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Viruses That Cross Borders: Factors Responsible for Global Dissemination of Viral Infections

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Epidemiology · Genotypes · Epidemic · Endemic · Globalization

Abstract
Objective: Pandemic viral infections as emerging infectious diseases are of a great global concern. However, for some viruses, particular strains are endemic to specific areas and can be genetically distinguished from strains in other regions. In contrast, for some other viruses, genetically similar strains can spread and circulate all over the world. This study addresses global dissemination of various viral infections. ***Methods:*** We classified 34 viruses as per their ability to cross borders by review. We also described factors responsible for and the dynamics of global dissemination. We examined biological characteristics of viruses, manners or routes of transmission, host responses and epidemiological factors. ***Results:*** Factors required for viruses to cross borders include 'non-blood infection', 'short incubation period', 'short infectious period', 'frequent re-infection', 'small basic reproductive number (R_0)' and 'high annual incidence'. ***Conclusion:*** Knowing the factors responsible for global dissemination of pathogens is useful for controlling and/or containing both classic and emerging infectious diseases.

Introduction

Today, many emerging and re-emerging infectious diseases are quickly becoming a global issue. Human immunodeficiency virus (HIV) was first observed in the human population between the 19th and 20th centuries [1, 2]. Then, the virus spread all over the world within decades [3]. In 2002–2003, a new variant of coronavirus from southern China, which caused severe acute respiratory syndrome, spread throughout many countries across continents within a few months [4]. Pandemic influenza remains a great global concern. In 2009, swine-origin H1N1 virus caused a pandemic [5]. This virus from North America spread all over the world and caused substantial morbidity and mortality [5]. Knowing the factors responsible for global dissemination of pathogens is useful for controlling and/or containing both classic and emerging infectious diseases. Moreover, many vaccine-unpreventable viral infections can turn to be vaccine-preventable diseases in near future [6]. Knowledge of global dynamics and distribution of pathogens can guide us in establishing vaccination strategies.

Many human viruses are present in all parts of the world. For some viruses, particular strains are endemic to specific areas and can be genetically distinguished from strains in other regions. We refer to such human

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viruses as LOCAL. In contrast, for some other viruses, genetically similar strains spread and circulate throughout the world. We term such viruses as GLOBAL.

What causes some viruses to be LOCAL and others GLOBAL? Today, people can travel freely to different parts of the world in no time because of globalization and advancements in aviation technology. This, however, fails to explain the spread of diseases such as the Spanish flu in the early 20th century that led to a pandemic, even with slower modes of transportation [7]. Localization of a virus can be attributed to its distribution by non-human reservoirs. A good example is a tropical disease like yellow fever that is transmitted by mosquitoes. The disease is endemic only in areas where there are mosquitoes transmitting the yellow fever virus.

Yet, some viral strains that do not require a non-human vector for transmission circulate within specific areas. A viral strain in a particular area can be distinguished from strains in other areas, even though the virus can be found throughout the world. Then what type of human viruses can be called LOCAL? Why are they endemic regionally? What type of viruses can be called GLOBAL? Why and how do they cross borders? In this paper, we discuss factors that determine the distribution of viruses.

Materials and Methods

Virus

Subjects of viruses were selected by criteria that virus causes disease in human and is no or little related to non-human species (i.e. its natural host is human and it does not need vectors to transmit). The classification of viruses is listed in table 1.

Review and Grouping

Reviewing published articles was also done to classify viruses into each group, LOCAL or GLOBAL. Virus was classified as LOCAL if published molecular-epidemiological studies had shown that strains in some region are genetically distinct from strains in other geographically distant regions. Virus was classified as GLOBAL if published studies had shown that similar strains to ones circulating in some region had been frequently detected in other geographically distant regions.

Factors

Data related to 4 factors were examined: (1) biological characteristics of viruses, (2) manners or routes of transmission, (3) host responses, and (4) epidemiological factors. Data were obtained from textbooks and published scientific articles. Individual variables were described in nominal or ordinal scale.

Statistical Analysis

All data were analyzed using SPSS (version 17). Comparisons were made with the Mann-Whitney U test or Fisher's exact test when appropriate as univariate analysis. Principal component analysis (PCA) was conducted as multivariate analysis, without factors of 'mutation rate' and 'R0' because of many missing values. The principal component whose eigen value was more than one was identified. The factor whose factor loading was larger than critical value (r (0.10)) was inferred as a factor related significantly.

Results and Discussion

Classification: LOCAL and GLOBAL Viruses

We classified viruses as LOCAL or GLOBAL by reviewing molecular epidemiological studies concerning geographical distribution of genotypes (table 1). Viruses can be classified into LOCAL or GLOBAL by phylogenetic analysis of their genomes. Among LOCAL viruses, strains from a particular area are more closely related to each other than those from other areas, regardless of time restrictions. These viruses form a cluster in a phylogenetic tree that consists of strains from the same region. In contrast, among GLOBAL viruses, strains from distant countries are intermixed within the phylogenetic tree in a certain time frame.

For example, strains of influenza virus circulating within a particular region are genetically and antigenically similar to strains circulating in other regions at the same time rather than strains within the same region in the previous year(s) [8, 9]. They form evidence for global circulation (external seeding) but not for local persistence, indicating GLOBAL virus. Respiratory syncytial virus (RSV) develops new variants almost annually and these new variants are present simultaneously in widely separated areas [10–13]. These data suggest that new variants of RSV can spread worldwide within a year, qualifying it to be GLOBAL. It was reported that new identical variants of norovirus were identified throughout the world during the same period, suggesting them to be GLOBAL as well [14, 15].

In contrast, sequence analyses of measles viruses have revealed limited geographic distribution of genotypes in countries that have not yet curbed viral transmission [16, 17], indicating LOCAL. For viruses such as mumps virus and hepatitis B virus, genotypes also show geographical clustering suggesting that they are LOCAL [18–24].

In reality, many viruses should be positioned on a continuum between strongly geographically structured (LOCAL) and fully panmictic (GLOBAL). With regard to

Table 1. Classification of viruses

Virus	Group	Reference
Adenovirus	LOCAL	Wadell et al., J Clin Microbiol (1985); Mizuta et al., Virus Res (2008)
Enteric adenovirus (type F)	GLOBAL	Li et al., J Clin Microbiol (2004)
Astrovirus	GLOBAL	Victoria et al., J Med Virol (2007); Guix et al., J Clin Microbiol (2002)
Coronavirus	–*	Lai et al., Fields Virology (2007)
Cytomegalovirus	GLOBAL	Mocarski Jr. et al., Fields Virology (2007); Pignatelli et al., J Gen Virol (2003)
Enterovirus	GLOBAL	Savolainen et al., Arch Virol (2001); Palacios et al., J Virol (2002); Bible et al., Rev Med Virol (2007)
Epstein-Barr virus	LOCAL	Ikegaya et al., J Virol Methods (2008); Rickinson et al., Fields Virology (2007)
Hepatitis A virus	GLOBAL	Hollinger et al., Fields Virology (2007)
Hepatitis B virus	LOCAL	Kramvis et al., Vaccine (2005); Alam et al., BMC Infect Dis (2007); Norder et al., Intervirology (2004)
Hepatitis C virus	LOCAL	Lindenbach et al., Fields Virology (2007); Cha et al., Proc Natl Acad Sci (1992)
Hepatitis E virus	LOCAL	Emerson et al., Fields Virology (2007); Schlauder et al., J Med Virol (2001)
Herpes simplex virus 1	LOCAL	Umene et al., Arch Virol (1999); Bowden et al., Infect Genet Evol (2006)
Herpes simplex virus 2	GLOBAL	Kaneko et al., J Clin Microbiol (2008)
Herpes virus 6	GLOBAL	Rapp et al., Virology (2000)
Herpes virus 8	LOCAL	Kazanji et al., J Infect Dis (2005); Boralevi et al., J Infect Dis (1998)
HIV-1	LOCAL	Takebe et al., Pediatr Int (2004)
Human metapneumovirus	GLOBAL	Samransamruajkit et al., J Infect (2006); Boivin et al., Emerg Infect Dis (2004)
HTLV-1	LOCAL	Scadden et al., UpToDate (website cited 2008)
Influenza virus A	GLOBAL	Russell et al., Science (2008)
Influenza virus B	GLOBAL	Paiva et al., Int Congr Ser (2004)
JC polyoma virus	LOCAL	Demeter, UpToDate (website cited 2008)
Measles virus	LOCAL	CDC. MMWR (2005)
Mumps virus	LOCAL	Inou et al., J Med Virol (2004); Muhlemann et al., Infect Genet Evol (2004)
Norovirus	GLOBAL	Motomura et al., J Virol (2008); Noel et al., J Infect Dis (1999); Greeen, Fields VIROLOGY (2007); Siebenga et al., J Infect Dis (2009)
Papilloma virus	LOCAL	Yamada et al., J Virol (1997); Stewart et al., J Virol (1996)
Parainfluenza virus	LOCAL	Hetherington et al., J Infect Dis (1994); Henrickson et al., J Infect Dis (1992)
Parvovirus B19	LOCAL	Parsyan et al., J Gen Virol (2007)
Poliovirus	LOCAL	Anand et al., Epidemiol Infect (2002); Mulders et al., J Infect Dis (1995)
RSV	GLOBAL	Lukic-Grlic et al., Arch Virol (1998); Peret et al., J Gen Virol (1998); Kuroiwa et al., J Med Virol (2005); Choi et al., J Infect Dis (2000)
Rhinovirus	–*	Lee et al., PLoS One (2007); Savolainen-Kopra [cited 2008; available from: ethesis.helsinki.fi/julkaisut/bio/bioja/vk/savolainen-kopra/]
Rotavirus	GLOBAL	Laird et al., J Clin Microbiol (2003); Estes et al., Fields Virology (2007)
Rubella virus	LOCAL	CDC. MMWR (2005)
Sapovirus	GLOBAL	Farkas et al., Arch Virol (2004)
Varicella-zoster virus	LOCAL	Loparev et al., J Virol (2004); Quinlivan et al., J Infect Dis (2002)

* After review, it was hard to classify as LOCAL or GLOBAL.

As to coronavirus, 229E isolated at geographically distinct locations showed little evidence of variability, whereas isolates of OC43 from distant areas differed in sequence. As to rhinovirus, few studies were conducted investigating intra-subtypic diversity since the virus has more than 100 serotypes.

measles virus, which we regarded as LOCAL, the multiple genotypes in Morocco, the US, Canada and the UK were attributed to multiple importations, suggesting frequent importation and lack of endemic strains [16]. In several European countries, some previously endemic genotypes appear to have been replaced by imported strains [16]. With regard to human immunodeficiency virus 1 (HIV-1), certain HIV-1 genotypes are geographically clustered, inferring that they are LOCAL, although demographic clustering is not absolute [3, 25, 26]. Certain recombinant viruses have already contributed substantially to the global pandemic [3, 25]. It has been suggested that HIV-1 subtypes can influence viral transmissibility and pathogenicity [27, 28]. This implies that only specific 'strong' (in replication ability and/or transmission ability) strains could be GLOBAL. We could not define obvious borderline between LOCAL and GLOBAL such as P-distance because each study had used different ways. Although the classification into the two categories is not robust, we classified viruses, if anything, into LOCAL or GLOBAL.

Table 2. Risk factors for GLOBAL viruses

Factor	Variables	Description	Variable associated with GLOBAL viruses	p value†
Biological characteristics	genome	RNA or DNA	RNA	0.289
	envelope	absent or present	absent	0.721
	evolutionary rate	mutation rate (nucleotide substitutions per nucleotide per year)	high	0.149
Manners or routes of transmission	contact	virus transmits commonly from human to human via daily life activities or not (rare)	common	0.113
	respiratory	virus transmits commonly via respiratory route or not (rare)	no (rare)	1
	fecal-oral	virus transmits commonly via fecal-oral route or not (rare)	common	0.062
	sexual	virus transmits commonly via sexual contacts or not (rare)	no (rare)	0.412
	blood	**virus transmits commonly via blood (e.g. contaminated blood transfusion or syringe) or not (rare)**	**no (rare)**	**0.044**
	vertical*	virus transmits commonly from mother to child or not (rare)	no (rare)	1
Host responses	**incubation period**	**length of incubation period**	**short**	**0.001**
	infectious period	**length of infectious period**	**short**	**0.036**
	asymptomatic infection	rate of asymptomatic infection	high	0.401
	persistent	virus persists commonly in host cell or not (rare)	no (rare)	0.087
	re-infection	**frequent re-infection with virus (of same serotype) occurs or not (rare)**	**frequent**	**0.004**
Epidemiological factors	**the basic reproductive number (R_0)**	**mean number of secondary cases from single infected case**	**small**	**0.008**
	annual incidence	**occurrence of the disease**	**high**	**0.002**
	seroprevalence	proportion of people with antibody to the virus	high	0.068
	seasonality	infection has seasonality (in temperate zone) or not	existence of seasonality	0.722

Bold characters indicate significant results.

* Virus that can be transmitted from mother to child, but the child is not infectious (e.g. rubella) was inferred as 'no (rare) vertical transmission'. † Comparisons were made by the Mann-Whitney U test or Fisher's exact test, as appropriate.

Factor Differences between LOCAL and GLOBAL Viruses

It would be practical if we could predict the spread of a disease from its known characteristics. We attempted to find factors associated with differences between LOCAL and GLOBAL viruses. We constructed a datasheet describing factors we examined, in which data were obtained from textbooks and published scientific articles. Factors that were significantly ($p < 0.05$) associated with GLOBAL viruses include 'non-blood infection', 'short incubation period', 'short infectious period', 'frequent re-infection', 'small basic reproductive number (R_0)' and 'high annual incidence' (table 2). PCA showed these factors were correlated each other (table 3). Incidentally, principal component 3 did not include group factor (LOCAL or GLOBAL). Principal component 3 could be interpreted as characteristics of gastrointestinal virus.

No biological factors were found to be significantly associated with classification of viruses as LOCAL and GLOBAL by univariate analysis (table 2). We expected RNA viruses to be GLOBAL as they were prone to mutations due to RNA-dependent RNA polymerases with high error rates. Measles virus, mumps virus, parainfluenza virus, RSV and human metapneumovirus are members of the Paramyxoviridae family, negative-sense single-stranded RNA viruses. Although they share similar biological characteristics, some are LOCAL while others are GLOBAL (table 1).

In terms of transmission, 'blood infection' requires considerable intimate contact, resulting in endemicity in a specific area (LOCAL). Hepatitis B virus and human T lymphotropic virus 1 (HTLV-1) are examples of viruses transmitted via blood route. We did not find any other modes of transmission, apart from blood infection, to determine viruses as LOCAL or GLOBAL. Global dissemi-

Table 3. Principal components analysis

	Proportion %	Variables related significantly
Principal component 1	40.2	GLOBAL, genome (RNA), envelope (absent), contact (common), respiratory (common), fecal-oral (common), sexual (no), blood (no), vertical (no), incubation period (short), infectious period (short), persistent (no), reinfection (frequent), annual incidence (high), seroprevalence (high), seasonality (existence)
Principal component 2	13.4	GLOBAL, genome (DNA), contact (common), blood (no), vertical (common), incubation period (short), persistent (common), annual incidence (high), seasonality (absent)
Principal component 3	12.7	envelope (absent), respiratory (no), fecal-oral (common), asymptomatic infection (high)
Principal component 4	9.0	GLOBAL, genome (RNA), envelope (present), contact (no), reinfection (common)

nation can occur regardless of whether a virus is respiratory or enteric. While some respiratory (e.g. influenza virus) and enteric (e.g. norovirus) viruses are GLOBAL, other respiratory (e.g. varicella zoster virus) and enteric (e.g. poliovirus) viruses are LOCAL.

'High annual incidence' and 'frequent re-infection' were the other two factors associated with GLOBAL viruses. Viral infections seen commonly and frequently may tend to be GLOBAL. Ability for frequent re-infection may allow a virus to either co-circulate with or outcompete indigenous strains when imported into a new area. Examples include RSV and norovirus.

Small R_0 was also associated with GLOBAL viruses. This result was surprising as reasonably high R_0 (strong infectious ability) should be advantageous for dissemination of a GLOBAL virus. An explanation could be that small R_0 favors frequent re-infection since infection by a virus for which R_0 is high confers life-long immunity, as is the case with infections caused by measles virus, rubella virus and poliovirus. Re-infection with such viruses is rare. If we look at this from a LOCAL virus perspective, herd immunity could provide an explanation. Most people in a community are infected with indigenous strains of a virus with high R_0 resulting in herd immunity, thus protecting them from re-infection with imported strains. Therefore, high R_0 tends to make a virus LOCAL.

Short incubation period and short infectious period (i.e. short generation time) were associated with GLOBAL viruses. These results were unexpected because normally these factors do not allow travelers to carry a virus over long distances during the incubation and/or infectious period. It is reasonable to think that a long generation time would allow travelers to carry a virus during a long distance journey. However, considering current flight times, which are a matter of hours, even viruses with short incubation and infectious periods can be transported to distant areas within a short period. Therefore, a short generation time cannot sufficiently explain differences between LOCAL and GLOBAL viruses, which might be confounded by other factors. The result of PCA showed correlations between 'short incubation period', 'short infectious period', 'high annual incidence', 'frequent re-infection', and 'GLOBAL' (table 3).

In addition to factors listed in table 2, 'existence of epicenters' can be another factor for GLOBAL. Influenza virus, which possesses advantageous factors for GLOBAL, is actually GLOBAL (tables 1, 2). Local epidemics are not triggered by the climate-driven reactivation of influenza viruses, but by the introduction of new viruses from outside [9, 29–31]. It has been proposed that new variants first emerged in East and Southeast Asia and subsequently spread to other regions of the world [8, 9, 32]. Influenza infections in tropical countries show a year-round pattern or weak seasonality [8, 33, 34], and this extended viral transmission may make tropical regions a source of viral spread [8, 9, 32].

HIV, which possess few factors advantageous for GLOBAL, was classified into LOCAL (tables 1, 2). Although certain HIV-1 genotypes are geographically clustered, all subtypes have been identified in Central sub-Saharan Africa, suggesting that Africa is the source for the current pandemic, from which the virus has spread worldwide [2, 3, 35]. Moreover, several genotypes of measles virus have been detected in countries that have already eliminated measles [16, 17, 36], although measles virus is LOCAL. This suggests frequent importation from endemic countries.

Epicenters like East and Southeast Asia for influenza virus, Africa for HIV, and endemic countries for measles virus might play an important role in global dissemination of these viruses. An epicenter is characterized by high incidence and continuous transmission of the infec-

tion. In fact, our analysis found 'high annual incidence' as a factor associated with GLOBAL viruses.

Population density can also affect spread of infectious diseases. Especially, the spread of measles has been studied focusing on the synchrony between endemicity and spatiotemporal factors. Sparsely populated regions appear to act as barriers to local diffusion of measles and may act to channel and isolate epidemics in urban centers [37]. Breaks in the continuity of measles transmission were found for communities with small population (e.g. rural areas and small islands) [38–41]. Thus, waves of infection moved regionally from large cities to peripheral small towns at the domestic level [39, 42]. There is also a tendency for the influenza season to start in California more often than in any other state [43]. This can be attributed to population size and international connectivity.

Here, we show that viruses that cross borders possess unique characteristics. In future, advancements in globalization will make LOCAL viruses lose their geographical clustering as more people will be able to easily travel abroad, thereby importing and exporting viruses all over the world. We should closely monitor the trends of global dissemination of emerging and classic infectious diseases by tireless surveillance and investigation. In addition, the focus should be not only on global areas but also on isolated aboriginal communities like those in the Amazon. In such communities, it would be interesting to note what type of viruses can be imported there with little communication with the outside world.

We should conduct additional spatiotemporal analyses, which would clarify the dynamics of global dissemination of various viral infections. We should employ more epidemiological and genetic surveillance for in-depth analysis. Collaboration and communication among researchers and policy makers from all over the world are vital for understanding the trends of viral infections, as are infection control practices that must be implemented on a global scale.

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