

Opinion

An Increasing Danger of Zoonotic Orthopoxvirus Infections

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Abstract: On May 8, 1980, the World Health Assembly at its 33rd session solemnly declared that the world and all its peoples had won freedom from smallpox and recommended ceasing the vaccination of the population against smallpox. Currently, a larger part of the world population has no immunity not only against smallpox but also against other zoonotic orthopoxvirus infections. Recently, recorded outbreaks of orthopoxvirus diseases not only of domestic animals but also of humans have become more frequent. All this indicates a new situation in the ecology and evolution of zoonotic orthopoxviruses. Analysis of state-of-the-art data on the phylogenetic relationships, ecology, and host range of orthopoxviruses—etiologic agents of smallpox (variola virus, VARV), monkeypox (MPXV), cowpox (CPXV), vaccinia (VACV), and camelpox (CMLV)—as well as the patterns of their evolution suggests that a VARV-like virus could emerge in the course of natural evolution of modern zoonotic orthopoxviruses. Thus, there is an insistent need for organization of the international control over the outbreaks of zoonotic orthopoxvirus infections in various countries to provide a rapid response and prevent them from developing into epidemics.

The genus *Orthopoxvirus* of the family *Poxviridae* comprises the species variola (smallpox) virus (VARV), with human as its only sensitive host; zoonotic species monkeypox virus (MPXV), cowpox virus (CPXV), vaccinia virus (VACV), and camelpox virus (CMLV); and several others. These orthopoxviruses are immunologically cross-reactive and cross-protective, so that infection with any member of this genus provides protection against infection with any other member of the genus [1,2]. Traditionally, the species of the *Orthopoxvirus* genus have been named primarily according to the host animal from which they were

isolated and identified based on a range of biological characteristics [1]. Most frequently, zoonotic orthopoxviruses have been initially isolated from animals immediately close to humans being incidental hosts for the virus, the natural carriers of which are, as a rule, wild animals. Correspondingly, the name of an orthopoxvirus species does not reflect the actual animal that is its natural reservoir.

With accumulation of the data on complete genome nucleotide sequences for various strains of orthopoxvirus species, it has been found that an interesting feature of the orthopoxvirus genomes is the presence of genes that are intact in one species but fragmented or deleted in another [3–8]. These data confirm the concept of a reductive evolution of orthopoxviruses, according to which the gene loss plays an important role in the evolutionary adaptation of progenitor virus to a particular environmental niche (host) and emergence of new virus species [9]. CPXV has the largest genome of all the modern representatives of the genus *Orthopoxvirus*, and this genome contains all the genes found in the other species of this genus [2,4,10–12]. Therefore, *Cowpox virus* was proposed as the closest of all the modern species to the progenitor virus for the genus *Orthopoxvirus*, while the remaining species, *Variola virus* included, had appeared as a result of multistage reductive evolution [4,9,13].

VARV, the most pathogenic species for humans, has the smallest genome of all the orthopoxviruses [2–7]. This suggests a potential possibility for emergence of a VARV-like variant from the currently

existing zoonotic orthopoxviruses with longer genomes in the course of natural evolution. It is known that although mutational changes are rather a rare event for the poxvirus DNA [13], characteristic of these viruses is the possibility of intermolecular and intramolecular recombinations, as well as genomic insertions and deletions [14,15]. It has been recently found that duplication/amplification of genomic segments is typical of poxviruses, and in the case of a certain selective pressure (for example, host antiviral defenses), certain genes are able to relatively rapidly accumulate mutations that would provide the virus adaptation to new conditions, including a new host [16].

The conducted analysis of the available archive data on smallpox and the history of ancient civilizations as well as the newest data on the evolutionary relationships of orthopoxviruses has allowed me to suggest the hypothesis that smallpox could have repeatedly emerged in the past via evolutionary changes of a zoonotic progenitor virus [17].

Because of the cessation of the vaccination against smallpox after its eradication 35 years ago, a tremendous part of the world human population currently has no immunity not only against smallpox, but also against any other zoonotic orthopoxvirus infections. This new situation allows orthopoxviruses to circulate in the human population and, as a consequence, should alter several established concepts on the ecology and range of sensitive hosts for various orthopoxvirus species.

The most intricate case is the origin of VACV. For many decades, VACV has

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been used for vaccinating humans against smallpox, and it was considered that this virus, *variola vaccinae*, originates from zoonotic CPXV, introduced to immunization practice by Jenner as early as 1796 [1]. Only in the 20th century was it found out that the orthopoxvirus strains used for smallpox vaccination significantly differ in their properties from both the natural CPXV isolates recovered from cows and the other orthopoxvirus species examined by that time [18]. Correspondingly, they were regarded as a separate species, *Vaccinia virus* [19]. Moreover, it was inferred that the VACV natural reservoir was unknown and numerous hypotheses attempted to explain the origin of this virus while passing progenitor viruses in animals in the process of vaccine production [1,2,20].

The issue of VACV origin was somewhat clarified after sequencing the complete genome of horsepox virus (HSPV) [21], which appeared to be closely related to the sequenced VACV strains. Only after this was attention paid to the fact that Jenner specified the origin of his vaccine from an infection of the heels of horses (“grease”) and indicated that the vaccine became more suitable for human use after passage through the cow [20]. This suggests that VACV may originate from a zoonotic HSPV, which naturally persisted concurrently with CPXV. Some facts suggest that the infectious materials not only from cow lesions but also from horse lesions were used for smallpox vaccination in the 19th century. The vaccine lymph from the horse gave the most satisfactory results in inducing an anti-smallpox immunity as well as less side reactions [1]. By all accounts, they gradually commenced using HSPV isolates for smallpox vaccination, the future generations of which recovered decades later were ascribed to the separate species *Vaccinia virus* [19], rather than CPXV for smallpox vaccination everywhere.

Since the 1960s, VACVs have been repeatedly isolated in Brazil [22]. The first VACV isolates were recovered from wild rodents (sentinel mice and rice rat) [23]. Since 1999, an ever-increasing number of exanthematous outbreaks affecting dairy cows and their handlers have been recorded [24–27], supplemented recently with outbreaks among horses [28,29]. Several VACV strains have been isolated during these outbreaks from cows, horses, humans, and rodents [22,27,28,30,31]. The questions that arise are when and how VACV entered Brazil and the wild nature of the American continent. The more widespread point of view is that VACV

strains could be transmitted from vaccinated humans to domestic animals and further to wild ones with subsequent adaptation to the rural environment [22]. My standpoint implies that HSPV/VACV could have been repeatedly accidentally imported from Europe to South America with the infected horses or rodents to be further introduced into wildlife. Possibly, the latter hypothesis more adequately reflects the actual pathway of VACV transmission to the Brazilian environment, since recent phylogenetic studies have suggested an independent origin for South American VACV isolates, distinct from the vaccine strains used on this continent during the WHO smallpox eradication campaign [22,32]. Presumably, genome-wide sequencing of the viruses will give a more precise answer to the origin of VACV variants isolated in Brazil.

In the past, the outbreaks of buffalopox had occurred frequently in various states of India as well as in Pakistan, Bangladesh, Indonesia, Egypt, and other countries [33]. The causative agent, buffalopox virus (BPXV), is closely related to VACV and affiliated with the species *Vaccinia virus*, genus *Orthopoxvirus* [2,34]. Recently, mass outbreaks of buffalopox in domestic buffaloes along with severe zoonotic infection in milk attendants were recorded at various places in India [35,36]. In several buffalopox outbreaks, the BPXV-caused infections were recorded in cows in the same herds [37]. An increase in BPXV transmission to different species, including buffaloes, cows, and humans, suggests the reemergence of zoonotic buffalopox infection [35,38]. The buffalopox outbreaks recorded in different distant regions of India are likely to suggest the presence of an abundant natural BPXV reservoir represented by wild animals, most probably rodents. Correspondingly, it is of the paramount importance to perform a large-scale study of the presence of orthopoxviruses in wild animals of India.

Thus, yet incomplete data on the modern ecology of VACV and BPXV allow for speculation that the orthopoxviruses belonging to the species *Vaccinia virus* have a wide host range, are zoonotic, are currently spread over large areas in Eurasia and South America, and that their natural carriers are several rodents.

CPXV has relatively low pathogenicity for humans but has a wide range of sensitive animal hosts [2,39]. Human cowpox is a rare sporadic disease, which develops when CPXV is transmitted from an infected animal to human [2,40]. This disease is mainly recorded in Europe. In wildlife, CPXV carriers are asymptotically

infected rodents [41,42]. During the last two decades, reports on an increasing number of CPXV infections in cats, rats, exotic animals, and humans have been published [43–47]. Comparative studies of the properties of CPXV isolates recovered from various hosts at different times and in several geographic zones have shown sufficient intraspecific variations [2,48,49]. A recent phylogenetic analysis of the complete genomes of 12 CPXV strains recovered from humans and several animal species suggests that they be split into two major *Cowpox virus*-like and *Vaccinia virus*-like clades [50]. This means that the criteria of the separation of orthopoxviruses into these two species should be corrected.

MPXV is a zoonotic virus causing a human infection similar to smallpox in its clinical manifestations with a lethality rate of 1–8% [51]. The natural reservoir of MPXV is various species of African rodents [8,10]. The active surveillance data in the same health zone (Democratic Republic of Congo) from the 1980s to 2006–2007 suggest a 20-fold increase in human monkeypox incidence 30 years after the cessation of the smallpox vaccination campaign [52]. This poses the question of whether MPXV can acquire the possibility of a high human-to-human transmission rate, characteristic of VARV, under conditions of a long-term absence of vaccination and considerably higher incidence of human infection. If this occurs, humankind will face a problem considerably more complex than with the smallpox eradication. First and foremost, this is determined by the fact that MPXV, unlike VARV, has its natural reservoir represented by numerous African rodents [2,53].

In its biological properties and according to the data of phylogenetic analysis of the complete virus genomic sequence, CMLV is closest to VARV, the causative agent of smallpox, as compared with the other orthopoxvirus species [1,8]. Camelpox is recognized as one of the most important viral diseases in camels. This infection was first described in India in 1909. Subsequently, camelpox outbreaks have been reported in many countries of the Middle East, Asia, and Africa [54,55]. Until recently, it has been commonly accepted that the host range of CMLV is confined to one animal species, camels [1,55]. However, the first human cases of camelpox have been recently confirmed in India [56]. This suggests that camelpox could be a zoonotic disease. Since camelpox outbreaks occur irregularly in distant regions of the world and the viruses isolated during these outbreaks display different degrees of virulence [55], it is

possible to postulate the presence of a wildlife animal reservoir of CMLV other than camels. Since the camelpox outbreaks are usually associated with the rainy season of the year, when rodents are actively reproducing, it is likely that rodents could be the natural carriers of CMLV.

It is known that most of the emerging human pathogens originate from zoonotic pathogens [57–59]. Many viruses do not cause the disease in their natural reservoir hosts but can be highly pathogenic when transmitted to a new host species. Emerging and reemerging human pathogens more often are those with broad host ranges. The viruses able to infect many animal species are evolutionarily adapted to utilizing different cell mechanisms for their reproduction and, thus, can extend/change their host range with a higher probability [58].

There are no fundamental prohibitions for the possible reemergence of smallpox or a similar human disease in the future as a result of natural evolution of the currently existing zoonotic orthopoxviruses. An ever-increasing sensitivity of the human population to zoonotic orthopoxviruses, resulting from cessation of the mass smallpox vaccination, elevates the probability for new variants of these viruses, potentially dangerous for humans, to emerge. However, the current situation

is radically different from the ancient one, since many outbreaks of orthopoxvirus infections among domestic animals and humans are recorded and studied.

Recently, the efforts of scientists under WHO control are directed to the development of state-of-the-art methods for VARV rapid identification as well as design of new generation safe smallpox vaccines and drugs against VARV and other orthopoxviruses [60]. The designed promising anti-orthopoxvirus drugs display no pronounced virus species specificity. Therefore, they are applicable in the outbreaks caused by any orthopoxvirus species. International acceptance of the designed highly efficient anti-orthopoxvirus drugs ST-246 and CMX001 [60] is of paramount importance.

In the areas of high incidence of zoonotic orthopoxviral infections, it would be purposeful to vaccinate domestic and zoo animals as well as the persons closely associated with them using state-of-the-art safe vaccines based on VACV, which has a wide range of sensitive hosts. This would considerably decrease the likelihood for such infections to spread from wildlife into the human environment.

In the African region endemic for monkeypox, which also displays a high rate of HIV infection, the population could be vaccinated with the VACV strain MVA, which has been recently demonstrated to

be safe even for HIV-infected persons [61].

Taking into account the above mentioned increased incidence of outbreaks of animal and human orthopoxvirus infections and their potential danger, it is important to accelerate organization of the international Smallpox Laboratory Network, discussed by the WHO Advisory Committee on Variola Virus Research [62,63], and orient this network to express diagnosing not only of VARV but also of other zoonotic orthopoxviruses. This will provide constant monitoring of these infections in all parts of the world and make it possible to prevent the development of small outbreaks into expanded epidemics, thereby decreasing the risk of evolutionary changes and emergence of an orthopoxvirus highly pathogenic for humans.

The international system for clinical sampling and identification of infectious agents has been worked out and optimized while implementing the global smallpox eradication program under the aegis of the WHO as well as anti-epidemic measures and methods for mass vaccination [1]. The accumulated experience is of paramount importance for the establishment of international control not only over currently existing orthopoxvirus infections but also other emerging and reemerging diseases.

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