USA had been deliberately spiked with HIV for delivery destined to Muslim countries, and urged mothers to withhold polio immunisation for their infants. Within a few months, outbreaks of paralytic polio were reported across seven Nigerian provinces and neighbouring countries. WHO has responded by arranging and supplying polio vaccine manufactured in Indonesia, a Muslim country, and the eradication programme is now back on track. This episode however, is redolent of the MMR scare in the UK. It illustrates how easily one or two persuasive scientists, physicians or community leaders can destroy public confidence. An important aim for the avoidance of risk in the future will be the maintenance of trust in medicines and vaccines in a climate where rumours and myths spread faster than viruses.

Risk and Logistics

It will be important for the estimation of risk to be clear-headed in identifying which cofactors in the complex web of social and microbiological causes of infectious diseases need to be targeted to make the greatest impact on disease control. Whereas it is over-simplistic to suggest that that poverty rather than HIV causes AIDS, it is also inappropriate to focus exclusively on the proximate agent of a specific disease while ignoring the underlying social conditions that exacerbate its spread. Thus in the 19th century sanitation played a greater role than the identification of specific microbes in reducing enteric infections. With the current absence of an HIV vaccine, health education, safer sexual practices and provision of sterile injecting equipment are crucial weapons in the battle to contain AIDS. But the deployment of resources will need to change with the advent of an efficacious vaccine.

In infectious disease, there is much to be learned from military logistics in translating risk analysis and risk estimate into containment. Algorithms of critical path analysis should be given greater weight than warm, woolly sentiments about empowerment. Nonetheless, community consensus is crucially important for the issues of trust outlined above.

Smallpox was not eradicated in 1977 by the alleviation of poverty; rather, a precisely targeted, logistically robust vaccination campaign put paid to the disease. Even with an efficacious AIDS vaccine, however, eradication of HIV will not be achievable by 2015, 2030 or much later, because it establishes a life-long persistent infection. For HIV, the population models of susceptible versus immune individuals are more complex than those for acute infections such as polio, smallpox, measles and influenza.

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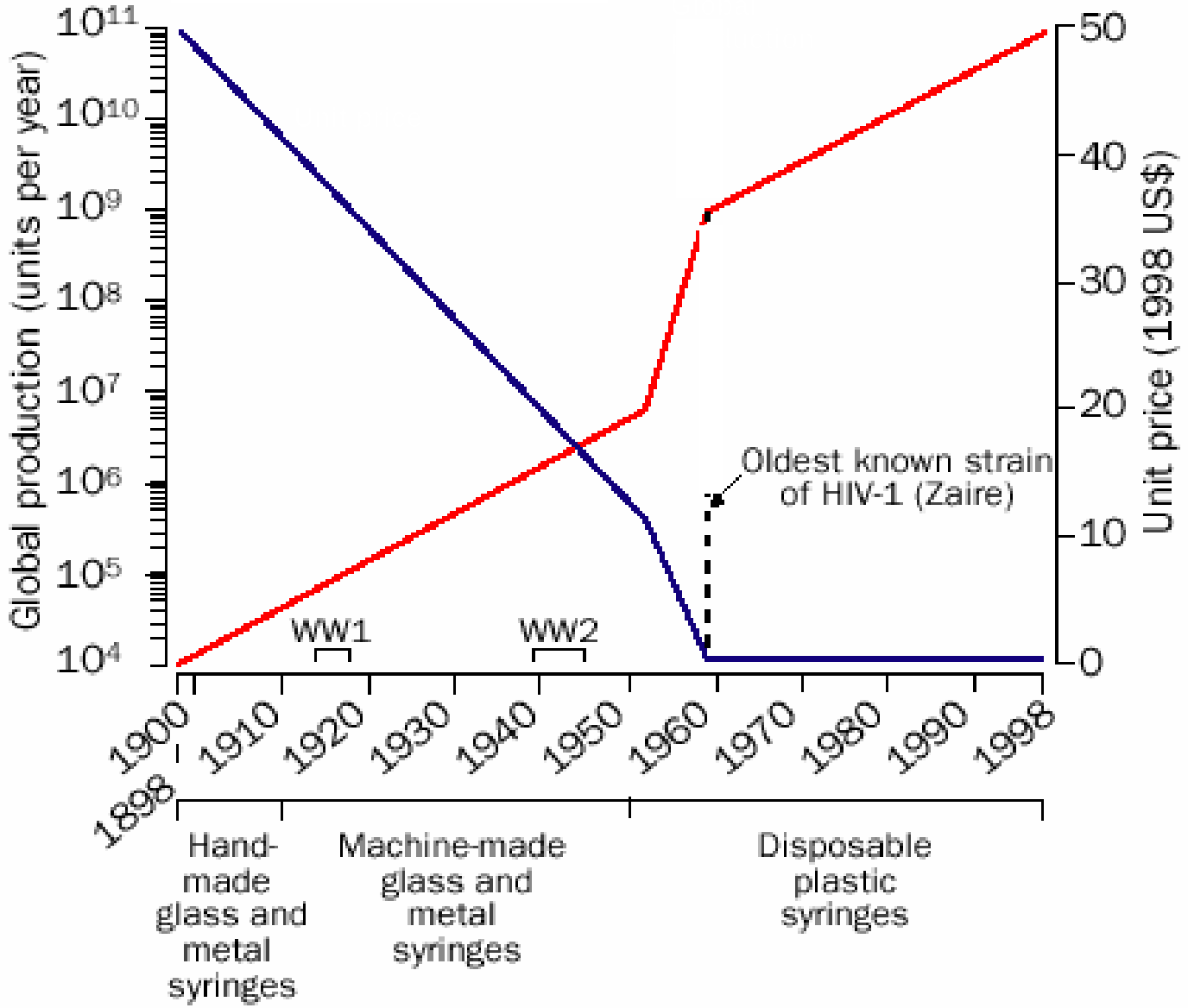


Figure 1. How Syringes Sped the Spread of HBV, HCV & HIV (from Drucker *et al*. Lancet: 358, 1989-1992, 2001).

Figure 2.

Adults and children estimated to be living with HIV as of end 2005

Total: 40.3 (36.7 – 45.3) million

Joint United Nations Programme on HIV/AIDS
UNAIDS
UNHCR • UNICEF • WFP • UNDP • UNFPA
UNODC • ILO • UNESCO • WHO • WORLD BANK

00003-E-2 – December 2005

World Health Organization

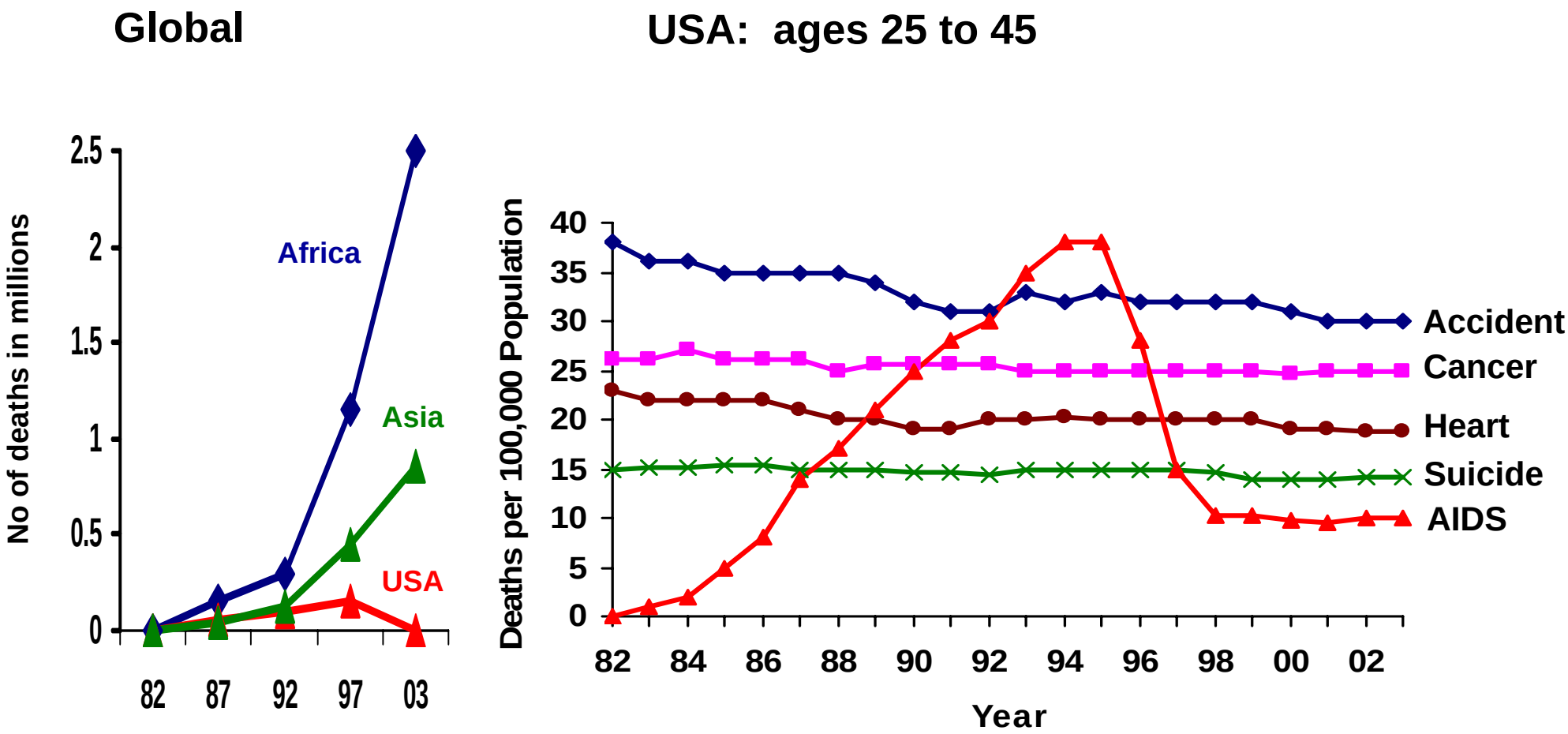


Figure 3. HIV / AIDS Mortality 1982 - 2004

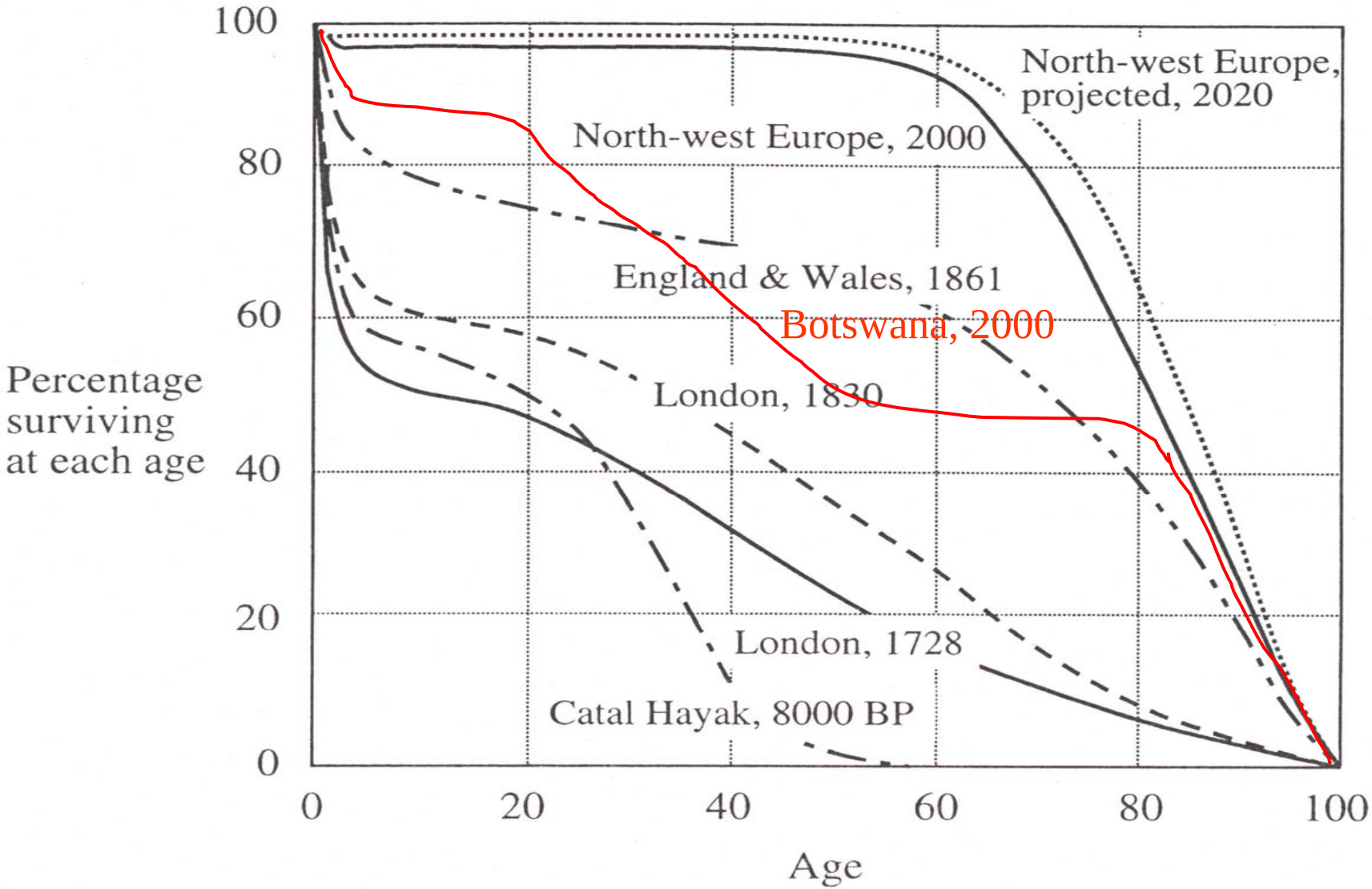
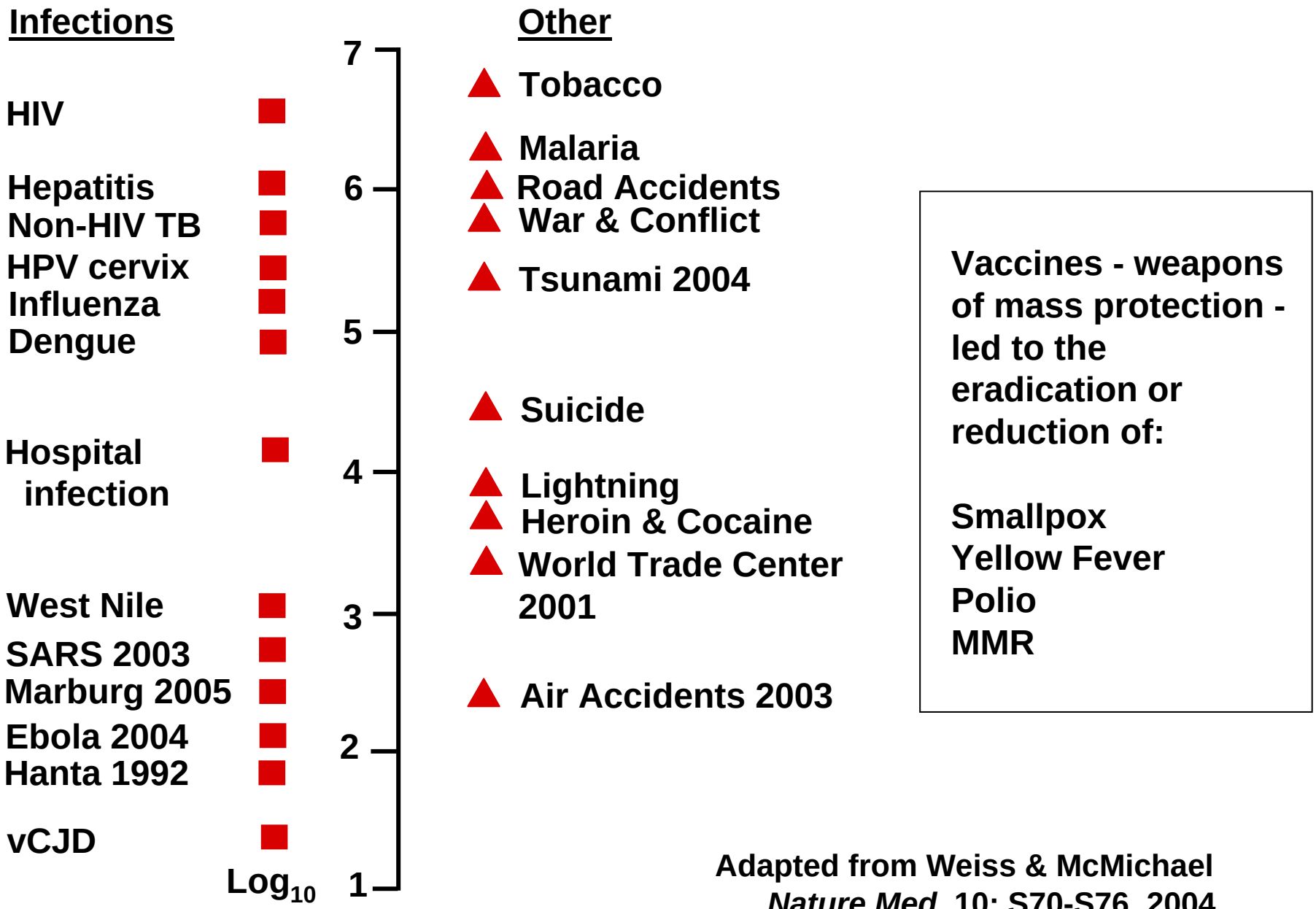
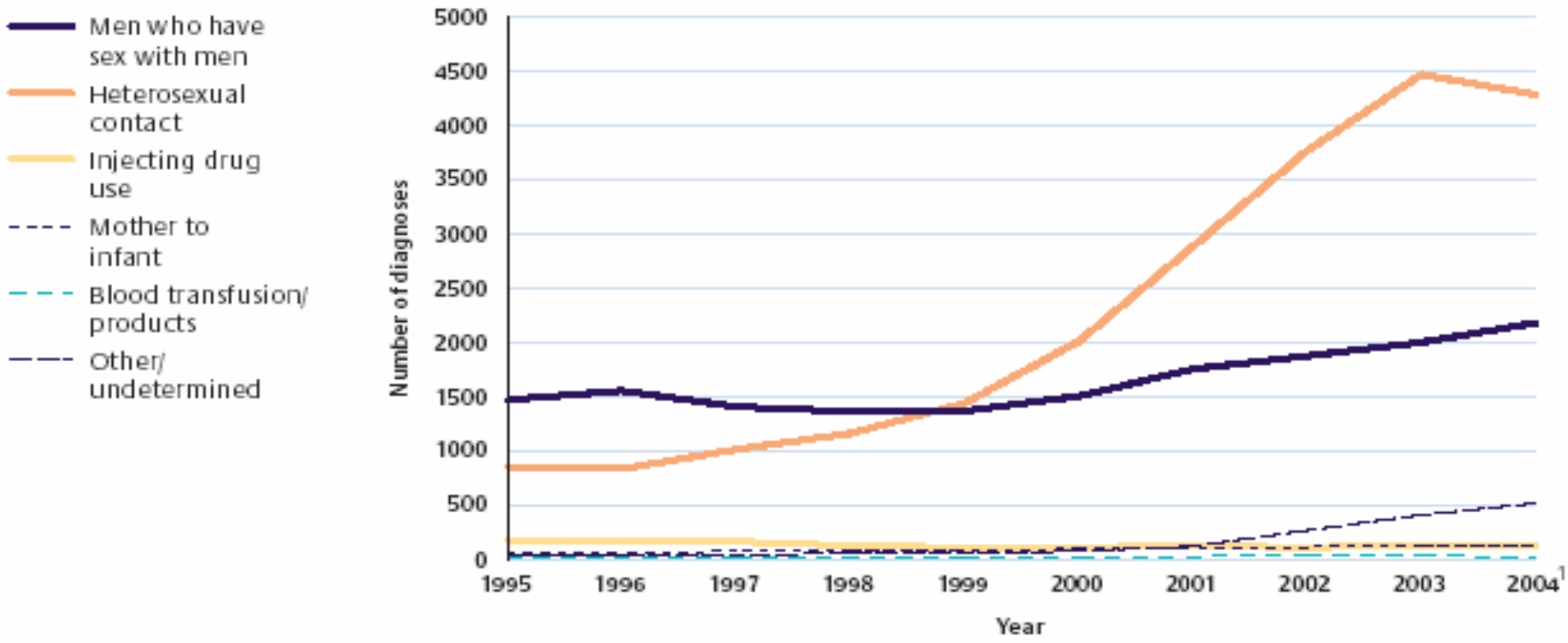


Figure 4. Estimated changes in life expectancy over the last 8,000 years. The doubly inflected figure for Botswana shows the high mortality of young adults due to AIDS. (Adapted from Tony McMichael, *Human frontiers, environments and disease,* CUP, 2001)

Figure 5. Weapons of mass destruction placed on a 'Richter' scale of annual global mortality



Adapted from Weiss & McMichael
Nature Med, 10: S70-S76, 2004



[1] Numbers will rise for recent years, as further reports are received
Data source: HIV/AIDS diagnosis and death reports

Figure 6. Exposure category of HIV-infected individuals by year of diagnosis in the United Kingdom, 1994-2004 (from HPA Annual Report, 2005).

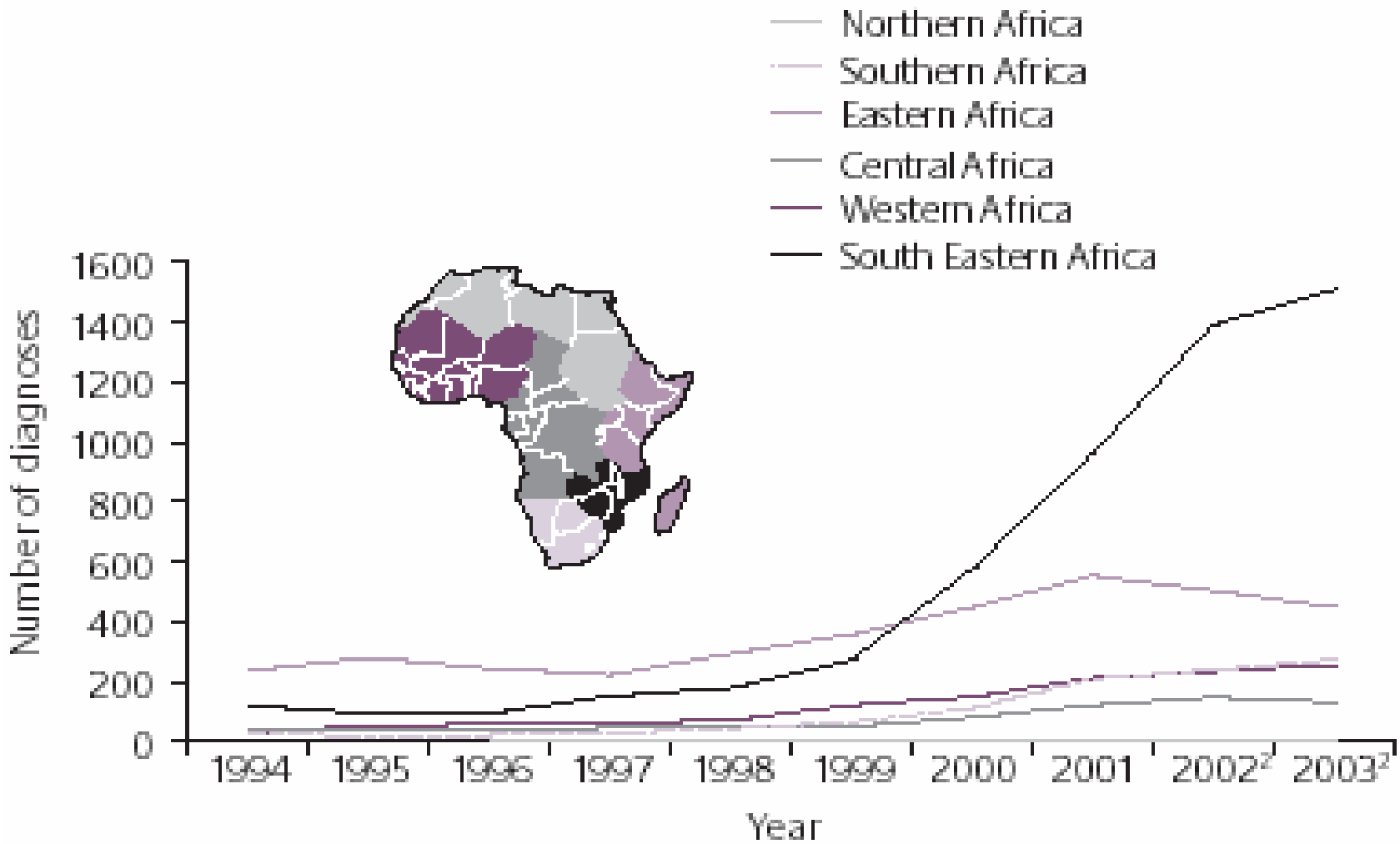


Figure 7. Probable source for heterosexual HIV infections diagnosed in the UK, 1994-2003 (from HPA Annual Report, 2004).

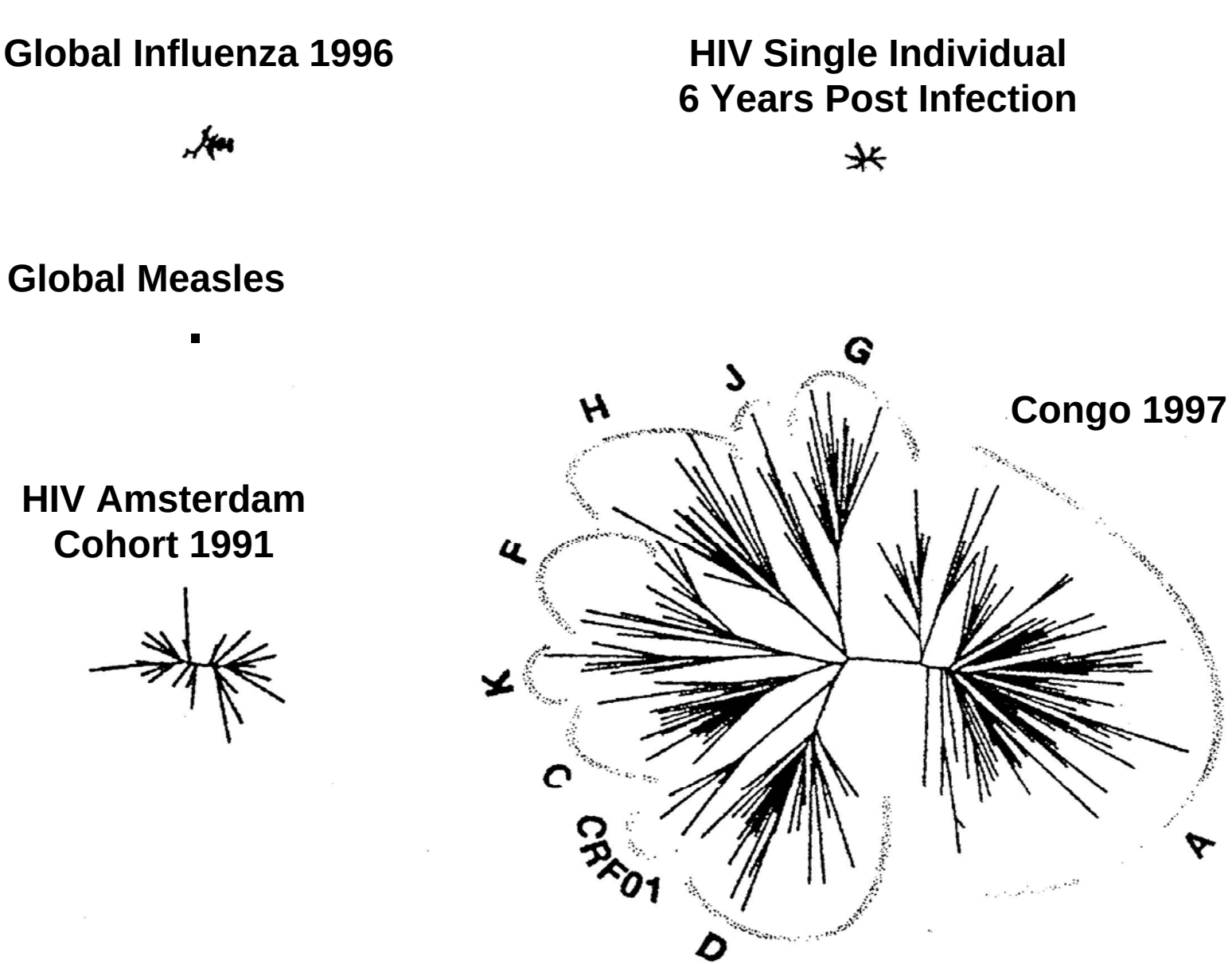


Figure 8. The rapid genetic diversification of HIV increases the emergence of drug resistance, and impedes vaccine development. The length of each spoke denotes the % of nucleotide change (adapted from Weiss *Nature Med* 9: 887-891 (2003)

All the reports and papers produced within the Foresight project 'Infectious Diseases: preparing for the future,' may be downloaded from the Foresight website (www.foresight.gov.uk). Requests for hard copies may also be made through this website.

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