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Vaccines for hantaviruses: progress and issues

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“The high cost of vaccine development and the rarity of hantavirus-associated diseases point toward a need for innovative vaccines and licensing strategies for vaccines for hemorrhagic fever with renal syndrome and/or hantavirus pulmonary syndrome.”

Hantaviruses, hemorrhagic fever with renal syndrome & hantavirus pulmonary syndrome

The *Hantavirus* genus of the family *Bunyaviridae* comprises more than 20 viruses, including several human pathogens. Hantaviruses are maintained in rodent reservoirs and are usually transmitted to humans in aerosols of rodent excreta. Old-world rodents carry viruses that cause hemorrhagic fever with renal syndrome (HFRS) and new-world rodents carry viruses that cause hantavirus pulmonary syndrome (HPS). Four hantaviruses cause most cases of HFRS in Asia and Europe: Hantaan (HTNV), Seoul (SEOV), Puumala (PUUV) and Dobrava (DOBV) viruses. HPS- and HPS-causing hantaviruses were discovered in 1993 when an outbreak of severe respiratory distress of unknown etiology occurred in the USA. Most HPS cases result from infections with Sin Nombre virus in North America or Andes virus in South America [1,2].

Is there a need for hantavirus vaccines?

The answer to the question of vaccine need depends on several considerations. Vaccine requirements based on the likelihood of routine exposure to rodents persistently infected with hantaviruses in endemic regions engenders one answer, whereas the possibility of greatly increased exposure due to infrastructure breakdown,

as could occur during natural disasters such as earthquakes or as the result of war or terrorism, suggests another. In China, the need for vaccines is clear, in that more than 1.5 million cases of HFRS, resulting in more than 46,000 deaths, were reported between 1950 and 2007 [3]. Approximately 2 million doses of inactivated rodent brain- or cell culture-derived HFRS vaccines are given annually in China [3]. Although vaccination, along with public education and rodent control measures, have coincided with a reduction in HFRS cases to less than 20,000 per year, China still has the highest number of HFRS cases and deaths in the world [3]. A rodent brain-derived inactivated HFRS vaccine has also been used in the Republic of Korea since the early 1990s and has similarly corresponded with reduced numbers of HFRS cases [4].

HFRS is also widespread in Europe, with PUUV causing the largest number of cases, although in some areas, DOBV-associated HFRS is more common [5,6]. Currently, there are no HFRS vaccines approved for use in Europe, no reported clinical studies and no attempts made to license the Asian vaccines. Even if the Chinese or Korean vaccines were shown to meet European regulatory standards, animal studies suggest that vaccines derived from HTNV or SEOV would not protect against PUUV [7,8]. Consequently, vaccination for HFRS in Europe requires development of a novel vaccine, a prospect

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that depends mostly on commercial considerations. The cost:benefit ratio is probably the most favorable in Finland and European Russia, which have the highest incidence of HFRS; that is, approximately 32,000 Finnish cases between 2005 and 2010; and approximately 90,000 Russian cases between 1996 and 2006 [5,6]. Marketability of HFRS vaccines in other European countries is supported by recent studies suggesting that the extent and impact of hantavirus infections are underappreciated. For example, a serosurvey from Bosnia and Herzegovina revealed a higher hantavirus seroprevalence than expected, with former soldiers displaying significantly elevated rates (16.1%) compared with the general population of the endemic area (6.2%) [9]. This finding is consistent with the long history of HFRS as a wartime problem and provides insight into the potential need for hantavirus vaccines under circumstances resulting in increased exposure to rodents. In another study conducted recently in Germany, hantavirus-associated diseases were placed in the highest priority category of public health concerns and were suggested to be much more common than currently recognized [10]. Thus, several lines of evidence endorse the need for an HFRS vaccine in Europe.

“...if vaccines for hantaviruses are to be developed, either significant government or industry investments, or a nontraditional licensure strategy will probably be required.”

In contrast to HFRS, HPS is a rare disease under normal peacetime conditions, with fewer than 600 cases of HPS having been reported in the USA since its discovery [2,11]. HPS is more common in South America; for example, almost 900 cases were identified in Brazil between 1993 and 2007 [12] and more than 700 cases in Argentina between 1995 and 2008 [13]. As HPS is seen so infrequently and sporadically, the cost:benefit ratio probably prohibits developing an HPS vaccine for routine use; however, the high mortality of HPS (~35%) argues that in scenarios where increased contact with rodents is expected, vaccination would be advisable. This argument is further underscored by the inclusion of the HPS-causing hantaviruses as Category A pathogens on the National Institute of Allergy and Infectious Disease priority list of biological diseases. Perhaps a commercially viable HPS vaccine would be one that could protect against both HFRS and HPS and could be sold worldwide.

Toward US FDA licensure

To date, three hantavirus vaccines have been evaluated in clinical studies that were designed to conform to FDA licensure requirements. First, a recombinant vaccinia virus (VACV), expressing genes of HTNV, was tested in Phase I and II studies in approximately 150 volunteers [14]. Although the vaccine was immunogenic in VACV-naïve individuals, it was poorly immunogenic in recipients previously vaccinated for smallpox, which was probably due to pre-existing antibodies that limited the replication of the recombinant VACV [14]. The other two vaccines tested were HTNV- or PUUV-derived DNA vaccines, which were administered to 27 volunteers using a particle-mediated

epidermal delivery device (gene gun) [15]. Both vaccines elicited high levels of neutralizing antibodies in volunteers, but the overall seroconversion rate was low, with the best rate (56%) observed in the group of volunteers who received both vaccines. These vaccines are currently being evaluated in a Phase I study using intramuscular electroporation administration, a method which that is expected to provide more consistent delivery. A subsequent study is also planned in which the vaccines will be given using intradermal electroporation.

Licensure issues & strategies

Assuming that safe and immunogenic hantavirus vaccines are identified in early clinical studies, the regulatory and economic challenges of Phase III efficacy trials would still need to be overcome. There is no region of the world with sufficient HPS to provide statistically valid efficacy data; and outside of China, a Phase III study of HFRS vaccines might be difficult to accomplish and enormously expensive. Although it would be possible to test a PUUV vaccine in European Russia or Finland, where disease incidence has been estimated to be as high as 70 out of 100,000 in certain populations [6,16], and although a combined PUUV and HTNV vaccine would be expected to protect against all European hantaviruses, there is no known region with sufficient DOBV-related HFRS to support a traditional Phase III trial to verify that. Even in regions where a Phase III trial is possible, thousands of volunteers would need to be enrolled and the cost of such a study would probably be more than US\$100 million [17,18]. Given these issues, if vaccines for hantaviruses are to be developed, either significant government or industry investments, or a nontraditional licensure strategy will probably be required.

Government investment would necessitate the astute recognition of the potential threat that hantaviruses pose in addition to the current threat. The US Army has wisely recognized this potential since the Korean War, when thousands of cases of HFRS occurred among UN troops, and consequently has continued to support development of a vaccine for HFRS through early clinical studies. Licensure, however, would require a commercial partner to bear some of the costs. For nongovernment investment, marketing incentives would probably be needed. Two such incentives that might be applicable to hantavirus vaccine development already exist. One of these is Orphan Drug Status, which the FDA can grant for vaccines that will be administered to less than 200,000 people per year in the USA. Orphan drug vaccine developers receive a 50% tax credit for qualified clinical research expenses, a waiver of fees for the Biologics License Application (BLA) and a 7-year marketing exclusivity period. The other incentive for commercial involvement is the ‘Priority Review Voucher’, which can be awarded by the FDA when a BLA is filed for a vaccine for a neglected disease, and can shorten the normal FDA review time by half a year or more. The vaccine developer can save this voucher to use for priority review of a different product with greater commercial potential or they can even transfer or sell it to another company.

Alternative strategies to licensure include the recently defined ‘animal rule’, but for hantaviruses, this strategy would have limited

potential, as only Andes virus has been found to cause a frank disease in an animal model (Syrian hamsters) that mimics human HPS [19]. One possible unconventional strategy might be to obtain marketing approval as defined in FDA 314.510, in which the FDA can allow marketing based on surrogate end points obtained in well-controlled clinical studies that are shown to be reasonably likely to predict clinical benefit. If granted, postmarketing studies would also be required to verify and describe the clinical benefit. For example, if neutralizing antibodies could be established as a surrogate marker of protection, then it might be possible to license a hantavirus vaccine that could not be tested in a traditional Phase III study.

Conclusion

Hantaviruses are widespread endemic disease pathogens and they have the potential to cause epidemics in situations where rodent

control is not possible. The high cost of vaccine development and the rarity of hantavirus-associated diseases point toward a need for innovative vaccines and licensing strategies for vaccines for HFRS and/or HPS.

Disclaimer

The opinions, interpretations, conclusions and recommendations contained herein are those of the author and are not necessarily endorsed by the US Army.

Financial & competing interests disclosure

CS Schmaljohn is an inventor on a Government patent for DNA vaccines for hemorrhagic fever with renal syndrome. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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