Virus perpetuation in populations: biological variables that determine persistence or eradication

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Summary. In this review, I use the term "perpetuation" for persistence of a virus in a population, since this is a different phenomenon from persistence of a virus in an infected host. Important variables that influence perpetuation differ in small (<1,000 individuals) and large (>10,000) populations: in small populations, two important variables are persistence in individuals, and turnover of the population, while in large populations important variables are transmissibility, generation time, and seasonality. In small populations, viruses such as poliovirus that cause acute infections cannot readily be perpetuated, in contrast to viruses such as hepatitis B virus, that cause persistent infections. However, small animal populations can turnover significantly each year, permitting the perpetuation of some viruses that cause acute infections. Large populations of humans are necessary for the perpetuation of acute viruses; for instance, measles required a population of 500,000 for perpetuation in the pre-measles vaccine era. Furthermore, if an acute virus, such as poliovirus, exhibits marked seasonality in large populations, then it may disappear during the seasonal trough, even in the presence of a large number of susceptible persons. Eradication is the converse of perpetuation and can be used as a definitive approach to the control of a viral disease, as in the instance of smallpox. Therefore, the requirements for perpetuation have significant implications for practical public health goals.

Introduction

From the viewpoint of the individual host, viral infections can be conveniently divided into those that are acute and those that are persistent. However, all viruses – by definition – must be able to persist in their host population, regardless of whether they cause acute or persistent infection in individual members of that population. Thus, persistence in a population is a distinct phenomenon and in this discussion I will use the term "perpetuation" to distinguish it from persistence in the individual host.

Table 1. Biological parameters that influence perpetuation of a virus in a host population. Based in part on [30][a]

Parameter	Small population <1,000	Large population >10,000
Persistence in the individual host	++++	
Population turnover	++++	
Transmissibility and generation time		++++
Seasonality		++++

[a]++++: particularly important parameter

Once a virus has infected a defined population, it may either perpetuate indefinitely or may disappear. If disappearance is a natural occurrence, it is often described as "burn out" or "fade out", while if it is induced by human intervention, it may be described as "eradication" or "elimination". Eradication represents a definitive approach to prevention of a viral disease, as in the instance of smallpox. However, to develop a strategy for eradication it is necessary first to understand the requirements for perpetuation. Thus, the subject has significant implications for practical public health goals.

Virus persistence and perpetuation has been the subject of numerous discussions, and this presentation draws heavily on some of these publications [1, 26, 30]. Some of the biological variables that influence perpetuation are shown in Table 1. Implicit in this table is the generality that most viruses can infect a given host only once. In the instance of an acute infection, the host acquires lifelong immunity to the infecting virus and is – from an epidemiological perspective – no longer capable of acting as a link in the chain of infection. If the virus causes persistent infection, then the outcome varies. Some persistent virus infections can be transmitted as long as the host is infected (for instance hepatitis B virus and human immunodeficiency virus [HIV]). Other viruses (such as varicella zoster and herpes simplex) persist in a latent form and are infectious only during intermittent episodes of recrudescence.

Virus perpetuation within a human population involves a fragile equilibrium between three different categories of hosts: those who have not been infected and are susceptible; those who are actively infected and are potentially infectious; and those who have been infected and are immune. If the infection spreads too slowly within the population (transmissibility quotient, $\mathrm{Ro} < 1$) the virus will ultimately disappear for absence of actively infected hosts. On the other hand, if the infection spreads too rapidly ($\mathrm{Ro} \gg 1$), the susceptible population will be "exhausted", also leading to disappearance of actively infected hosts.

The size of the population under consideration is an important determinant of the dynamics of perpetuation, since the relative importance of other variables is different in smaller (<1,000 individuals) and larger (>10,000) groups (Table 1).

In small populations, two of the most important variables are persistence in the individual host and population turnover (the rate at which new susceptible animals are introduced into the population). In large populations, variables of high importance include transmissibility, generation time, and seasonality. Transmissibility (Ro) is the number of new infections that are generated by each existing infection and is a property (in part) of each virus, since under a given set of conditions, some viruses will be transmitted at a much higher rate than will others. Generation time is the average time between the infection of two individuals who are successive links in an infection chain; generation time may be a short as 2–3 days in the case of influenza and as long as many years in the case of HIV or hepatitis B infection. Seasonality refers to the variation in transmissibility of a given virus in a specific population at different times of year.

Perpetuation in small populations

Viruses that cause acute infections are often unable to perpetuate in small populations [3]. Figure 1 shows a seroepidemiological study of poliovirus in a small Eskimo village in Greenland, conducted in the 1950s. Each of the three types of poliovirus had been introduced into this population. Type 1 virus had caused an outbreak of infection 25 years prior to the study and had then disappeared; type

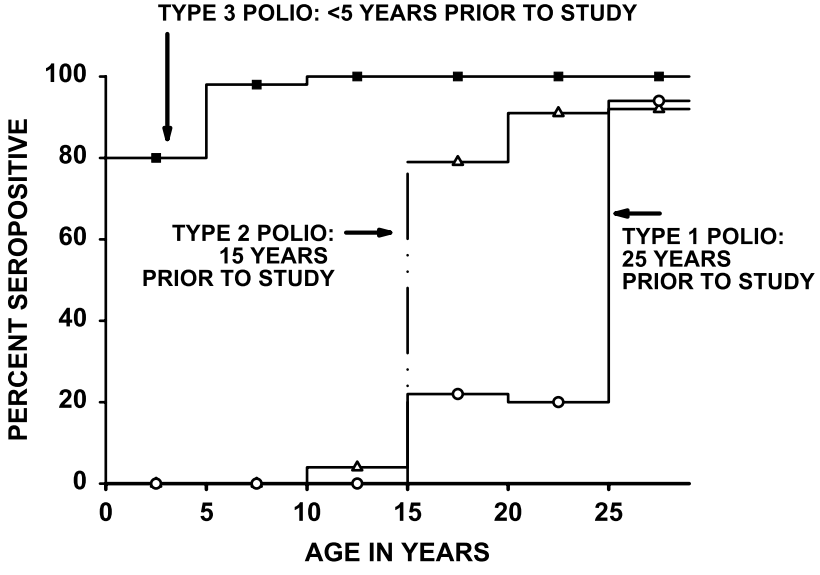

Fig. 1. Age distribution of poliovirus antibodies in an isolated Eskimo village, Narssak, Greenland. The data show three separate introductions of types 1, 2, and 3 poliovirus, respectively. The low frequency of type 1 antibodies in persons ages 15–25 probably represents cross-reacting antibodies induced by infection with type 2 virus. It appears that this acute infection "burned out" in this small (<1,000) isolated population because it spread rapidly through persons who had not been previously infected and "exhausted" the susceptible population. After [19]

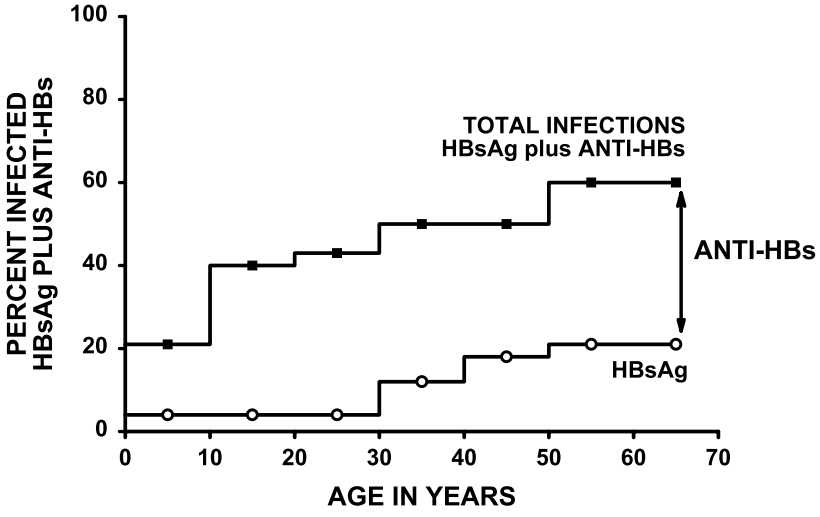

Fig. 2. Age distribution of hepatitis B surface antigen (*HbsAg*) and antibody to HbsAg (*anti-HBs*) in Eskimos of southwest Greenland. HBV was perpetuated in this small isolated population (<1,000) because it caused lifelong persistent infections in some persons (*HbsAg-positive*) who could continue to spread infection to susceptible newborn infants. Perpetuation was also enhanced by the low transmissibility of HBV, resulting in a pool of susceptible adults (persons who escaped infection as children and were infected as adults). After [25]

2 virus had been introduced 15 years prior to the study date and had likewise disappeared; and type 3 had been introduced within the prior 5 years and (likely) had also disappeared. In such small populations, viruses that cause acute infections spread so rapidly that they quickly exhaust the susceptible population and then fade out. Conversely, hepatitis B virus, which causes both acute and persistent infections can persist in small populations as shown in Fig. 2, a study of another small Eskimo population in Greenland. In such populations hepatitis B virus is often transmitted during birth, from infected mothers to their newborn infants, which frequently results in persistent infections.

Another parameter that favors virus perpetuation is rapid turnover of the population itself. This is seen most often in animal populations some of which, in nature, may have an average lifespan of 1–2 years, so that a large fraction of the population consists of relatively young and susceptible hosts. Although difficult to document in wildlife populations, this phenomenon can be more readily documented in groups of laboratory animals that are under constant surveillance. One example is a study conducted in a colony of laboratory rats that was maintained for nutritional studies [21]. This colony was infected with rat parvovirus, a small DNA virus that did not cause overt disease and was only detected by serological surveillance. Rat parvovirus caused an acute infection, transmitted by the enteric route, that spread rapidly through the relatively small population of about 500 young animals. Based on the rate of spread, the virus might have been expected to exhaust all susceptibles by 10 months of age. However, every month about 25% of the animals aged

4–5 months were removed to another room to be used for experiments and the same number of one-month susceptible weanling animals was introduced from a breeding colony. This continual introduction of young susceptible animals was sufficient to perpetuate an acute virus infection in a small population.

Perpetuation in large populations

As mentioned above, although a number of viruses cannot be maintained in small human populations, all human viruses are capable of perpetuation in large populations. Important biological determinants of perpetuation include transmissibility, generation time, and seasonality, and these three may, in turn, determine the minimum size of the population required for perpetuation. Transmissibility (Ro) reflects in part the innate infectivity of a given virus, but is also determined by the density of the population, by the proportion of that population that is susceptible, and by the frequency of significant contact between different individuals within the population. The following examples illustrate the interaction of all these variables, and indicate the complexity of these relationships.

Measles

Measles has a special place as an example of virus perpetuation, since it is a rare instance where public health statistics can be used to monitor the ebb and flow of a specific virus infection in large human populations. Measles has several attributes that – in the aggregate – are not seen for other common viral diseases: (i) There are longterm records of measles incidence, collected by many health departments in the United States and other countries; (ii) 95% of all measles infections manifest as illness (in contrast to 1% for poliomyelitis for example); (iii) the symptoms of measles are sufficiently pathognomonic so that it can be distinguished from other viral infections by clinical observers; and (iv) population-wide reports can be corrected for under-reporting (about 15% of measles cases were reported in most cities in the United States prior to the introduction of measles vaccine in 1963).

Exploiting these facts, Bartlett [2] published several classical studies showing that in the pre vaccine era in the United States, measles was perpetuated in cities of 500,000 or greater population but not in cities below that size. Similar observations could be made in other parts of the world. For instance, in Iceland, with a population of 150,000 to 200,000, measles was introduced about 6 times during the period 1900 to 1940; each time it caused an outbreak that lasted 1–3 years, and then disappeared (Tauxe, unpublished, 1979).

Although these data are striking, they remained unexplained for a number of years. Why was 500,000 the limiting population size, at least in the cities included in Bartlett's study? A putative explanation was put forth in several papers that focused on the seasonality of measles in temperate climates [30]. Data for Baltimore (one of the cities included in Bartlett's study), for the period 1928–1961, are shown in Fig. 3. Absent seasonality, 8% of annual incidence

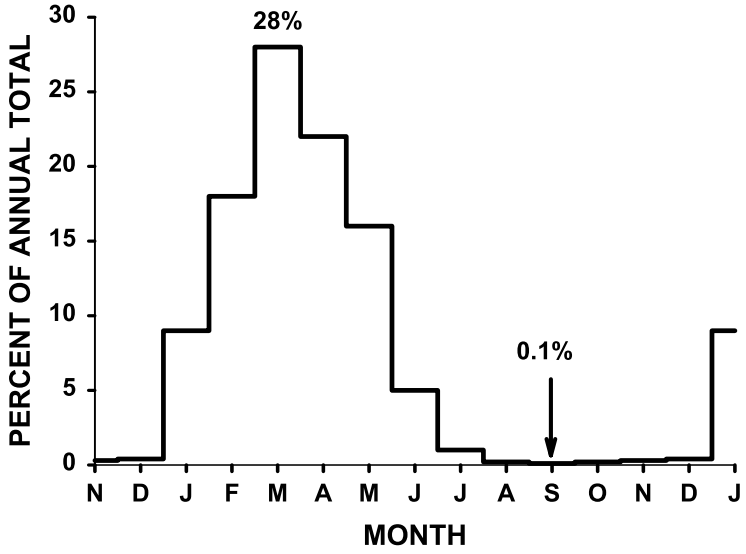

Fig. 3. The seasonality of measles in Baltimore, MD, 1928–1961, for 16 years of high incidence, showing the relative numbers of cases for each month. After [31]

Table 2. The number of measles cases during the trough period in a hypothetical North American city of 500,000 population, prior to the introduction of measles vaccine, based on data from [30][a]

Population	500,000
Measles susceptibles (estimated 10% of population)	50,000
Annual measles incidence (estimated average)	10,000
Cases in trough month (0.1%)	10
Cases in trough generation period (12 days)	3

[a]An age profile for measles susceptibles was constructed from the age distribution reported for measles in Baltimore, MD, for 1900–1931, supplemented with serosurveys conducted prior to the introduction of measles vaccine. The average number of annual measles infections was estimated as the size of an annual birth cohort, assuming a steady state and 100% cumulative attack rate for measles. Cases in trough month based on data from Baltimore, MD, 1928–1961, after [30]

would have been expected each month; however measles peaked in March at 28% while only 0.1% was reported in September, the trough month. Based on these observations, a hypothetical reconstruction for a city of 500,000 with 0.1% of measles in the trough month is shown in Table 2. In such a city, during a single trough generation period, only 3 cases of measles would be expected. Under these circumstances, it is plausible that measles infection could fade out.

A further test of the hypothesis that seasonality played a critical role in the fade out of measles is provided by data from New York City and Baltimore, prior to and after the introduction of measles vaccine (Table 3). The data in Table 2 imply

Table 3. The effect of measles immunization on the perpetuation of measles in a large population, after [30][a]

	Year	New York City		Baltimore	
		No. of susceptibles	Measles cases reported in the trough month	No. of susceptibles	Measles cases reported in the trough month
Pre vaccine	1958	900,000	47	90,000	14
	1959		97		22
	1960		43		11
	1961		123		19
Measles vaccine introduced	1963				
Post vaccine	1968	400,000	11	40,000	0
	1969		39		0
	1970		31		0
	1971		39		0

[a]The estimated number of susceptibles is based on the age distribution of measles cases and serosurveys of measles antibody, after [30]

that a population of about 50,000 susceptibles (data not shown indicate that about 10% of the total population was susceptible to measles) was required to perpetuate measles in cities of North America prior to the introduction of measles vaccine. In New York City, it can be estimated that there were about 900,000 susceptibles prior to measles vaccine and about 400,000 in the late 1960s, after the introduction of measles vaccine. As Table 3 shows, measles was perpetuated in New York City after the introduction of the vaccine. In Baltimore, vaccination was estimated to reduce the susceptible population from 90,000 to 40,000, just below the threshold for perpetuation. In fact, measles was perpetuated in Baltimore prior to measles vaccination, but showed an annual fade out each year in the late 1960s, after the introduction of measles immunization.

Poliomyelitis

Currently, the global effort to eradicate poliovirus is moving towards its goal. In 1988, when WHO enunciated the eradication of polio as a goal, there were an estimated annual 350,000 cases of paralytic poliomyelitis worldwide; in 2001, there were fewer than 1,000. As we approach eradication, it is interesting to look back at the origins of this effort, the eradication of wild poliovirus in the United States in 1972 (Fig. 4). Amazingly, although poliomyelitis was being tracked carefully by the Centers for Disease Control and other public health specialists, no one anticipated eradication of wild poliovirus [16]. The explanation for this apparent paradox is not hard to find. Public health surveillance was focused on

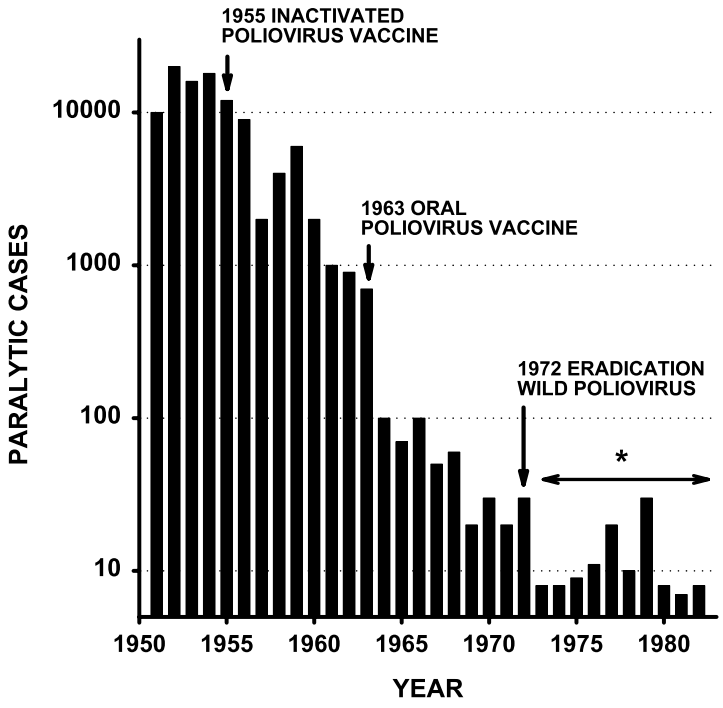

Fig. 4. Annual reported cases of paralytic poliomyelitis in the United States, 1951–1982. For the years 1973–1982, marked with an asterisk, residual cases are either vaccine-associated or imported, with the exception of a 1979 outbreak in the unvaccinated Amish population resulting from an importation. After [6]

poliovirus immunization surveys to determine the percent of children receiving OPV, and serosurveys of immunityindicated that there was a residual susceptible population estimated at up to 10,000,000 [5, 12, 15]. It was widely assumed that this pool of susceptible hosts would continue to circulate wildtype polioviruses indefinitely, and eradication was not contemplated. Under these circumstances, how could eradication occur?

Again, I would postulate that seasonality played a critical role in eradication [15, 16]. Figure 5 shows that, as for measles, poliovirus infections were highly seasonal, particularly in the northern United States. In Table 4, the seasonal curves are used to estimate the incidence of poliovirus infection in a hypothetical metropolitan area with a population of 10,000,000, both for the northern and the southern United States. Vaccine-induced reduction of susceptible individuals in such a population can be guesstimated to reduce the number of new infections per trough generation period below the threshold for virus perpetuation. When poliomyelitis incidence data for the period 1960 through 1972 are plotted by state (Fig. 6), it can be seen that each year a decreasing number of States reported paralytic polio. It can be surmised that, in area after area, the virus disappeared during the wintertime trough and was not introduced in the following summer, eventually leading to eradication. Although space does not permit, it is noted

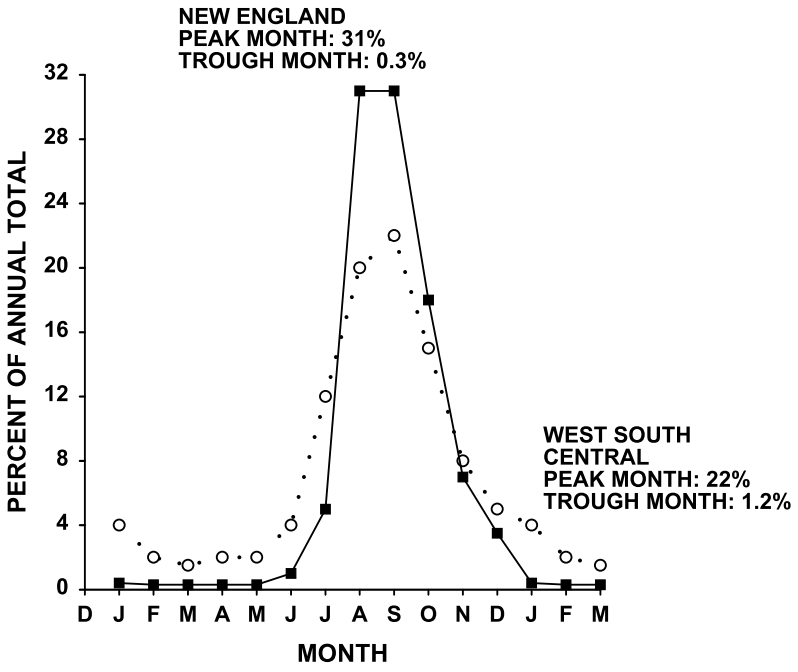

Fig. 5. Seasonal distribution of poliomyelitis (paralytic and nonparalytic) for two regions (New England and West South Central) of the United States, 1942–1951. After [23]

Table 4. Calculated number of poliovirus infections per generation period during the seasonal trough, in a population of 10,000,000 in the United States, prior to poliovirus vaccine and after the introduction of poliovirus vaccine (after [15])[a]

Parameter	Pre vaccine era 1950–1955	Post vaccine era 1960–1970
Total population	10,000,000	10,000,000
Susceptible population	2,200,000	360,000
Annual poliovirus infections	200,000	400
Infections per month at seasonal low (0.1%–0.4% of annual total)	200–800	0.4–1.6
Infections per generation period at seasonal low (10 day generation period)	70–280	0.1–0.5

[a]Susceptible population estimates based on the age distribution of poliomyelitis and upon serosurveys of poliovirus antibodies. Infections back-calculated from cases of paralytic poliomyelitis. Seasonal trough based on monthly distribution of poliomyelitis cases. Generation period based on studies of secondary polio cases in families. See [15] for references

that a similar phenomenon occurred with measles, but measles – with a greater transmissibility than poliovirus – was reintroduced after each fade out [15].

The elimination of wild poliovirus in the United States gave credibility to the extension of eradication. Major efforts were initiated in Central and South

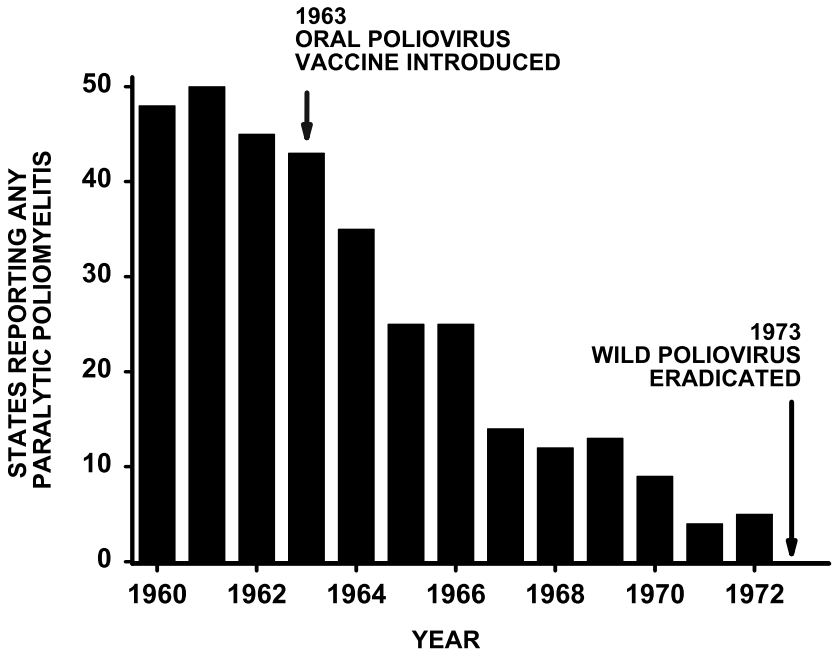

Fig. 6. The number of states reporting any cases of paralytic poliomyelitis, United States, 1960–1973, excluding imported and vaccine-associated cases. Based on data in [4]

America, leading to successful eradication in the 1980s. Emboldened by these successes, WHO embarked on global eradication, a goal that appears within reach within the next several years. The principal residual sites where wild poliovirus continues to circulate are Pakistan, India, and Nigeria, and it is likely that the absence of seasonality [7, 28] in these semi-tropical nations has been one of the impediments to eradication.

HIV and AIDS

One of the salient questions regarding the biology of HIV is: how did it emerge as a human virus? I will argue that the ability of HIV to cause persistent infections likely played a key role in its emergence, and is therefore worth a brief consideration in this essay on viral perpetuation.

Although circumstantial, the evidence is quite persuasive that HIV arose when a simian lentivirus, SIVcpz, jumped from chimpanzees to humans [9, 11, 13]. Many animal viruses cause zoonotic infections of humans but very few of them are subsequently transmitted from person to person. Most of those zoonotic viruses that are capable of limited human-to-human transmission exhibit marginal transmissibility, as evidenced by their containment using rudimentary quarantine measures and their fade out after a limited number of cycles. Examples are Crimean Congo hemorrhagic fever virus [20]; arenaviruses [14]; Ebola virus [22]; swine influenza virus in 1976 [17, 24]; and monkeypox virus [8]. The SARS coronavirus may be another example although to date it has not established itself as a human

Table 5. Speculative reconstruction of events following the hypothetical transmission of SIVcpz to humans[a]

Dates	Events
1915–1941	Transmission of SIVcpz to humans
∼1930–1980	HIV-1 maintained in rural villages in Africa
	HIV and AIDS are not recognized
1980–1985	AIDS recognized
	HIV-1 isolated
1980–2004	HIV-1 spreads rapidly through some urban and rural populations in Africa
	Global spread of HIV-1 and AIDS

[a]This reconstruction is based on data in [9, 11, 13, 18]

virus, even though it underwent at least 30 human-to-human passages in China in 2003 before being controlled by quarantine measures [27].

Rare indeed are those zoonotic viruses that become established permanently as human viruses. The best documented examples are influenza viruses, since avian influenza virus has on several occasions established itself in humans. It is noteworthy that, in several of these instances (such as the Asian pandemic of 1957 and the Hong Kong pandemic of 1968) the avian virus re-assorted with a human influenza virus, to produce a genetic chimera that endowed it with novel antigenic determinants, while maintaining the capability to transmit to humans [29].

These observations raise the questions as to how SIVcpz became established as a human virus. Recent studies have produced a speculative reconstruction of historical events following the hypothetical transmission of SIVcpz to humans (Table 5). Particularly relevant to this discussion is the inference that, following transmission to humans, SIVcpz was perpetuated as an unrecognized infrequent infection in rural villages in central Africa during the period 1930 to 1980 [18]. Different regions of the viral genomes of SIVcpz and of HIV-1 differ by 10%–25% [10] and it may be assumed that many of these changes were introduced during that 50-year interval. I speculate that some of these genetic changes have led to the metamorphosis of SIVcpz into HIV-1, to become an agent that can spread among humans with sufficient ease to be considered a virus of humans. If this is correct, then it would seem likely that the ability of SIVcpz to persist lifelong in the humans that it first infected might have provided an essential window of opportunity for a virus of chimpanzees to evolve into a human virus. Although tentative, these speculations offer interesting hypotheses for future research.

Acknowledgement

This review draws heavily upon earlier reviews that are cited in the references, particularly Yorke et al., 1979, and Nathanson and Martin, 1979.

References

1. Ahmed R, Chen ISY (eds) (1999) Persistent viral infections. Wiley, Chichester
2. Bartlett MS (1960) The critical community size for measles in the United States. J Royal Stat Soc Series A 123: 37–44
3. Black F (1975) Infectious diseases in primitive societies. Science 187: 515–518
4. Centers for Disease Control (1961–1974) Annual poliomyelitis summaries for the years 1960–1973. Atlanta, Georgia
5. Centers for Disease Control (1977) Poliomyelitis summary, 1974–1976. Atlanta, Georgia
6. Centers for Disease Control (1982) Morb Mortal Wkly Rep 30: 12–17
7. Enright JR (1954) The epidemiology of paralytic poliomyelitis in Hawaii. Hawaii Med J 13: 350–354
8. Esposito JJ, Fenner F (2001) Poxviruses. In: Knipe DM, Howley PM (eds) Fields virology, 4th edn. Lippincott Williams and Wilkins, Philadelphia
9. Gao F, Bailes E, Robertson DL, Chem Y, Roberston DL, Michael SF, Cummins LB, Arthur LO, Peeters M, Shaw GM, Sharp PM, Hahn BJ (1999) Origin of HIV-1 in the chimpanzee *Pan troglodytes troglodytes*. Nature 397: 436–441
10. Gaschen B, Taylor J, Yusim K, Foley B, Gao F, Lang D, Novitscky V, Haynes B, Hahn BH, Bhattacharya T, Korber B (2002) Diversity consideration in HIV-1 vaccine selection. Science 296: 2354–2360
11. Hahn BH, Shaw GM, De Cock KM, Sharp PM (2000) AIDS as a zoonosis: scientific and public health implications. Science 287: 607–614
12. Hall WJ, Nathanson N, Langmuir AD (1957) The age distribution of poliomyelitis in the United States in 1955. Am J Hyg 66: 214–234
13. Korber B, Muldoon M, Theiler J, Gao F, Gupta R, Lapedes A, Hahn BH, Wolinsky S, Bhattacharya T (2000) Timing the ancestor of the HIV-1 pandemic strains. Sci 288: 1789–1796
14. Monath TP (1975) Lassa fever: review of epidemiology and epizootology. Bull World Health Organ 52: 577–591
15. Nathanson N (1984) Epidemiological aspects of poliomyelitis eradication. Rev Infectious Dis 6[Suppl] 2: 308–312
16. Nathanson N, Martin JP (1979) The epidemiology of poliomyelitis: enigmas surrounding its appearance, epidemicity, and disappearance. Am J Epidemiol 110: 672–692
17. Neustadt RE, Fineberg HV (1978) The swine flu affair. US Department of Health, Education, and Welfare, US Superintendent of Documents, Washington DC
18. Nsilambi N, De Cock KM, Forthal DN, Francis H, Ryder RW, Malebe I, Getchell J, Laga M, Piot P, McCormick JB (1988) The prevalence of infection with human immunodeficiency virus over a 10-year period in rural Zaire. New England J Med 318: 276–279
19. Paffenbarger RS, Bodian D (1961) Poliomyelitis immune status in ecologically diverse populations, in relation to virus spread, clinical incidence, and virus disappearance. Am J Hyg 74: 311–325
20. Peters CJ (2000) California encephalitis, hantavirus pulmonary syndrome, and bunyavirid hemorrhagic fevers. In: Mandell GL, Bennett JE, Dolin R (eds) Principles and practice of infectious diseases, 5th edn. Churchill Livingstone, Philadelphia
21. Robinson GW, Nathanson N, Hodous J (1971) Sero-epidemiological study of rat virus infection in a closed laboratory colony. Am J Epidemiol 94: 91–100
22. Sanchez A, Khan AS, Zaki SR, Nabel GJ, Ksiazek TG, Peters CJ (2001) Filoviridae: Marburg and Ebola viruses. In: Knipe DM, Howley PM (eds) Fields virology, 4th edn. Lippincott Williams and Wilkins, Philadelphia

23. Serfling RE, Sherman IL (1953) Poliomyelitis distribution in the United States. Public Health Rep 68: 453–466
24. Silverstein AM (1981) Pure politics and impure science: the swine flu affair. The Johns Hopkins University Press, Baltimore, Maryland
25. Skinhoj P (1977) Hepatitis and hepatitis B-antigen in Greenland. II. Occurrence and interrelation of hepatitis B associated surface, core, and "e" antigen-antibody systems in a highly endemic area. Am J Epidemiol 105: 99–106
26. Stevens JG, Todaro GJ, Fox GF (eds) (1978) Persistent viruses. Academic Press, New York
27. The Chinese SARS molecular epidemiology consortium (2004) Molecular evolution of the SARS coronavirus during the course of the SARS epidemic in China. Sci 303: 1666–1669
28. Timothee RA, Morris L, Feliberti M et al. (1963) Epidemic of poliomyelitis in Puerto Rico, 1960. Public Health Rep 78: 65–76
29. Wright PF, Webster RG (2001) Orthomyxoviruses. In: Knipe DM, Howley PM (eds) Fields virology, 4th edn., Lippincott Williams and Wilkins, Philadelphia, pp 1533–1579
30. Yorke JA, Nathanson N, Pianigiani G, Martin J (1979) Seasonality and the requirements for perpetuation and eradication of viruses in populations. Am J Epidemiol 109: 103–123
31. Yorke JA, London WP (1973) Recurrent outbreaks of measles, chickenpox, and mumps. II. Systematic differences in contact rates and stochastic effects. Am J Epidemiol 98: 469–482

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