Vaccines for epidemic infections and the role of CEPI

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ABSTRACT

The author reviews the foundation of the Coalition for Epidemic Preparedness and Innovations and the choices it has made for funding of vaccine development against epidemic diseases. He comments on those decisions as well as proposing how CEPI could remain relevant for the long term.

KEYWORDS

chikungunya; ebola; commercialization; development; emerging infections; field delivery; infectious disease; lassa; MERS; Nipah

Whither CEPI? short term and long term development

Viruses and bacteria, like other organisms, are always trying to extend their host range by mutation and selection, as well as by adaptation to new hosts. Humans have witnessed this phenomenon ever since we have lived in organized settlements. Thus, recent outbreaks of Ebola and Zika viruses, as well as historical outbreaks of plague, West Nile virus, and SARS are not unexpected, and future outbreaks of pathogens now known and unknown are certain to occur.

The human responses to outbreaks of infectious agents include flight, quarantine, antibiotics, antivirals, control of vectors, and more recently vaccination. However, the development of vaccines is a long, complicated and expensive process, such that epidemics may be over by the time vaccines are available. The 2015–16 outbreak of Ebola virus in West Africa with its high death toll illustrates this point: vaccines became available only at the end of the epidemic, when the incidence was declining.

The need for a new way of doing things became obvious to many observers, including the author of this article.1 By the end of 2015, several groups proposed the creation of a fund for development of vaccines against emerging pathogens, both those now known, and in anticipation of new ones. The need for a fund was underlined by the paradigmatic case of Zika, in that the virus was discovered in 1947 but despite its spread from Africa to Asia and Polynesia did not cause concern until its importation into Brazil, probably in 2013, where its clinical effects became notorious.2,3

Aside from the cost of development, manufacturers face uncertainty as to whether once developed, a vaccine will be recommended and used. An example of this problem is meningococcal Group B vaccines, which seemed high on the priority list for development once vaccines against the other meningococcal serogroups were put into routine use, but when once developed, the enthusiasm of recommending bodies for the use of a Group B vaccine had waned.5 The partial remedy for this type of situation may be Advanced Marketing Commitments, meaning that once licensed, a government would commit itself to recommend and purchase a particular vaccine. Of course, epidemiology might change in the interval between a commitment and licensure, as it did for Group B meningococcus,6 in which case there is no mechanism for the manufacturer to be recompensed for the costs of development.

Recent history has seen the emergence and expansion of many new threats to public health, from AIDS to Zika. In some cases the agent had an animal reservoir from which it passed to humans via an arthropod vector, or there was a mutation that adapted the animal virus to humans. The former was the case for Zika and the latter was the case for HIV/AIDS and SARS.7,9

The remarkable although unsurprising fact is that once an agent is identified as a threat to humans, scientists always rush to attempt prophylaxis, whether through antibodies, drugs, or vaccines. However, moving from animal studies to human clinical trials is inhibited by both safety concerns and insufficient facility. Much of this cost relates to the phase III trial that is normally necessary to demonstrate safety and efficacy in comparison to a placebo, and which allows licensure. Licensing authorities in the United States and Europe place a high bar of safety and efficacy for licensure. This is not a criticism, because the public demands that a product used in healthy people to avoid possible infection be free of serious side effects and also highly effective.

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funds. Thus, possible preventive measures are rapidly developed but may not be licensed for lack of commercial interest or other sources of funding. There are many infections that have been known for years, but for which vaccine development is stalled for perceived lack of a market.

The WHO and other organizations have made lists of pathogens for which vaccine development is a priority, but there has been no mechanism for acting on those priorities. A central problem has been that the likely recipients of a vaccine against those pathogens will be in Asia and Africa, whereas the markets that enable an acceptable return on investment, as well as the competent regulatory authorities, are largely in North America and Europe.

**Market failure**

A significant part of the difficulty in responding to epidemics of emerging diseases with vaccines is the vaccine industry itself. The high cost of vaccine development alluded to above means that marketing departments of vaccine companies are loath to recommend allocation of resources to a project unlikely to result in financial recompense, and markets of less than hundreds of millions of dollars annually are unattractive.

Moreover, the vaccine industry is constricted. Today there are only 4 transnational major manufacturers that have the resources to focus on research and development of multiple vaccines: GlaxoSmithKline, Merck, Pfizer and Sanofi Pasteur. There are also smaller organizations that are growing in size, such as Astellas, Astra Zeneca, Johnson & Johnson, the Serum Institute of India, and Takeda. There is a growing vaccine industry in China, Brazil, and India, as well as many smaller national companies, but by and large they do not spend large amounts of money on research vaccines. In any case, when an outbreak occurs even the larger companies must decide to devote resources from more remunerative projects such as drugs to pursue vaccine development against the new target. Aside from the financial issue, switching personnel from more profitable projects is disruptive.

**The origin of CEPI**

The organization now called the Coalition for Epidemic Preparedness and Innovations (CEPI) came into being because in the light of Ebola and Zika there were multiple proposals to establish an international fund to develop vaccines against emerging epidemic infections.10 The lists of such infections vary, but Table 1 gives a consensus of the most important. The basic idea of CEPI is that when there is a perception that the commercial market is insufficient to justify private investment in vaccine development against an emerging pathogen, that manufacturers be reimbursed for the production of candidates that can be taken through phases 1 and 2 to provide initial evidence for safety and efficacy, followed by the production and maintenance of a stockpile for emergency use [Table 2]. Inherent in this concept is that applicants must have a means of producing the candidate under Good Manufacturing Practice. In situations where a phase III trial is feasible owing to continued incidence of infection it would be done, although identification of a correlate of protection might be sufficient for confidence that the particular vaccine could be deployed in the event of an outbreak. Licensure might be obtained eventually if efficacy is confirmed in a phase III trial or if that is not feasible, by showing protection in 2 relevant animal models.

To select pathogens against which immediate vaccine development will be supported by CEPI, various lists have been proposed [Table 3]. One list put together by the Foundation for Vaccine Research was long and it is clearly not possible to attack all listed, although it had the virtue of completeness; another list put together by a WHO group was more restricted, but had the disadvantages of excluding bacteria and including pathogens for which vaccine candidates do not yet exist. Their defects, common to all lists, is that they cannot include a pathogen yet unknown that could emerge tomorrow. Another defect is that they focus on infections that are or have been epidemic, excluding those that are endemic but not yet prevented by vaccination.

An important aspect of CEPI’s mission is to create stockpiles for emergency use. This is not as easy as it sounds, since those stockpiles must be properly maintained over years with demonstration of stability, requiring periodic replenishment; rules must be established for the use of vaccine from the stockpile, perhaps without the vaccine having been licensed; and epidemics may require urgent expansion of production, for which arrangements must be made in advance. Regulatory issues for the use of CEPI-produced vaccines are still unsettled.

**Table 1. Pathogens for which vaccines are needed selected by various organizations.**

| Pathogen                                    | Recommended by all as first priority | Recommended by most for immediate development | Recommended for later development |
|---------------------------------------------|-------------------------------------|----------------------------------------------|----------------------------------|
| Ebolavirus                                  | Lassa, Nipah, MERS                   | Crimean-Congo Hemorrhagic Fever               |
| Lassa                                       |                                     | Rift Valley Fever                             |
| Nipah                                       |                                     | Zika                                          |
| MERS                                        |                                     |                                               |

**Organizations:** Foundation for Vaccine Research, CEPI Scientific Committee, Norwegian Institute of Public Health, UK Vaccine R&D Committee, WHO

| Table 2. Stages of development supported by CEPI. |
|--------------------------------------------------|
| Immunogenicity and safety in mice                |
| Protection in relevant animal challenge model    |
| GMP production, validation of methods – CEPI     |
| Toxicity studies                                |
| Phase I                                         |
| Phase II                                        |
| Phase IIb – if possible                         |
| Stockpile                                       |
| Conditional approval for emergencies – CEPI      |
| Phase III                                       |
| Licensure                                       |
Memories are short, whereas funding must be regular and uninterrupted. It should be remembered that despite the disruption caused by the SARS outbreak it was insufficient to generate new mechanisms, leading to a lack of preparedness for the West African Ebola epidemic, to say nothing of MERS and Zika. Fortunately, multiple governments and philanthropic organizations have contributed at least 800 million dollars to launch CEPI, as announced on January 19, 2017.10

**Platforms**

With regard to possible outbreaks of agents yet unknown, it would be desirable to have platforms that can be readily used for rapid development of vaccines, even if those vaccines are temporary stopgaps while better prophylactics are developed. Two general classes of platforms suggest themselves at this juncture: nucleic acids and vectors [Table 4]. DNA plasmids are readily developed from viral sequences and although they are better at inducing cellular responses than antibody responses, recent improvements have made them attractive in emergencies.11 RNA vaccines of different types are less advanced but commercial development is moving rapidly and ultimately they may offer advantages.12

On the vector side there are multiple possibilities, although at this point 4 vectors are obvious candidates: vesicular stomatitis virus,13 measles virus,14 animal adenoviruses,15 and vaccinia mutants.16 Many of these approaches were used to develop candidate vaccines to prevent Ebola Zaire strain infections. Efficacy in humans could be demonstrated with the VSV vector before the West African epidemic subsided, and the other platforms have shown protection in non-human primates.

A question that CEPI will have to answer is how many of these platforms should be maintained in a state that would allow them to respond urgently to a new pathogen? Or to put it another way, will manufacturers using these platforms be willing to immediately move personnel and facilities to a project responding to an urgent health problem? Note that better surveillance may identify outbreaks when they are small, with less terror and disruption than that seen with Ebola. It may be necessary to contract with manufacturers to maintain the readiness of platforms and to divert resources toward synthesis of vaccines against new pathogens at the request of CEPI. The maintenance of these platforms should permit at least rapid development of stopgap vaccines, while not excluding vaccines developed by other technologies.

### The short term: Filoviruses and chikungunya

Memories are short and needs for financial support are many. My view is that CEPI must have rapid successes early on, or funders will lose interest. The Scientific Advisory Committee of CEPI has given priority to fund efforts to develop vaccines against Filoviruses, MERS, Nipah and Lassa. No one can doubt the importance of these diseases to the concept of CEPI, but one can doubt the ease of vaccine development.

The success of the VSV vectored Ebola Zaire vaccine in human trials implies that vaccines can be made against the other related filoviruses, and there is general agreement that protection should be ensured against at least Ebola Sudan, Bundibugyo, and Marburg viruses.17-19 However, unless fortuitous outbreaks occur we will be unable to demonstrate the efficacy of those other filovirus vaccines except by determination of correlates of protection in 2 relevant animal models or by analogy to human responses to Ebola Zaire vaccine. It is not yet clear how CEPI will choose among the many filovirus candidate vaccines.

In the case of MERS, it appears clear that the Spike glycoprotein of coronaviruses, and particularly its receptor binding domain, is the best target for a vaccine, although cellular immunity may be important.20-26 Also, SARS and MERS teach us that animal coronaviruses may be infectious from human to human and that new coronaviruses are evolving. However, as MERS appears to be an infection of young dromedaries a fair question is should we develop and deploy a veterinary vaccine to prevent exposure and infection of humans?27,28 A veterinary vaccine would be much easier and faster to develop.

Nipah is a paramyxovirus, and therefore the target antigens are the F and G proteins. Multiple candidate vaccines exist, but all are in the preclinical stage. The most advanced is a vaccine

### Table 3. Prioritization of pathogens by different groups.

| WHO | NIPH | FVR |
|-----|------|-----|
| Crimean-congo hemorrhagic fever | Ebola virus | Ebola hemorrhagic fever virus |
| Filovirus diseases (i.e., EVD & Marburg) | Hepatitis E virus | Lassa hemorrhagic fever virus |
| Highly pathogenic emerging coronaviruses relevant to humans (MERS Co-V & SARS) | Enterovirus 71 | Marburg hemorrhagic fever virus |
| Lassa Fever | West Nile virus | MERS coronavirus |
| Nipah | Chikungunya virus | SARS coronavirus |
| Rift Valley Fever | Marburg virus | Crimean-congo hemorrhagic fever virus |
| R&D preparedness for a new disease | Yersinia pestis | Chikungunya virus |
| Chikungunya | Rift valley fever virus | Nipah virus |
| Severe fever with thrombocytopenia syndrome | SARS-CoV | Hepatitis E virus |
| Zika | MERS-CoV | Zika virus |
| | Lassa virus | Enterovirus 71 |
| | Nipah virus | Enterovirus 68 |
| | Coxackievirus A16 | Coxackievirus 16 |
| | Crimean-Congo hemorrhagic fever virus | Paratypoid A (Salmonella enterica) |
| | SFTS virus | West Nile virus |
| | Zika virus | Rift Valley fever virus |
| | Enterovirus 68 | Plague (Yersinia pestis) |

### Table 4. Platforms that might be made constantly available for unforeseen epidemics.

| DNA Plasmids |
| mRNA (self-appllying) |
| VSV vector |
| Measles vector |
| Animal adenoviruses vectors |
| MVA vector |

All of this means that CEPI must be a real organization, with a leader, a staff, a sufficient budget, and a continuing mission that must not fade in the temporary absence of an epidemic. Memories are short, whereas funding must be regular and uninterrupted. It should be remembered that despite the disruption caused by the SARS outbreak it was insufficient to generate new mechanisms, leading to a lack of preparedness for the West African Ebola epidemic, to say nothing of MERS and Zika. Fortunately, multiple governments and philanthropic organizations have contributed at least 800 million dollars to launch CEPI, as announced on January 19, 2017.10

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against the related Hendra virus that is cross-protective against Nipah and VSV vectors for Nipah have shown promise in animals. Passive protection with antibodies has also been successful in experimental studies. Although a vaccine is probably feasible, problems may arise as they have with vaccine development against another paramyxovirus, respiratory syncytial virus.

Lassa virus is an arenavirus, and a vaccine already exists for another arenavirus, Argentine Hemorrhagic Fever. However, there appear to be multiple distinct strains of Lassa. Moreover, passively administered antibody doesn’t work and protection against arenaviruses is mediated through cellular immunity. The vaccine world has little experience with vaccines that depend on T cell responses to protect, the exceptions being vaccines against tuberculosis and zoster. That fact creates the need for extensive safety studies to show that unwanted cellular immune responses are not also evoked.

Thus, the first targets chosen by CEPI are certainly ones for which vaccines are needed, but except for the filoviruses, for which efficacy has been demonstrated, one may doubt that success will be achieved with lightning speed. In contrast, the mosquito-borne Chikungunya virus suggests itself as an easier target, with multiple candidates in far advanced development. Chikungunya has spread from Africa to around the world, including to the Western Hemisphere in 2013, and in the process picked up a mutation that allows it to infect Aedes albopictus as well as Aedes aegypti. It is far from benign, causing residual arthralgia in about half of those infected and a chronic rheumatoid arthritis-like syndrome in 5%. Among the factors that make vaccine development relatively easy is the fact that Chikungunya is an arenavirus with a genome that synthesizes envelope proteins against which antibodies are typically effective. Although there are multiple lineages of the virus, depending on geography, there is only one serotype. Moreover, years ago formalin-inactivated and attenuated Chikungunya vaccines were developed and shown to induce neutralizing antibodies in humans. Those antibodies were protective in multiple models, including primates.

In contrast to some other pathogens, the cupboard of Chikungunya candidate vaccines is full. A list of already developed candidates, probably incomplete, is given in Table 5. At least 4 vaccines have been tested in humans, and at least 17 others have shown promise in animals. The most advanced are a virus-like particle vaccine using the envelope proteins and a 2 live, attenuated vaccines (one of which is a recombinant with another arenavirus); and a measles-vector Chikungunya envelope. Neutralizing antibodies at a level of 1/10 have been shown to be the correlate of protection. The VLP vaccine and the measles-vector vaccine have both been tested in phase 2 trials. If a review of those results by CEPI were satisfactory, manufacture of stockpiles could be immediately financed, and given a supply of vaccine, trials could be done in countries where Chikungunya is endemic. Thus, CEPI could quickly show its abilities and value for the world.

Note that with Chikungunya or any other disease, if a candidate not supported by CEPI appears to have a faster track to licensure, funding could be terminated. In all cases, CEPI will have to carefully assess the field to avoid inhibiting competing candidates.

Another relatively easy target is West Nile Virus. This infection started in Africa, spread to North Africa, Europe and eventually the United States, where it migrated from New York City to virtually the entire country through mosquito-borne infection of birds, from which vector mosquitoes could transmit the virus to humans. Although the incidence of West Nile Virus has decreased recently, presumably because the reservoir has diminished due to death of many infected birds and post-infection immunity in others, there were still over 2,000 cases in the US in 2015. Moreover, chronic sequelae of the infection in humans have recently been identified involving premature deaths of previously West Nile infected individuals. This shows that survival is not always unaccompanied by consequences. Moreover, it appears that transmission can occur between mosquitoes during multiple bites, lessening the possibility of viral extinction.

Military strategy teaches us to attack weak points of an enemy, not the strongly defended ones. Mortality is easy to measure, and I do not suggest that death due to MERS, Nipah, or Lassa isn’t a major disability (!), but strategically it may be desirable for CEPI to attack an easier target first rather than a highly fatal disease if the candidate vaccines are uncertain to work. A practical step would be to replace MERS with Chikungunya and to use a veterinary vaccine approach to control MERS.

### The long term — Emerging pathogens

All of the lists of pathogens for which vaccine development is needed have relied on current epidemiology. Let us suppose that CEPI is successful in developing and stockpiling vaccines for the known epidemic agents. Is there a role for continued existence of CEPI?

I submit that science is progressing to the point where prediction of epidemic potential is possible. To make this claim I rely on the work of several groups of theoretical biologists, who

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**Table 5.** Chikungunya candidate vaccines.

| Phase 2 | VLPs |
|---------|------|
|         | Measles vector |
|         | Formalin inactivated |
| Phase 1 | Envelope proteins |
|         | Chimeric alphavirus |
| Preclinical | Live, attenuated |
|           | VSV (live) vector |
|           | Chimp adeno vector |
|           | MVA vector |
|           | DNA plasmids (several) |

Nota bene: Neut titers ≥ 1/10 are a good correlate of protection

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**Table 6.** Viruses isolated from bats (selected).

| Virus          | Duvenhage |
|----------------|-----------|
| Rabies         | Sindbis   |
| SARS           | Nipah     |
| Hendra         | Ebola     |
| Marburg        | Rift Valley Fever |
| Tacaribe reovirus | Kyasun flavivirus |
have studied multiple pathogens that have reservoirs in bats or are transmitted by mosquitoes. The inherent mutability of genomes of RNA viruses which may allow those viruses to adapt to humans is important to keep in mind in this regard. Ebola is a good example of this. The divergence of the West African virus from the Central African virus occurred about 2004, presumably in the primate population. The closest virus sequence to that found in the West African epidemic from a human case was that from the 2007 epidemic in the Democratic Republic of the Congo, 7 y before the human epidemic in Guinea started in 2014. Rapid accumulation of genetic variation was seen in the Ebola virus genomes. I don’t think we know if the West-African virus is better adapted to humans than the Congo virus, but that is possible.

However, we know that increases in Ro, the reproductive number, often accompanies genetic changes, resulting in an increase in outbreak size. Arinaminpathy and McLean have compared the outbreak size for an agent with an Ro of 0.1 and an agent with an Ro of 0.9. Even though the latter is less than 1, many more outbreaks will occur with that increase in infectivity.

Cross-species transmission is exemplified by the origin of HIV. Many primates carry simian immunodeficiency lentiviruses related to HIV. Crossover to humans has apparently happened 4 times, leading to several different clades of HIV 1 and also to HIV 2. HIV-1 Clade M has been the best-adapted to humans.60

Virtually all animal-derived human pathogens arose from pathogens of other warm-blooded vertebrates, primarily mammals plus in two cases (influenza A and ultimately *falciparum* malaria) birds. Primates constitute only 0.5% of all vertebrate species but have contributed about 20% of our major human diseases. (Adapted from Ref. 62.)

### Table 7. The five stages through which pathogens of animals evolve to cause diseases confined to humans. Virtually all animal-derived human pathogens arose from pathogens of other warm-blooded vertebrates, primarily mammals plus in two cases (influenza A and ultimately *falciparum* malaria) birds. Primates constitute only 0.5% of all vertebrate species but have contributed about 20% of our major human diseases. (Adapted from Ref. 62.)

| Stage | Characteristic | Example | Transmission to Humans | Reproductive Number |
|-------|----------------|---------|------------------------|---------------------|
| 1     | Only in animals | Foot and Mouth Disease | Present only in animals | Ro = 0 |
| 2     | Primary infection | Rabies | Only from animals | Ro > 0 |
| 3     | Limited outbreak | MERS | From animals | Ro < 1 |
| 4     | Long outbreak | Ebola | Bats (?), then human-to-human | Ro = 1 |
| 5     | Exclusively humans | Measles | Only human-to-human | Ro > 1 |

What we need, then, is heightened surveillance for small outbreaks of agents that do not currently attract much attention. Such surveillance could be undertaken by WHO based on electronic reporting from around the world. If such surveillance could be organized, then CEPI could establish a DNA plasmid library of those agents, which would enable rapid development of at least DNA vaccines and rapid translation to other types of vaccine platforms. As a result there would be less chance of being surprised by a large outbreak of an unknown agent, and a faster development of candidate vaccines against such an agent.

In addition to viral diseases, there are several uncontrolled bacterial and parasitic diseases, which have been largely ignored by CEPI. The former include various species of salmonella, including paratyphoid organisms, whereas the latter include schistosomiasis and leishmaniasis. Perhaps an even better example in relation to the need for a vaccine is the recent discovery that the cryptosporidia protozoa are a common cause of infantile diarrhea, second only to rotavirus.

### Table 8. Virus traits potentially relevant for capacity to emerge and cause disease in human populations (modified from Ref. 65).

| Trait | Definition |
|-------|------------|
| Reservoir host relatedness |Viruses derived from primate species increases exposure|
| Height and duration of virus replication |Viruses with a broad host range are of greater concern|
| Virus host range |Higher substitution rates make it easier to adapt to human hosts|
| Evolvability |Certain transmission routes are more infectious|
| Transmission route |Determines whether a virus causes mild or severe disease in humans|
| Virulence |Lack of a shared evolutionary history is associated with higher virulence|
| Host-virus coevolution | |
I would argue that if the mission of CEPI is to create vaccines for diseases that do not interest industry because those vaccines are not likely to be profitable, then that mission should be extended into the long-term future to include infections that are prevalent or that if rare, have the potential for increased infectiousness to humans. The lists that CEPI, WHO and other organizations began with were limited to diseases already known. This is a worthy long-term goal for this CEPI over the long-term future to act as a worldwide safeguard against other agents and therefore to justify the extension of tools of modern biology those lists could be expanded to include other agents and therefore to justify the extension of CEPI over the long-term future to act as a worldwide safeguard against an unanticipated epidemic of an agent not yet well known. This is a worthy long-term goal for this fledgling organization.

Conclusion

Isaac Newton famously said “if I have seen further it is because I stand on the shoulders of giants.” CEPI stands on the shoulders of numerous scientists, on the shoulders of vaccine manufacturers and on the shoulders of WHO. However, neither vaccine developers, nor manufacturers nor WHO can accomplish what CEPI can do if it learns from the past, sets the right targets for the present and looks far into the future.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

References

[1] Plotkin SA, Mahmoud AA, Farrar J. Establishing a Global Vaccine Development Fund. N Engl J Med 2015; 373(4):297-300; PMID:26200974; https://doi.org/10.1056/NEJMep1506820

[2] Abushouk AI, Negida A, Ahmed H. An updated review of Zika virus. J Clin Virol 2016; 84:53-8; https://doi.org/10.1016/j.jcv.2016.09.012

[3] Pierson TC, Graham BS. Zika virus: Immunity and vaccine development. Cell 2016; 167(3):625-31; PMID:27693357; https://doi.org/10.1016/j.cell.2016.09.020

[4] Pronker ES, Weenen TC, Commandeur HR, Osterhaus AD, Claassen HJ. The gold industry standard for risk and cost of drug and vaccine development revisited. Vaccine 2011; 29(35):5846-9; PMID:21722688; https://doi.org/10.1016/j.vaccine.2011.06.051

[5] MacNeil JR, Rubin L, Folaranmi T, Ortega-Sanchez IR, Patel M, Martin SW. Use of serogroup B meningococcal vaccines in adolescents and young adults: Recommendations of the advisory committee on immunization practices, 2015. MMWR Morb Mortal Wkly Rep 2015; 64(11):171-6; PMID:26492381; https://doi.org/10.15585/mmwr.mm6411a3

[6] MacNeil JR, Bennett N, Farley MM, Harrison LH, Lynfield R, Nichols M, Petit S, Reingold A, Schaffner W, Thomas A, et al. Epidemiology of infant meningococcal disease in the United States, 2006–2012. Pediatrics 2015; 135(2):e295-311; PMID:25583921; https://doi.org/10.1542/peds.2014-2035

[7] Kindhauser MK, Allen T, Frank V, Santhana RS, Dye C. Zika: the origin and spread of a mosquito-borne virus. Bull World Health Organ 2016; 94(9):675-686c; PMID:27708473; https://doi.org/10.2471/BLT.16.171082

[8] Gao F, Bailes E, Robertson DL, Chen Y, Rodenburg CM, Michael SF, Cummins LB, Arthur LO, Peeters M, Shaw GM, et al. Origin of HIV-1 in the chimpanzee Pan troglodytes troglodytes. Nature 1999; 397(6718):436-41; PMID:9989410; https://doi.org/10.1038/17130

[9] Donnelly CA, Fisher MC, Fraser C, Ghani AC, Riley S, Ferguson NM, Anderson RM, Ferguson DN. Epidemiological and genetic analysis of severe acute respiratory syndrome. Lancet Infect Dis 2004; 4(11):672-83; PMID:15522679; https://doi.org/10.1016/S1473-3099(04)01173-9

[10] Rottingen JA, Goulas D, Feinberg M, Plotkin S, Raghavan KV, Witty A, Draghia-Aiki R, Stoffels P, Pirot P. New vaccines against epidemic infectious diseases. N Engl J Med 2017; 376:610-13; PMID:28099066; https://doi.org/10.1056/NEJMc1613577

[11] Ferraro B, Morrow MP, Hutnick NA, Shin TH, Lucke CE, Weiner DB. Clinical applications of DNA vaccines: current progress. Clin Infect Dis 2011; 53(3):296-302; PMID:21765081; https://doi.org/10.1093/cid/cir334

[12] Kramps T, Elbers K. Introduction to RNA Vaccines. Methods Mol Biol 2017; 1499:1-11. https://doi.org/10.1007/978-1-4939-6481-9_1

[13] Geisbert TW, Feldmann H. Recombinant vesicular stomatitis virus as a platform for vaccines against influenza and other viral respiratory diseases. Viruses 2014; 6(7):2735-61; PMID:25034642; https://doi.org/10.3390/v6072735

[14] Tang F, Naim HY. Live attenuated measles vaccine as a potential multivalent pediatric vaccination vector. Viral Immunol 2005; 18(2):317-26; PMID:16059493; https://doi.org/10.1098/vim.2005.18.317

[15] Capone S, D’Alise AM, Ammendola V, Colloca S, Cortese R, Nicolosi A, Folgori A. Development of chimpanzee adenoviruses as vaccine vectors: challenges and successes emerging from clinical trials. Expert Rev Vaccines 2013; 12(4):379-93; PMID:23560919; https://doi.org/10.1586/erv.13.15

[16] Aalenburg AF, Kreijtz JH, de Vries RD, Song F, Fux R, Rimmelzaan GF, Sutter G, Vole A. Modified vaccinia virus ankara (MVA) as production platform for vaccines against influenza and other viral respiratory diseases. Viruses 2014; 6(7):2735-61; PMID:25034642; https://doi.org/10.3390/v6072735

[17] Martins KA, Jahrling PB, Bavi S, Kuhn JH. Ebola virus disease candidate vaccines under evaluation in clinical trials. Expert Rev Vaccines 2016; 15(9):1101-12; PMID:27160784; https://doi.org/10.1080/14760584.2016.1187566

Table 9. Viruses (n = 37) that are known or suspected of being transmissible (directly or indirectly) between humans but to date have been restricted to short transmission chains or self-limiting outbreaks (modified from Ref. 65).

| Genome, virus family | Virus name |
|----------------------|------------|
| Single stranded RNA (ambisense) | Guanarito, Junin, Lassa, Lujo, Machupo, Sabia, Dandemong, lymphocytic choriomeningitis | |
| Bunyaviruses | Andes, Bwamba, Crimean-Congo |
| Single-stranded RNA (positive sense) | Japanese encephalitis, Usutu, West Nile |
| Flaviviruses | Middle East respiratory syndrome |
| Coronaviruses | Bamah Forest, o'nyong-nyong, Ross River, Semliki Forest, Venezuelan equine encephalitis |
| Single-stranded RNA (negative sense) | Bundibugyo Ebola, Lake Victoria Marburg, Sudan Ebola |
| Paramyxoviruses | Nipah |
| Rhabdoviruses | Bas-Congo, rabies |
| Double-stranded RNA | Nelson Bay, Colorado tick fever |
| Reoviruses | Titi monkey |
| Polyomaviruses | Macaque herpesvirus 1 |
| Herpesviruses | Simian virus 40 |
| Poxviruses | Monkeypox, Orf, vaccinia |

* human transmission of these viruses is known only by iatrogenic or vertical routes
MERS-CoV vaccine candidates in development: The current landscape. Vaccine 2016; 34(26):2982-7; PMID:27083424; https://doi.org/10.1016/j.vaccine.2016.03.104

Ma C, Wang L, Tao X, Zhang N, Yang Y, Tseng CT, Li F, Zhou Y, Jiang S, Du L. Searching for an ideal vaccine candidate among different MERS coronavirus receptor-binding fragments—the importance of immunofocusing in subunit vaccine design. Vaccine 2014; 32(46):6170-6; PMID:25240756; https://doi.org/10.1016/j.vaccine.2014.08.086

Cooley CM, Sisk JM, Halasz G, Zhong J, Beck SE, Matthews KL, Venkatakrishnan T, Rajagopalan S, Kyratsous CA, Fiore MM. CD8+ T cells and macrophages regulate pathogenesis in a mouse model of Middle East respiratory syndrome. J Virol 2017; 91(1); https://doi.org/10.1128/jvi.01825-16

Wang C, Zheng X, Gai W, Wong G, Wang H, Jin H, Feng N, Zhao Y, Zhang W, Li N, et al. Novel chimeric virus-like particles vaccine displaying MERS-CoV receptor-binding domain induce specific humoral and cellular immune response in mice. Antiviral Res 2017; 140:55-61; https://doi.org/10.1016/j.antiviral.2016.12.019

Liu WJ, Zhao M, Liu K, Xu K, Wong G, Tan W, Gao GF. T-cell immunity of SARS-CoV-2: Implications for vaccine development against MERS-CoV. Antiviral Res 2017; 137:82-92; https://doi.org/10.1016/j.antiviral.2016.11.006

Papaneri AB, Johnson RF, Wada J, Bollinger L, Jeltsch BA, Dawes BE, Milligan GN. Status of vaccine research and development of vaccines for Nipah virus. Vaccine 2016; 34(26):2971-5; PMID:26973068; https://doi.org/10.1016/j.vaccine.2015.12.075

Broder CC, Weir DL, Reid PA. Hendra virus and Nipah virus animal vaccines. Vaccine 2016; 34(30):3525-34; PMID:27154493; https://doi.org/10.1016/j.vaccine.2016.03.075

Prescott J, DeBuyscher BL, Feldmann F, Gardner DJ, Haddock E, Martellaro C, Scott D, Feldmann H. Single-dose live-attenuated vesicular stomatitis virus-based vaccine protects African green monkeys from Nipah virus disease. Vaccine 2015; 33(24):2823-9; PMID:25865472; https://doi.org/10.1016/j.vaccine.2015.03.089

Yoneda M, Georges-Courbot MC, Ikedo F, Ishii M, Nagata N, Jacquot F, Raoel H, Sato H, Kai C. Reombinant measles virus vaccine expressing the Nipah virus glycoprotein protects against lethal Nipah virus challenge. PLoS One 2013; 8(3):e58414; PMID:23516477; https://doi.org/10.1371/journal.pone.0058414

Ambrosio A, Saavedra M, Mariani M, Gamboa G, Maiza A. Argentinian hemorrhagic fever vaccines. Hum Vaccin 2011; 7(6):694-700; PMID:21451263; https://doi.org/10.4161/hv.7.6.15198

Emmerich P, Gunther S, Schmitz H. Strain-specific antibody response to Lassa virus in the local population of west Africa. J Clin Virol 2008; 42(1):40-44; PMID:18164653; https://doi.org/10.1016/j.jcv.2007.11.019

McCormick JB, King JJ, Webb PA, Scribner CL, Craven RB, Johnson KM, Elliott LH, Belmont-Williams R. Lassa fever. Effective therapy with ribavirin. N Engl J Med 1986; 314(1):20-6; PMID:3940312; https://doi.org/10.1056/NEJM198610233140104

Lukashevich IS. Advanced vaccine candidates for Lassa fever. Viruses 2012; 4(11):2354-57; PMID:23202493; https://doi.org/10.3390/v7102867

Safronetz D, Mire C, Rosenke K, Feldmann F, Haddock E, Geisbert T, Feldmann H. A recombinant vesicular stomatitis virus-based Lassa fever vaccine protects guinea pigs and macaques against challenge with geographically and genetically distinct Lassa viruses. PLoS Negl Trop Dis 2015; 9(4):e0003736; PMID:25884628; https://doi.org/10.1371/journal.pntd.0003736

Zeller H, Van Bortel W, Sudre B. Chikungunya: Its history in Africa and Asia and its spread to new regions in 2013-2014. J Infect Dis 2016; 214(suppl 5):S436-40; PMID:27290168; https://doi.org/10.1093/infdis/jiw391

Moorens DM, Favia V. Meeting the challenge of chikungunya. J Infect Dis 2016; 214(suppl 5):S434-5; PMID:27290168; https://doi.org/10.1093/infdis/jiw291

Thiberville SD, Moyen N, Dupuis-Maguiraga L, Nougarede A, Gould EA, Roques P, de Lamballerie X. Chikungunya fever: epidemiology, clinical syndrome, pathogenesis and therapy. Antiviral Res 2013; 99(3):345-70; PMID:23812181; https://doi.org/10.1016/j.antiviral.2013.06.009

Muthumani K, Block P, Flignat S, Muruganathan N, Chaiithanya IK, Tingey C, Wise M, Reuschel EL, Chung C, Muthumani A, et al. Rapid and long-term immunity elicited by DNA-encoded antibody prophylaxis and DNA vaccination against chikungunya virus. J Infect Dis 2016; 214(3):369-78; PMID:27009160; https://doi.org/10.1093/infdis/jiw111

Erasmus JH, Auguste AJ, Kaebler JT, Luo H, Rossi SL, Fenton K, Leal G, Kim DY, Chiu W, Wang T, et al. A chikungunya fever vaccine utilizing an insect-specific virus platform. Nat Med 2017; 23(3):192-199; https://doi.org/10.1038/nm.4253

Schwaemis M, Buchele N, Wadowski PP, Schoergenhofer C, Jilma B. Chikungunya vaccines in development. Hum Vaccin Immunother 2016; 12(3):716-31; PMID:26554522; https://doi.org/10.1080/21645515.2015.1101197

Erasmus JH, Rossi SL, Weaver SC. Development of vaccines for chikungunya fever. J Infect Dis 2016; 214(suppl 5):S484-96; PMID:27290179; https://doi.org/10.1093/infdis/jiw271

DeZure AD, Berkowitz NM, Graham BS, Ledgerwood JE. Whole-inactivated and virus-like particle vaccine strategies for chikungunya virus. J Infect Dis 2016; 214(suppl 5):S497-9; PMID:27920180; https://doi.org/10.1093/infdis/jiw352

Ramshaur K, Tang F. Chikungunya virus vaccines: Viral vector-based approaches. J Infect Dis 2016; 214(suppl 5):S500-5; PMID:27920181; https://doi.org/10.1093/infdis/jiw369

Metz SW, Piljman GP. Production of chikungunya virus-like particles and subunit vaccines in insect cells. Methods Mol Biol 2016; 1426:297-309; PMID:27233282; doi: 10.1007/978-1-4939-3618-2_27

Smalley C, Erasmus JH, Chesson CB, Beasley DW. Status of research and development of vaccines for chikungunya virus. Vaccine 2016; 34(26):2976-81; PMID:27026149; https://doi.org/10.1016/j.vaccine.2016.06.076

Akarahaya W, Yang ZY, Andersen H, Sun S, Holdaway HA, Kong WP, Lewis MG, Higgs S, Roossmann MG, Rao S, et al. A virus-like particle vaccine for epidemic Chikungunya virus protects nonhuman primates against infection. Nat Med 2010; 16(3):334-8; PMID:20111039; https://doi.org/10.1038/nm.2105

Goo L, Dowd KA, Lin TY, Mascola JR, Graham BS, Ledgerwood JE, Pierson TC. A virus-like particle vaccine elicits broad neutralizing antibody responses in humans to all chikungunya virus genotypes. J Infect Dis 2016; 214(10):1487-91; PMID:27655886; https://doi.org/10.1093/infdis/jiw431
[51] Ramsauer K, Schwameis M, Firbas C, Mullner M, Putnak RJ, Thomas SJ, Després P, Tauber E, Jilma B, Tangy F. Immunogenicity, safety, and tolerability of a recombinant measles-virus-based chikungunya vaccine: a randomised, double-blind, placebo-controlled, active-comparator, first-in-man trial. Lancet Infect Dis 2015; 15(5):519-27; PMID:25739878; https://doi.org/10.1016/S1473-3099(15)70043-5

[52] Yoon IK, Alera MT, Lago CB, Tac-An IA, Villa D, Fernandez S, Thaisomboonsuk B, Klungthong C, Levy JW, Velasco JM, et al. High rate of subclinical chikungunya virus infection and association of neutralizing antibody with protection in a prospective cohort in the Philippines. PLoS Negl Trop Dis 2015; 9(5):e0003764; PMID:25951202; https://doi.org/10.1371/journal.pntd.0003764

[53] Poore EA, Slifka DK, Raue HP, Thomas A, Hammarlund E, Quintel BK, Torrey LL, Slifka AM, Richner JM, Dubois ME, et al. Pre-clinical development of a hydrogen peroxide-inactivated West Nile virus vaccine. Vaccine 2017; 35(2):283-92; PMID:27919629; https://doi.org/10.1016/j.vaccine.2016.11.080

[54] Chancey C, Grinev A, Volkova E, Rios M. The global ecology and epidemiology of West Nile virus. Biomed Res Int 2015; 2015:376230; PMID:25866777; https://doi.org/10.1155/2015/376230

[55] Murray KO, Garcia MN, Rahbar MH, Martinez D, Khuwaja SA, Arafat RR, Rossmann S. Survival analysis, long-term outcomes, and percentage of recovery up to 8 years post-infection among the Houston West Nile virus cohort. PLoS One 2014; 9(7):e102953; PMID:25054656; https://doi.org/10.1371/journal.pone.0102953

[56] Weatherhead JE, Miller VE, Garcia MN, Hasbun R, Salazar L, Dimachkie MM, Murray KO. Long-term neurological outcomes in West Nile virus-infected patients: an observational study. Am J Trop Med Hyg 2015; 92(5):1006-12; PMID:25802426; https://doi.org/10.4269/ajtmh.14-0616

[57] Higgs S, Schneider BS, Vanlandingham DL, Klingler KA, Gould EA. Nonviremic transmission of West Nile virus. Proc Natl Acad Sci U S A 2005; 102(25):8871-4; PMID:15951417; https://doi.org/10.1073/pnas.0503835102

[58] Gire SK, Goba A, Andersen KG, Sealoff RS, Park DJ, Kanneh L, Jalloh S, Momoh M, Fullah M, Dudas G, et al. Genomic surveillance elucidates Ebola virus origin and transmission during the 2014 outbreak. Science 2014; 345(6202):1369-72; PMID:25214632; https://doi.org/10.1126/science.1259657

[59] Arinaminpathy N, McLean AR. Evolution and emergence of novel human infections. Proc Biol Sci 2009; 276(1675):3937-43; PMID:19692402; https://doi.org/10.1098/rspb.2009.1059

[60] Sharp PM, Hahn BH. Origins of HIV and the AIDS pandemic. Cold Spring Harb Perspect Med 2011; 1(1):a006841; PMID:22229120; https://doi.org/10.1101/cshperspect.a006841

[61] Han HJ, Wen HL, Zhou CM, Chen FF, Luo LM, Liu JW, Yu XJ, Bats as reservoirs of severe emerging infectious diseases. Virus Res 2015; 205:1-6; PMID:25997928; https://doi.org/10.1016/j.virusres.2015.05.006

[62] Wolfe ND, Dunavan CP, Diamond J. Origins of major human infectious diseases. Nature 2007; 447(7142):279-83; PMID:17507975; https://doi.org/10.1038/nature05775

[63] Morse SS, Mazet JA, Woolhouse M, Parrish CR, Carroll D, Karesh WB, Zambrana-Torrelio C, Lipkin WI, Daszak P. Prediction and prevention of the next pandemic zoonosis. Lancet 2012; 380(9857):1956-65; PMID:23200504; https://doi.org/10.1016/S0140-6736(12)61684-5

[64] Woolhouse ME, Rambaut A, Kellam P. Lessons from Ebola: Improving infectious disease surveillance to inform outbreak management. Sci Transl Med 2015; 7(307):307-5; https://doi.org/10.1126/scitranslmed.aab0191

[65] Woolhouse ME, Brierley L, McCaffrey C, Lycett S. Assessing the epidemic potential of RNA and DNA viruses. Emerg Infect Dis 2016; 22(12):2037-44; PMID:27869592; https://doi.org/10.3201/eid2212.160123

[66] Teh CS, Chua KH, Thong KL. Paratyphoid fever: splicing the global analyses. Int J Med Sci 2014; 11(7):732-41; PMID:24904229; https://doi.org/10.7150/ijms.7768

[67] Gillespie PM, Beaumier CM, Strych U, Hayward T, Hotez PJ, Bottazzi ME. Status of vaccine research and development of vaccines for leishmaniasis. Vaccine 2016; 34(26):2992-5; PMID:26973063; https://doi.org/10.1016/j.vaccine.2015.12.071

[68] Merrifield M, Hotez PJ, Beaumier CM, Gillespie P, Strych U, Hayward T, Bottazzi ME. Advancing a vaccine to prevent human schistosomiasis. Vaccine 2016; 34(26):2988-91; PMID:27036511; https://doi.org/10.1016/j.vaccine.2016.03.079

[69] Ryan U, Zahedi A, Paparini A. Cryptosporidium in humans and animals—a one health approach to prophylaxis. Parasite Immunol 2016; 38(9):535-47; PMID:27454991; https://doi.org/10.1111/pim.12350