Workshop on Practical approaches to Hospital Infection Prevention and Control
Review Paper – Surgical Site Infections

The injection century: massive unsterile injections and the emergence of human pathogens

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Unsterile medical injections are common in the less-developed world, where most visits to a doctor result in the (generally unnecessary) administration of intramuscular, or subcutaneous drugs. WHO estimates[1] that every year unsafe injections result in 80 000–160 000 new HIV-1 infections, 8·16 million hepatitis B infections, and 2·3–4·7 million hepatitis C infections worldwide (this figure does not include transfusions). Together, these illnesses account for 1·3 million deaths and 23 million years of lost life.[1] Even under the auspices of WHO regional immunisation programmes, which constitute 10% of all mass vaccination campaigns, an estimated 30% of injections are done with unclean syringes that are commonly reused. And, for other medicinal injections, over 50% are deemed unsafe, with rates as high as 90% in some campaigns.[1]

Injections outside of medical practice

Unsterile administration of drugs also takes place on a large scale outside of formal medical practice. In many places in the less-developed world, injectable medications, and syringes and needles, are readily available in rural villages, where injecting by indigenous practitioners (injectionists) and self-injection are common practice.[2,3] Furthermore, syringes are now widely used for administration of illicit substances. Once restricted to North America and Europe, intravenous opioids are now taken in more than 120 countries,[4] where millions of drug addicts inject themselves daily using unsterile equipment. There are between 10 and 15 million people who inject illicit drugs worldwide,[4,5] and this number continues to grow as heroin production is established in new areas; most notably in Mexico, Colombia, and some of the republics of the former Soviet Union. Use of illegal drugs is especially widespread in the former Soviet Union (with 2–3 million injectors), and in a growing number of countries in Asia,[6] Africa, and Latin America.

As awareness of the health consequences of unsterile injecting grows, there are calls for better sterilisation supplies and instruction (**figure 1**).[1] Many people are calling for the introduction of autodestruct injecting equipment, and for the provision of sterile equipment to drug addicts through harm reduction programmes.[6,7]

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Figure 1. Children scavenging dirty syringes for resale in Asia

The growth of injecting in the 20th century

After their invention in 1848 and until the end of World War I, hypodermic syringes were valuable medical instruments, individually handmade from glass and metal by skilled artisans, and priced accordingly—ie, in 1900, syringes cost about US$50 each (adjusted for inflation). In 1920, only 100 000 syringes were manufactured worldwide, even after production processes had been sped up to keep up with the demand associated with World War I.[8] However, beginning in the period between the World Wars, as their uses expanded—eg, for injection of insulin—syringe manufacture became increasingly mechanised, and interchangeable components and mass production methods were introduced. By 1930, global production had reached 2 million units per year, increasing to 7·5 million by 1952. Between 1920 and 1950 the unit price declined by 80%.

The greatest change in the demand for syringes arose when penicillin became available after World War II. Discovered in 1929, but not manufactured until World War II, the total amount of penicillin produced in 1941 was only sufficient to treat about 200 patients.[9] But, between 1949 and 1964, US production increased from 76 000 to 1·70 million pounds, and the price of the antibiotic decreased from $1144 to $49 per pound. The mass production and low prices of penicillin led to worldwide export, with USA generating more than 80% of penicillin available worldwide. By 1964, penicillin represented more than 50% of the market of all medicinal chemicals manufactured in USA.[10] In this era, penicillin therapy was synonymous with injections, since although oral antibiotics

were under development, they were far less well absorbed; a waste of a scarce and precious commodity.[10] Accordingly, most human antibiotics were available only in parenteral form.

The increased demand for injectable antibiotics was anticipated by the manufacturers of injecting equipment, and led to the development of mass produced and inexpensive single use syringes.[8–10] During 1950–60, steriliseable glass and metal units were largely replaced by these disposable syringes. New, high volume manufacturing technologies for this plastic injection equipment were developed and production soared. Prices fell noticeably, and availability increased massively worldwide,[8] with global production increasing 100-fold to 1 billion units per year in 1960. This increase was coupled with a 56-fold decline in price to $0·18 per unit when adjusted for inflation (**figure 2**).[11] Today, a small factory with six workers can make 100 million sets per year at a cost of about US 1·5 cents.

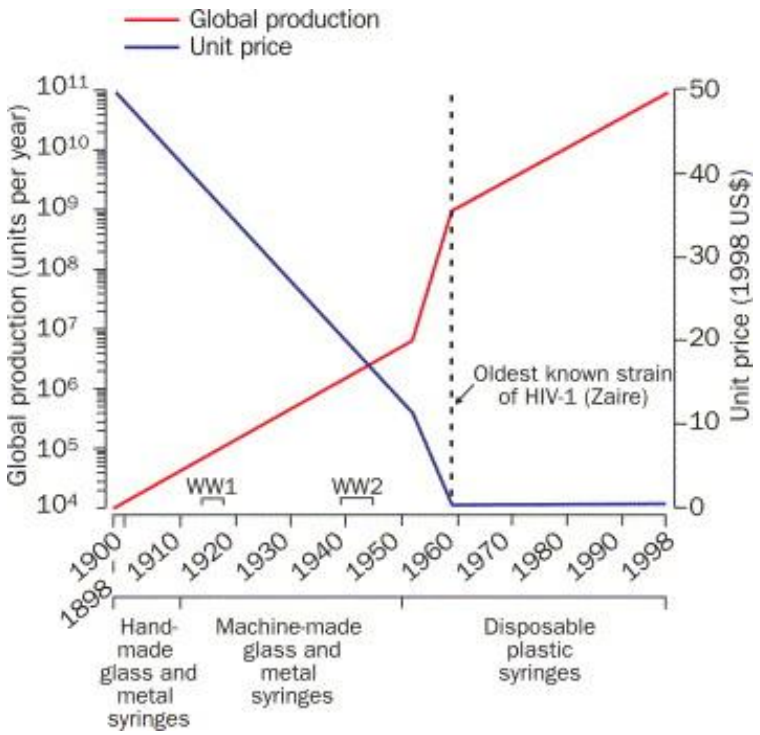

Figure 2. Global production and unit price of injecting equipment (1898–1998) WW=World War.

Public health consequences

The role of injecting in the AIDS epidemic was at first unrecognised. Now intravenous drug abuse is thought to account for most new incident HIV-1 infections in many cities in USA and Europe,[4,7] and is associated with regional outbreaks of HIV-1 throughout the former Soviet Union and Asia.[4,6,12] Of particular concern is the rapid growth of HIV-1 infection among heroin injectors in Russia, Ukraine, China, India, Pakistan, Indonesia, and southeast Asia—an area with more than 50% of the world's population and great vulnerability to the economic attractions of illicit drug markets.

Furthermore, although hepatitis C was not identified till 1989 (and is almost certainly an older human pathogen than HIV), its epidemic spread seems to be closely associated with 20th century medical developments, including (unsterile) injections, blood transfusions, and dialysis.[13] 170 million individuals worldwide are chronic carriers of hepatitis C, including 1–2% of the adult populations of developed countries and 5–10% in some less-developed countries.[14] The first documented large scale outbreak of the disease occurred in the early 1960s, at the time of a campaign for parenteral treatment of schistosomiasis in Egypt.[15] Between 1964 and 1969 more than 3 million injections were given per year to over 300 000 individuals. By the mid 1980s the campaign had infected 10% of the entire adult population of Egypt with hepatitis C, and it constituted the world's largest iatrogenic transmission of blood borne pathogens known to date.[15]

AIDS and hepatitis C pandemics are catastrophic events that establish massive unsterile injecting as an important factor determining global patterns of public health. By altering the ecological balance of the routes of transmission for human pathogens, massive unsterile injecting creates new biological links between humans and microorganisms—ie, every injection with a used syringe risks introducing the recipient to a sample of organisms circulating in that syringe's previous user and offering new opportunities for the transmission and recombination of these organisms.

Origins of HIV

Additionally, unsterile injecting might play a part in facilitating the adaptation of animal pathogens to human hosts. Laboratory studies have shown that cross-species serial passaging, by injection, of simian immunodeficiency viruses (SIV) increases their pathogenicity.[16,17] In 1995, Marx[18] hypothesised that unsterile injections could account for several SIVs crossover to humans in Africa via the serial passage of partially adapted simian viruses, which infect people through bites, cuts, and exposure to infected blood in the course of hunting and butchering monkeys. More than 70% of chimpanzees and Sooty Mangabys carry SIVs, which are the progenitors of HIV-1 and HIV-2, respectively.[19,20]

Although many animal viruses have made the genetic transition to human pathogens in the past—eg, smallpox—people have been exposed to SIVs for millennia, living in close proximity to and hunting primates in Africa[19] without the emergence of HIV. But, in the mid-20th century, at least three fully adapted HIV strains emerged to become epidemic (HIV-1 group M, and HIV-2 subtypes A and B), and five or six other HIVs also arose, but did not complete the full transition to epidemic status.[20–22] To become a transmissible pathogen in human beings, every one of these SIVs must have undergone full adaptation to human hosts in a short period. The crossover of several SIVs and the emergence of several fully adapted strains of HIV in a brief period suggests that some biologically relevant modern event (such as increases in the probability of serial passage through unsterile injecting) might be responsible.

Alternatively, if HIV existed in Africa earlier but was hidden in remote pockets that never emerged as visible or reportable disease, as Hahn and others have proposed,[23,24] the increased transmission opportunities associated with greatly increased unsterile injections in the 1950s could have operated similarly to their role in the Egyptian schistosomiasis campaign—ie, by disseminating previously sequestered viruses and enabling their epidemic emergence. In either case, the history of injecting in Africa is of great interest with respect to the origin and emergence of the AIDS pandemic.

Unsterile injecting in sub-Saharan Africa

In the 75 years before World War II, a network of colonial and missionary clinics was the principal base of modern medicine in sub-Saharan Africa.[1,25] Specific practices varied, dependent on the medical traditions of the French, British, or Belgian colonial powers, but most administered injectable drugs—largely arsenicals—for the treatment of syphilis. This was done under medical supervision, and access to the relatively costly drugs and injecting equipment was tightly controlled. Sterilisation equipment was available, and sterile injecting procedures were generally followed.

However, in the period after World War II, with independence movements growing, Europe's control of civic affairs in the region began to weaken—including its controls on medical practice.[26] Despite substantial new investments in educational and administrative preparation for independence,[25] the professional oversight and control of injection practices by a shrinking colonial medical care system (never adequate for the indigenous population in the first place) diminished rapidly, and was not quickly replaced by the newly independent, but impoverished, African states.[25,26] This era saw the rise of injection doctors working in country clinics,[1–3] soon constituting an indigenous parallel medical care system that persists to this day and has access to all sorts of injectable medications.[27]

The advent of antibiotic therapies, in the 1950s, quickly built popular faith in the power of the injections[1–3,27] and, by the 1960s, injections came to be expected at every medical visit for the treatment of any infection or fever, and also for malaise, fatigue, and the common cold.[1] Results of studies done in several sub-Saharan countries in the 1960s indicated that 25–50% of households had received an injection within the previous 2 weeks[25] and, by the 1990s, injections were being administered at 60–96% of outpatient visits.[1]

The early 1950s saw the first United Nations sponsored mass injection campaigns for eradication of Yaws.[25] In central Africa, where all the known strains of HIV-1 emerged during this period, United Nations International Children's Emergency Fund (UNICEF) administered over 12 million injections of penicillin between 1952 and 1957, and 35 million injections by 1963.[25] There were some earlier injecting campaigns (that could have facilitated serial passage and transmission of HIV) in French Equatorial Africa for direct person to person vaccination for small pox (up to 35 000 immunisations from 1893 to 1910) and another for sleeping sickness (90 000 cases between 1917 to 1919) that used

only six syringes.[28] Although these certainly could have spread other infections, there is no evidence that they were associated with the emergence of epidemic HIV in these areas at this time. And, if HIV had existed earlier, the social upheaval of the slave trade (which took over 20 million people to America) would have carried the virus with it. But, although other retroviruses did arrive in the New World through the slave trade, HIV did not.

Other important events in the history of sub-Saharan Africa (besides the rise of unsterile injecting) might explain the emergence of epidemic HIV by 1959. These include, population growth, urbanisation and deforestation, massive rural migration, regional wars, changing sexual practices, and the increased hunting of simians. But the most important effect of these factors arose after 1960—ie, after the emergence of HIV-1. Most recently, the contamination of oral polio vaccine by SIV has been blamed for the emergence of HIV in central Africa.[18] However, further research, and the analysis of archived polio vaccine samples has failed to verify this theory.[23] None of these alternatives to massive unsterile injecting offers a biologically plausible or timely explanation of the simultaneous appearance of multiple strains of HIV in the mid-20th century in multiple locations in Africa.

To examine these issues and better understand the historical and contemporary role of unsterile injecting in emergent infections, we are beginning to collect used syringes and blood samples in HIV endemic areas of Africa where populations also have frequent exposure to SIV. These used syringes and blood samples will be tested by PCR analysis for traces of viral contaminants (DNA of SIV, HIV, hepatitis B virus, and hepatitis C virus), and the patterns of exposure to simians and to unsterile injecting will be documented. These data will be used to establish boundary conditions and limiting rates of injection related transmission of blood-bone viruses to inform the precision of mathematical models attempting to date the species crossover of SIV and epidemic spread of HIV.[23]

Conclusions

It would be a cruel irony if the introduction of injectable antibiotics into Africa in the last years of the colonial period should be associated with the origins of the HIV pandemic. As with the probable crossover of scrapie from sheep to cattle (as bovine spongiform encephalopathy [BSE]) via new mass feeding methods in commercial agriculture, and then of BSE to humans, these results of massive unsterile injecting seem to be an unintended consequence of large scale technological innovation in health care.

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The emergence of epidemic HIV and hepatitis C virus in the 20th century suggest that massive unsterile injections can become an important new catalyst for biological change, capable of greatly accelerating the spread of many human pathogens and allowing previously isolated viruses to establish global pandemics. In this way, massive unsterile injecting can profoundly reorder some fundamental biological relations between agent, host, and environment, with unpredicted effects for human parasite ecology and public health.

Although there is greater awareness of this problem today—eg, the work of the Safe Injecting Global Network,[29] as recently as 1998, WHO still recommended re-use of syringes up to 200 times in vaccination programmes,[30] relying on sterilisation routines that WHO's own studies show are usually not followed.[1] And, of course, the huge frequency of use of unsterile medical injections outside formal health care and the growth of illicit drug use in less-developed countries have particularly ominous implications for attempts at control. Accordingly, the discussion of a possible role of massive unsterile injections in the emergence of epidemic HIV in Africa has some currency for the larger discussion on emerging pathogens worldwide.

Ultimately, the driving force behind massive unsterile injecting is the global demand for injectable drugs and their therapeutic effects. But the risks that injecting these drugs entail are a function of continuing disparities in access to modern medical care.[12,31] If these large political realities and the imbalances in the global marketplace in drugs and the technology to use them are not addressed, unsterile injections will continue to spread infectious diseases, and possibly create new ones, throughout the 21 st century.

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References

[1] Simonsen L, Kane A, Lloyd J, et al. Unsafe injections in the developing world and transmission of blood borne pathogens: a review. *Bull WorldHealth Organ* 1999; **77:** 789-800.

[2] Reeler AV. Injections: a fatal attraction. *Soc SciMed* 1990; **31:** 1119-1125.

[3]. van der Geest S. The illegal distribution of Western medicines in developing countries: pharmacists, drug peddlers, injection doctors and others: a bibliographic exploration. *Med Anthrop* 1982; **4:** 197-219.

[4]. Stimson VG. The Global diffusion of injecting drug use: implications for human immunodeficiency virus infection. *Bull Narc* 1993; **46:** 3-17.

[5]. United Nations International Drug Control Programme. World drug report. New York: Oxford University Press, 2000:.

[6]. In: , Crofts N, ed. Manual for reducing drug related harm in Asia. Center for Harm Reduction, Melbourne and Changmai, 2000:.

[7]. Drucker E, Lurie P, Alcabes P, Wodak A. Measuring harm reduction: the effects of needle and syringe exchange programs and methadone maintenance on the ecology of HIV. *AIDS* 1998; **12** (suppl A): 217-230. MEDLINE

[8]. Becton-Dickinson Corp. In: . The Echo. Vol 11:Spring, 1991: 1-3.

[9]. Hayward EG. Penicillin and other antibiotics. Chemurgic Papers, No 13. New York: National Farm Chemurgic Council, 1949:.

[10]. Hewitt WL. Penicillin: historical impact on infection control. *Ann NY Acad Sci* 1967; **145:** 212-215. MEDLINE | CrossRef

[11]. US Disposable Needles, Syringes, and Related Products Mkt. . *Frost and Sullivan Corp* 1996;.

[12]. Mann J, Tarantola D. AIDS in the World II. Cambridge: Harvard, 1996:.

[13]. Alter MJ. Epidemiology of hepatitis C. *Hepatology* 1997; **26:** 628-655.

[14]. Anon. Global surveillance and control of hepatitis C: WHO report. *J Viral Hepat* 1999; **6:** 35-47. MEDLINE

[15]. Frank C, Mohamed MK, Strickland GT, et al. The role of parenteral antischistosomiasis therapy in the spread of hepatitis C in Egypt. *Lancet* 2000; **355:** 1906-1911.

[16]. Cayabyab M, Karlsson GB, Etemad-Moghadam BA, et al. Changes in human immunodeficiency virus type 1 envelope glycoproteins responsible for the pathogenicity of a multiply passaged simian human immunodeficiency virus (SHIV-HXBc2). *J Virol* 1999; **73:** 976-984.

[17]. Holterman L, Niphuis H, ten Haaft PJ, Goudsmit J, Baskin G, Heeney JL. Specific passage of simian immunodeficiency virus from end-stage disease results in accelerated progression to AIDS in rhesus macaques. *J Gen Virol* 1999; **80:** 3089-3097.

[18]. Hooper E. The river. New York: Little Brown, 1999:.

[19]. Marx PA, Li NWY, Lerche S, et al. Isolation of a simian immunodeficiency virus related to human immunodeficiency virus type 2 from a West African Pet Sooty Mangabey. *J Virol* 1991; **65:** 4480-4485.
[20]. Chen Z, Telfer P, Reed P, et al. Genetic characterization of a new West African simian immunodeficiency virus SIVsm: geographic clustering of household-derived SIV strains with human immunodeficiency virus type 2 subtypes and genetically diverse viruses from a single feral sooty mangabey troop. *J Virol* 1996; **70:** 3617-3667.
[21]. Simon F, Mauclere P, Roques P, et al. Identification of a new human immunodeficiency virus type 1 distinct from group M and group O. *Nat Med* 1998; **4:** 1032-1037. MEDLINE | CrossRef
[22]. Hirsch VM, Olmsted RA, Murphy-Corb M, Purcell RH, Johnson PR. Are African primate lentiviruses (SIVsm) closely related to HIV-2. *Nature* 1989; **339:** 389-392. MEDLINE | CrossRef
[23]. Origins of HIV and the AIDS epidemic. Discussion Meeting, Proceedings of The Royal Society, London. Sept 11–12 (in press).
[24]. Zhu T, Korber BT, Nahmias AJ, Hooper E, Sharp PM, Ho DD. An African HIV-1 sequence from 1959 and implications for the origin of the epidemic. *Nature* 1998; **391:** 594-597. MEDLINE | CrossRef
[25]. UNICEF in Africa south of the Sahara: a historical perspective. . *UNICEF History Series, Monograph VI* 1987;.
[26]. Oliver R, Atmore A. Africa since 1800, 2nd edn. Cambridge: Cambridge University Press, 1977:.
[27]. Birungi H, Asiimwe D, Whyte SR. Injection use and practices in Uganda, WHO action program on essential drugs. Geneva: WHO, 1994:.
[28]. Hendrick R. Colonialism, health and illness in French Equatorial Africa (1885-1935). Atlanta: African Studies Assoc Press, 1994:.
[29]. Huytin Y. The safe injecting global network. Geneva: WHO, 2001:.
[30]. Product information sheets: global program for vaccine and immunization: expanded program on immunization. Geneva: WHO, 1999:.
[31]. Garrett L. In: The coming plagues: newly emerging infections in a world out of balance. New York: Farrar, Strauss, and Gioroux, 1994: 32.

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