Commentary

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Journal of MPE Molecular Pathological Epidemiology

2017
Vol.2 No.S1:06

Viral Epidemics and Vaccine Preparedness

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Rec date: Dec 06, 2016; **Acc date**: Dec 21, 2016; **Pub Date**: Dec 23, 2016

Citation: Nandy A, Basak SC. Viral epidemics and vaccine preparedness. J Mol Pathol Epidemiol. 2017, 2: S1.

Commentary

Viral epidemics are occurring with increasing frequency raising concerns on public health and preventive and therapeutic preparedness. At the turn of the new century it was the 2002-03 SARS (Severe Acute Respiratory Syndrome) epidemic, then the pandemic swine flu of 2009, followed by Ebola (2014-15) and now the Zika virus epidemic, apart from the seasonal flu epidemics that seem to occur every year [1-3]. Such epidemics arise from new viruses to which humans have no immunity, whether these arose fresh from zoonotic sources or by genetic shifts and drifts in existing strains. The ravages caused by the Human Immunodeficiency Virus (HIV) that is believed to have originated from non-human primate Simian Immunodeficiency Virus and adapted to human hosts, has spread across the world, with research labs still trying to fashion a reliable cure or preventive [4]. The Spanish flu of 1918 that killed millions worldwide was a H1N1 influenza that had no known precedent [5]. The recent incidences of Zika virus infections that spread rapidly through Lain America to the Caribbean and into the USA and has been detected in China and Singapore, is expected to increase its domains further as warmer climates assist in increasing the range of its vector, the *Aedes aegypti* and *Aedes albopictus* mosquitoes, and humans travel widely across the globe with no cures yet in sight [6].

In all these cases, and the H5N1 avian flu that started in the final years of the twentieth century, the medical and public health departments, faced with lack of any medication against the viruses, had to improvise stringent containment measures to prevent further spread of the infections [7]. Thus, millions of domestic and wild birds were culled with limited to futile results to contain avian flu, travel and tourism was restricted in south-east Asian countries to avoid the SARS epidemic, and several African regions were effectively quarantined to contain the Ebola virus within a limited range [7-9]. At the present time many Latin American countries have advised their citizens to avoid pregnancies until the Zika virus and its adverse effects on foetal neurological systems were well understood [10].

Containment is one part of the story, immunization or prevention through human intervention is another, fraught with major difficulties. Viral types in these epidemics are sufficiently varied in their actions and modes of transmission that no one routine can be effective against all. In fact, every viral epidemic is so different that in each instance the scientific pursuit for any effective remedy has to start from the beginning. The remedies themselves are time consuming to process: time taken from laboratory bench to patient bedside for an effective drug to be devised is estimated at ~10-15 years at a cost of about 1.8 billion dollars; thousands of compounds need to be tested in the drug discovery pipeline before an effective molecule is found, and then the compound has to undergo rigorous human trials before it can be introduced in the market, some times to remain effective for only a limited time [11,12]. Viruses themselves remain epidemically virulent for a few months to a year or so, and then may decrease in severity due to environmental or seasonal changes or perhaps sufficient people develop immunity and in effect inhibit the spread of further infections; the Zika virus, considered as Public Health Emergency of International Concern (PHEIC) by World Health Organization (WHO) on 1st February 2016 was subsequently, on 18th November 2016, considered by the WHO Emergency Committee that Zika virus and associated consequences remain a significant enduring public health challenge requiring intense action but no longer represent a PHEIC [13,14]. The problem is compounded by the fact that viruses by nature mutate very rapidly, especially RNA viruses, which renders drugs and vaccines effective for the initial period become ineffective in subsequent years. The history of rimantadine and amantadine against influenza is a recent example; resistant strains have even developed against oseltamivir (marketed as Tamiflu), the current most effective drug against influenza [15-18]. DNA viruses contain self-repair mechanisms and mutate at a lower rate, for which drugs and vaccines against such viruses can and do remain effective over many years, e.g., smallpox vaccine.

Even so, vaccines, rather than drugs, are considered as the preferred means to combat viral infections; the relatively lower development costs and times compared to drugs development are an advantage [19]. Vaccines began to be systematically used starting from the 1880's with smallpox vaccine by Louis Pasteur [20,21]. They have the benefit of prompting the body's own immune system to fight against the invader pathogens. Vaccination was done by inoculating with live, attenuated viruses. One problem with such vaccines has been that they

sometimes regenerate to a virulent form and infect the recipient; also, such vaccines require refrigeration and careful storage and handling that make them difficult for administration in many parts of the world. Vaccines with killed, or inactivated viruses where the DNA/RNA molecule are removed from the virion, cannot regenerate and have the advantage of relatively easier storage and transportation, but they evoke weaker immune response and require booster shots to remain effective. In recent times whole surface proteins of the virion in the form of virus like particles have also been used, e.g., as in Gardasil against human papillomaviruses; however, few vaccines of this type have been licensed so far, most vaccines are of the live attenuated or killed virus types (see Vaccine Types [22]).

Development, storage, transportation and administration of such vaccines are difficult to organize in the event of a viral epidemic where rapid deployment of new and available resources is important. It is estimated that such deficiencies could lead to loss of millions of lives during an influenza epidemic [23]. Due to the short time frame between identification of a pandemic strain and need for vaccination, novel technologies for vaccine design and production at affordable cost are being looked for with a view to applications in developing and low-income countries where the burden of epidemic and pandemic fallouts are the largest. Clearly, solutions must be sought in non-traditional methods, where new developments are showing promise.

Recent technological advancements and understanding in the fields of immunology and genetics and developments in bioinformatics, computer resources and web services have brought a new paradigm into play – vaccinomics [24,25]. "Reverse vaccinology" is another novel approach towards development of new vaccines [26,27]. These hold the promise of moving away from one standard vaccine against all human populations, a "one size fits all" concept to one where vaccines can be relatively easily tailor-fitted to individual, community and population specificity. This would be especially appropriate in the case of hypervariable viruses like coronavirus, influenza, etc. where traditional vaccination is failing to meet the challenges [24,25]. Effectively, this new approach to vaccine design focuses on the core system of immune response – the antigen-antibody interaction. The idea is that if we can identify and isolate the exact antigen that can lead to protective immune response and arrange to present only that to the immune system, it can be an effective agent to fight the virus using the body's own defences. This was in fact proven in a canine model against the parvovirus under the name of peptide vaccine [28]. However, there has not been any such vaccine against human infecting viruses marketed to date although many are under different stages of trials (see [29] for a brief list). Peptide vaccines, also referred to as subunit vaccines, in fact are primary contenders for immunotherapy against viral cancers and have shown good promise in the case of many cancerous diseases [30]. In relation to influenza epidemics, one amongst several approaches takes several conserved linear epitopes that activate both cellular and humoral arms of the immune system against influenza A and B, and are expected to evoke immune responses to pandemic influenza, to construct a recombinant peptide anti-influenza vaccine which at this time is undergoing phase IIb trials [31].

Production of such antigens is also an issue. An interesting technique that is being tried out in various labs is plant-based vaccine development. Viral genes are introduced in genetically modified plants and the antigens which are produced can be extracted and purified. Carrier plants such as potatoes and maize are readily acceptable and the antigens are stable, easy to administer and store. While several such vaccines have shown promise, only two plant-based vaccines have been licensed for use in animals and none for humans because of regulatory hurdles related to genetically modified crops and several technological challenges to be overcome, but some are in clinical trial phase [32,33].

The benefit of vaccinomics is to shorten the lead time that is normally required to identify the right virus like particle or the right attenuated virus to be used in the vaccine. Progress in immunogenetics allows us to identify the selection of peptides to be used for the vaccine which can then be ordered and tested without delay, thus shortening the production time. Some of the benefits of peptide, or subunit, vaccines are reduced time and costs, no risk of reversion to the live virus form, negligible risk of contamination by pathogens or toxins, quick adjustments to avoid allergenic threats, possibility to tailor-make to specific strains of a virus, reduced side effects if any, among others [34,35]. As of this writing, more than 580 peptide vaccines are registered for different phase trials in the NIH ClinicalTrials website [36].

The identification of antigenic peptide segments on the virion is the primary task in rational design of peptide vaccines against emergent and recurrent viral epidemics, based mainly on computerized approaches [29,37]. Applications software like VaxiJen [38] utilizes the physico-chemical properties of the pathogen proteins for antigen classification, IEDB (Immune Epitope Database) Analysis Resource [39], ABCpred (Artificial neural network based B-cell epitope prediction) [40] and PREDIVAC (prediction software for vaccine design) [41] among other web servers predict T-cell and B-cell binding to MHC (Major Histocompatibility Complex) classes I and II with high degree of accuracy **(Table 1)**. Such tools have been used by Oany et al to design subunit vaccines against human coronavirus (HCoV), which causes upper respiratory tract infections and which led to the SARS epidemic of 2002-03, by Islam et al to determine conserved epitope regions in the chikingunya virus, by Chakraborty et al to recommend six peptides in the dengue virus that had high antigenicity and low hydrophobicity as possible candidates for an anti-viral vaccine, among others [42-44].

Our group has approached this issue from a slightly different viewpoint. To bypass the problem of genetic drifts in a virus due to mutational changes, we have improvised upon the usual techniques of identifications of acceptable epitopes by analysing first all available sequences of the surface protein of the virus to determine those peptide segments that remain unchanged or least changed over the passage of time and strains so that our eventual peptide vaccines can remain effective over many cycles of mutations [45-48]. We next examine their hydropathy profile and identify those regions that are most hydrophilic and have been determined to be most conserved. These then are further

examined on a 3D crystal structure, if available, to ensure that they are not covered by neighbouring proteins in a multimeric structure. Those that pass are tested for T-cell and B-cell epitope potential using any one or more of several web-based servers available to ensure they have the capability to evoke immune response. Finally they are tested against auto-immune threats and those that pass all these tests are presented as candidates for peptide vaccine design. These are then augmented by appropriating carrier proteins, addition of adjuvants and the like before testing in murine models for in vivo immune response. Those that pass can then be ready as mono- or multi-valent vaccines for human trials, possibly in three months' time from the start of the process.

Table 1: Websites for epitope prediction and vaccine design covered in this commentary

Resource	Function	Web address	Ref.
IEDB (Immune Epitope Database) Analysis Resource	Prediction and analysis of T-cell and B-cell epitopes	http://www.iedb.org/home_v3.php	[39]
ABCPred	Predict B-cell epitopes in an antigen sequence	http://www.imtech.res.in/raghava/abcpred/	[40]
PREDIVAC	Predict HLA class II peptide binding	http://predivac.biosci.uq.edu.au/	[41]
VaxiJen	Predict protective antigens and subunit vaccines	http://www.ddg-pharmfac.net/vaxijen/VaxiJen/VaxiJen.html	[38]

Clearly, in an epidemic scenario, even this time difference is a problem. However, if the above stratagem should work, it is possible that the above processes can be further streamlined to reduce lead times even further and induce even more heightened immune responses; at the same time difficulties with peptide vaccine approaches such as peptide folding in vivo need to be worked out. Such strategies are urgently called for since the number and severity of newer viral epidemics have become more frequent over the years and more zoonoses seem likely. Increased travel and environmental changes such as global warming are causing some of the vectors of the viral diseases to spread further on the globe causing continuing infectivity farther than before [49]. The recent report of discovery of over 1500 unknown viruses in non-vertebrate fauna raises further fears of passage of some of these to humans, repercussions of which we cannot know at this time [50].

Anti-viral vaccine preparedness is a necessity now with viral epidemics spreading around the globe in faster time than ever before. Classical techniques of drug and vaccine developments are clearly unequal to the task, especially in the face of RNA viruses that evolve rapidly over short time scales to render painstakingly developed drugs and vaccines useless within a short time. New paradigms like vaccinomics are the need of the day, with rapid acquisition of genomic sequences and analytical and developmental processes even more streamlined than has been the case to date. These coupled with containment procedures for infected individuals and control of vectors could conceivably reduce the severity of new epidemics. Genetic surveillance will also be required to make timely adjustments to the subunit vaccines to ensure these remain up-to-date, a task more easily done with these types of vaccines than the classical ones.

For global health security against epidemic outbreaks, prompt response from governmental sources is of vital concern. The Ebola crisis has brought this necessity into sharp focus and the UK has responded by setting up a Public Health Rapid Support Team which can be deployed to tackle outbreaks of disease anywhere in the world within 48 hours [51,52]. The One Health Initiative taken up in recognition of global threat of emerging zoonotic diseases by several organizations around the world have developed strategies to work closely together to address the animal-human-ecosystem interface [53,54]. These efforts have to be complemented by the development of preventive and therapeutic medications for effective control. New paradigm vaccines with fast lead times for development hold the key and need to be researched and made ready for rapid deployment in crisis periods.

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This article was originally published in a special issue, entitled: **"Zika virus epidemiology and recent Epidemics"**, Edited by Dr Suzane Ramos da Silva