

Translational approach in emerging infectious disease treatment: an update.

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Abstract

While the rational understanding on the therapeutic and preventive care of epidemic diseases have enriched our knowledge, recent outbreak of complicated infectious diseases have presented newest challenges towards humankind. It started from the beginning of 19th century when disease infection from unknown origin preferred its host as human and mass mortality altered the socio-economic strata of various corners of the globe. For instance, human being witnessed some newly emerged global burdens such as HIV, Ebola hemorrhage fever, Zika Virus, Sever Acute Respiratory Syndrome (SARS) in the last century. Nevertheless, drastic changes in the environment, mutations in genetic composition and increased population extend the chances for new disease emergence. The inception of biomedical research has brought new diagnosis and treatment options; however, the outbreaks are being surprised and caused by new strains or modified strains. Translational biomedicine is a new context in this regard and raised the hope in integrated approaches to develop new diagnostic and treatment methods. In this review, we have summarized timely information about recently reported disease pathologies, which have challenged the world with mass mortality, and discussed about the causative agents, possible treatment strategies and future perspective for respective diseases.

Keywords: Infectious diseases, Disease control, Virus infection, Translational medicine, Therapeutic challenges.

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Introduction

In recent past, the threats of infectious diseases have increased rapidly. Regardless the casualties, the infectious diseases can be classified into two categories: emerging and re-emerging diseases. According to the types of pathogen, Zoonotic diseases can be divided into three distinct categories: viral (rabies, yellow fever, HIV infection), bacterial (brucellosis, tuberculosis, anthrax) and parasitic (toxoplasmosis, cysticercosis, and leishmaniasis). However, the main sources of the origin of disease pathologies are wild and domestic animals [1]. Available reports have related the association of infectious diseases and Zoonoses, which extends the host specific understanding of infectious disease. Interestingly, from the very first infectious disease i.e., Plague to the recent outbreak of HIV and Ebola, all are Zoonotic by transmission nature. It is estimated that nearly 75% of viruses and 50% of bacteria are associated with human zoonotic diseases. Zoonotic

infection is the major cause of human illnesses, which accounts major causalities mainly in tropical regions. However, in 14% of the human pathogens, the route, etiology and mode of transmission are equivocal [2,3]. There are wide spectra of infectious diseases that emerged and re-emerged are related to travel. The majority of cases of malaria (Traveler's Malaria) in the United States occur in individuals returning from travel abroad. Therefore, it is important to utilize the services of the specialized travel clinics [4].

As a context of eradication or prevention of infectious diseases, it is important to understand the biology of pathogens, hosts and the host-pathogen interactions. Identification of essential molecular events or biomarkers may provide strategies for development of new drugs or vaccine candidates. Some of the invertebrate models are reported as animal models for new drug design and discovery. This could be an alternative for the animal models; therefore, new technological approaches are

required to utilize invertebrates such as amoeba, *Drosophila*, Zebrafish as laboratory organisms. These animal models have a unique feature that the whole genomes have been sequenced, which could provide new insights in the association of pathogen-host genetics [5]. Another promising option is metagenomic approach that reveals the chemical diversity for discovery of resistant determinants in clinical and natural environment. As an alternative, metagenomic approach can be used as a potential source to explore the antimicrobial peptides, moreover, antibiotic resistance can also be tackled to reduce the infection and related mortality [6,7]. The manifestations of infectious diseases include both functional and physiological behaviors in immunology of infected individuals that are not clearly understood. The current diagnostic methods are not effective and time consuming procedures. The advancements in pharmacogenomics are believed to be the promising method in identification of adverse effects caused by the therapeutics used to treat the viral infections. More or less, these new technologies offer multidirectional diagnosis and treatment methods for these deadly diseases [8,9].

Zika Virus: The Re-emerged Challenge

Zika virus named after the ZIKA forest in Uganda where the virus was first isolated in 1947. Zika virus is member of Flavivirus family, like its close colleagues dengue, yellow fever, and West Nile fever of Flavivirus family, transmitted through infected *Aedes aegypti*. There are evidences for the outbreak of Zika virus in 2007 and 2013 in Africa and Southeast Asia but they are not considerably large. In July 2016, the large outbreak reported in USA [10-12]. Most of the cases in the US are travel related or individual exposure to the Zika affected countries [13,14].

Reports suggested that Zika virus infection is associated with neurological abnormalities. It also influences the neurological birth complications after affecting pregnant women in the ground zero zone. It is interesting that, Zika virus is able to cross the blood brain barrier and had a greater affinity to the nervous system. Most of the reported incidences of Zika infection in USA and Latin America are associated with microcephaly or Guillain-Barre syndrome. Solomon et al. reviewed the published data by Center for Disease Control and Prevention and reported that 1-4% of the reported cases are microcephaly, 29% are associated with fetal abnormalities [13]. Nguyen et al. reported that, till August 2016, 11,528 Zika virus cases were confirmed in USA, out of which 1396 were pregnant women and 33 were Guillain-Barre syndrome cases [15]. Diop et al. investigated the epidemiology of Zika virus in a systemic review and reported the endemic epidemiology of Zika virus in Africa, Asia and South and Central America. The study also concluded that there are many travel related infection incidences and diseases pathologies are reported in the Europe and North America [14]. Notwithstanding to the fact that, the mutations also play a key role in re-emerging or emerging infections, and in Zika virus perspective, it appears to have specific mutations in the genetic composition. Wickramasinghe and Steele reviewed the panspermia

hypothesis, evolutionary bursts and genome structure of Zika virus. According to the literature available on Zika outbreaks at various times, it is believed that the genome structure has changed at significant levels. Evidences suggested that there is no incidence of microencephaly in the cases reported before 2000, but the recent outbreak is predominant in microencephaly. This is a clear indication for the role of mutations in emerging diseases and new human phenotypes of causative agents [16].

As of now, there is no screening method or potential therapeutic vaccines reported. To prevent and control Zika virus, it is important to understand pathogenesis, circulation, mode of transmission, vector biology, risk factors and associated disorders and the impact of environmental changes. Awasthi reported that the discovery of fifth serotype of dengue virus has successfully completed the phase III trials and available in Brazil. Vaccine Research Center (VRC), National Institute of Allergy and Infectious Disease (NIAID) and other organizations are working to find effective vaccine candidates against Zika [17]. Recently, Bharat Biotech from India has claimed the invention of Zika vaccine under the trade name of ZIKAVAC™ and successfully completed the initial trial procedure [18], which could be promising for future therapeutics against Zika infection pathology.

Studies have shown that, identification of E protein regions may provide targets for developing of new vaccines. Weltman used information entropy (H) and predicted B cell epitope score to determine the E protein and epitope prediction provide information for potential vaccine design. This computer-assisted study facilitates development of an anti-ZIKV vaccine, one with a lowered susceptibility to viral mutational escape [19]. In another report, Ceron-Carrasco et al. summarized the application of computational drug discovery techniques in development of vaccine for the Zika. Advanced virtual screening tests docking techniques, blind docking simulations, Ligand-based virtual screening, etc., have been shown potential to provide valuable solutions and array of panels for biological problems. It is believed that integrated approaches are available for novel drug designing and developing in the context of Zika virus [20].

Methicillin-Resistant *Staphylococcus aureus*: Common Infection of Community

Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most common infectious diseases first reported in 1960s in United Kingdom, but soon after, large hospital outbreaks reported in the UK in 1970s. MRSA has become endemic due to simpler ways of infection. It is reported that the disease is community based infection, hospital-onset and healthcare-associated community infection. In 1968, the first hospital outbreak of MRSA was reported in Boston, USA. Later the infection became endemic in the United States. The reports suggested that the percentage of MRSA patients in US hospitals increased from 2.4% in 1975 to 29% in 1991 [21-23]. Furthermore, approximately 125,969 MRSA hospitalized cases per year were reported in between 1999 to 2000, in the United

States. Between 1998 and 2003, the average percentage of MRSA cases increased and reported 51.6% as ICU infected cases and 42% as non-ICU infected cases [24,25]. Williams summarized some statistical data from the literature and concluded that percentage of MRSA isolates increased from 35.9% in 1992 to 64.4% in 2003 and there were around 94,000 MRSA cases reported out of which 18,000 deaths occurred in 2005 [26]. Another study by Taniguchi et al. showed that antibiotic resistance has greatly increased in the second half of the period. Moreover, the study showed that there is regional difference in antibiotic susceptibility for CA-MRSA [27].

Available information on the respective issue suggested that, MRSA infection is largely due to the hospital setup and poorly maintained ICU conditions, which causes simple skin infection to life threatening infections such as pneumonia, osteomyelitis, etc. [28]. It is believed that there is an association between MRSA and minimum inhibitory concentration. This indicated that it is essential to investigate whether such a discrepancy exists between different MIC measurement methods. Kitano et al. reported various MIC measurement options by using 'Broth microdilution method'. The study also concluded that MicroScan® prompt method and the MicroScan® turbidity method had fewer discrepancies [29]. In another study, Chaudhary et al. demonstrated that combining ceftriaxone with vancomycin in presence of VRP1020 significantly reduces the MIC and MBEC values against strong biofilm producing MRSA isolates. The study also reported that Linezolid is the second best option after Vancoplus [30]. For the detection of simple microbiological tests take more time to yield the results. Therefore, there is a great need of developing new, efficient, cost-effective and rapid detecting system for screening. Ikeuchi et al. developed a simplified electrochemical method to detect the *mecA* Gene [31]. Khan et al. reported that, organic non-alkaloid extract derived from *R. stricta* have antibacterial activities against MRSA. The study successfully showed inhibition of growth in the zone of inhibition ranging between 6 and 19 mm. This study provides new insights in the development of novel drugs [32].

HIV and AIDS: Global Burden of the History

Over the past three decades, Acquired Immune Deficiency Syndrome (AIDS) came into light as a global epidemic, paving to numerous scientific advances to treat AIDS, which included the identification of Human Immunodeficiency Virus (HIV) disease mechanisms and the introduction of Antiretroviral Therapy (ART) [33]. HIV has maintained its status of being a grave public health problem during these decades firming its position as lethal emerging infection even after the incredible advances in therapeutic regimens and treatment. Since first discovery of HIV long back in the year 1983, there had been spectacular progress in understanding the complex biology of the virus [34]. There is a proverb by Benjamin Franklin that, "An ounce of prevention is worth a pound of cure", which holds true sense for HIV therapeutics. The virus finds its way of transmission through direct contact of body fluids, which mainly includes blood, semen, vaginal secretions and breast

milk. In the developed countries like the United States of America (USA) the risk behaviors like unprotected sex and the sharing of needles and syringes among drug users are the major causes of HIV infection [35].

It is recently reported that USA has about nearly 1.2 million people living with HIV infection, with a proportion that one in seven people are unaware of their diseased condition [36]. Even though the size of the epidemic is relatively small when compared to the total population of USA, it is heavily concentrated within several key affected populations located geographically in the Southern states which estimate nearly 49% of all new HIV infection cases occurring. Marked from the beginning of the epidemic nearly 659,000 people have died due to AIDS-related illnesses in the USA [37]. The major affected populations can be easily grouped by transmission category i.e. men who have sex with men (MSM), also by race [38].

A complex set of economic and socioeconomic factors drive risk to these populations, including a lack of access to care, discrimination, homophobia, stigma and poverty [39]. USA is the greatest national funder for HIV research globally, but still faces the major HIV epidemic by itself discovering nearly 50000 new infections each year. USA lacked a comprehensive plan on HIV prevention until 2010, when President Barak Obama created a National HIV/AIDS Strategy. In accordance with the latest strategies released in 2015, it mainly focused on four main aims—firstly, reducing new HIV infection, secondly increasing the access to care and improving the lifestyle of those individuals living with the HIV, thirdly reducing HIV health inequalities and finally achieving a coordinated national response to the epidemic [39].

The reports and statistics of many national and international organizations suggested HIV and AIDS as a predominant challenge to the world in the past century; therefore, it requires an emergency to find early detection and treatment methods for this disease [40]. Over the past two decades, advancements in the biomedical research offered new insights in the diagnosis and treatment options. Initially, researchers used to suggest simple chemicals to improve the quality of life of an HIV positive patient. On the other hand, there were reports for the mutants HIV and many co-infections such as tuberculosis, fungal and viral pneumonia [41]. Such incidents have motivated the research communities to find better ways to treat the disease. Notable breakthrough research on HIV infection was reported in 2008, which stated about the molecular structure of HIV virus and the discovery was awarded Noble Prize [42,43]. The discovery of Anti-retroviral therapy [44-46], which is believed to be the best available therapeutic option, however, need further understanding of the disease, which leads to the discovery of Highly Activated Anti-retroviral Therapy (HAART) [47-52]. Nevertheless, Neuro AIDS also reported as equal burden to the world, for which personalized nanomedicine [53-57] and advanced theranostic methods [56-58] are available now to cross the blood brain barrier and treat the Neuro-AIDS [59-61].

H1N1: The Altered Re-Emergency

The influenza virus, commonly known as 'Swine flu' is a type of acute respiratory disease caused by influenza 'A' virus belonging to the Orthomyxoviridae family. The primary clinical symptoms of the viral infection are fever and acute respiratory distress. It also infects many animal species including birds, seals, whales, humans, horses and swine [62]. Under normal conditions, the virus does not infect humans. However, a different strain of influenza virus called 'variant virus', which affect *via* circulation of the sporadic human infections. These variant strains are denoted by adding the letter 'v' to the end of the virus subtype designation. Human infections with H1N1v, H3N2v and H1N2v viruses have been detected in USA [63].

Sundar et al. built a model that enabled them to produce improvised estimate cases, hospitalizations, and death tolls that could be frequently updated as new information [64]. In USA, the cases of H1N1 are spreading rapidly, particularly in Texas, New York, Utah, and California. Early reports suggested that most of the cases are due to travel to Mexico and most of the reported cases are students [65]. During the last pandemic outbreak in 2009, CDC reported 1 death and 286 confirmed cases of H1N1 Flu across the 36 states. Among which, 35 cases of hospitalizations took place and several secondary factors have been recognized that assisted in the rise of victim numbers in the preceding days. The CDC and government officials had expressed their cautious optimism about the severity and the spread of H1N1 [66]. Since the last pandemic in 2009, the cases of influenza has not disappeared completely, despite of several national prevention programs conducted in many countries. According to the reports of World Health Organization (WHO) [67], on 2015-2016 influenza incident in December, nearly 35,732 samples were analysed, in which 89% of them were classified as influenza A and the rest 11% were classified as influenza B. Out of the number of virus classified as type A, 93.3% were influenza A (H1N1) and approximately 6.7% were influenza A (H3N2). Half-a-year later, during the month of June, more than 55,586 samples were analysed showing a shift among the statistical values. Nearly 60.1% were classified as influenza A and 39.9% as influenza B. Out of the viruses classified as influenza A, 86.2% were influenza A (H1N1) and 13.8% were influenza A (H3N2) [68-71]. On a better note, this year, the number of cases of influenza has remained within the expected range but there is higher possibility of an increase in the number of cases due to the circulation of new viral variants, which might increase the threat of the disease [72-75].

Seven years down from the last pandemic outbreak of influenza virus (AH1N1), which remained being the highest incidence, provided a new way to vaccination, where particle of influenza AH1N1 strain was represented as the source antigen in all vaccines against influenza, irrespective of trivalent or quadrivalent. This led to a query about still existing incident of this virus, which having no substantial changes that permits a change in the composition of currently available vaccines. Vega-Sánchez et al. highlighted this dilemma in their

work, which discussed the effect of the substrate used for production of vaccines, on the structural characteristics of influenza virus and there by proposing alternatives for the advancement of improved vaccines against this disease. The reason underlying such distinct behavior is due to the absence of significant changes in the nucleotide sequence of the Hemagglutinin (HA). Nevertheless, the effectiveness of the vaccine has not been as expected; therefore, at present new improvements against the existing vaccines remain under investigation [76-79].

Change in the surveillance pattern for detecting cases of influenza-like illness, resulted a spike increase in the percentage cases tested positive for influenza. Out of these positive cases, one third are due to novel strains, but a substantial number of cases are due to strains that are not subtyped [80,81]. The current trends of research on developing vaccines for influenza focus on achieving an acceptable platform that could be generated in a short time period with a higher performance rate. In addition, it also guarantees to confer adequate immunity to the patient. In the quest of such advancement, the researchers are aiming to develop cells or systems with specific enzymatic machinery identical to that of humans, helping the biosynthesis of vaccines against the virus [76].

Ebola Virus: Stranger at the Door Step

After witnessed few deadly infectious diseases the world consciously switching new biomedical research fields to protect the humankind from emerging infections. However, there are very rare burdens challenging the technological advancements by causing high mortality. Ebola hemorrhagic fever (Ebola virus) is such kind, which is completely a strange virus infection and first reported in West Africa in 2014 and spread to various countries within no time. According to the source and data from the various public health agencies Ebola is the most deadly disease reported in the last decade. On 8th August 2014 the World Health Organization declared the Ebola outbreak as a community health disaster of international concern and the diseases demands collective response [82]. Over the past four decades, Ebola virus infections are reported periodically, but, as far as the mortality is concerned, early 1990s outbreak was the most worst and reported in Congo, Sudan, Uganda, Gabon and Congo-Brazzaville. However, the recent outbreak is undoubtedly a surprise and unpredictable because the virus was silent for last 13 years 1980 to 1993 [83-89]. The interesting fact that the infected virus is different from outbreak to outbreak and country to country, for instance, the first outbreak was reported in 1976 in Congo and Sudan which is caused by two distinct species of Ebola viruses [90]. The vast diversity of the virus population and availability of wide range of hosts, both human and non-human primates are the major reasons for the frequent outbreaks in Africa [91].

Overall, in between 1976 and 2014, twenty-four were reported and the virus captured the attention due to the high fatality rate, which is estimated as more than 90% in each outbreak [92]. The mode of transmission is another advantage; Ebola could

transmit through simple contact of blood, body fluids and skin of the infected patients, even after the death because the Ebola victims are most contagious after death and the viral load in the blood is high [93-96].

There are no FDA approved treatments or vaccines available to prevent the disease. However, the life-threatening virus enforces the necessity of developing new vaccine candidates. Several vaccines are being tested and reported immune side effects; therefore, improvement is needed with better outcomes. Peptide vaccines are one of the possible options, which combine the desired immune response with minimal side effects. Abu-haraz AH et al. conducted a study to develop multi-epitope peptide prediction by using immunoinformatics approaches and successfully reported three epitopes as peptide vaccines for B cell against Sudan Ebola Virus, for which *in vivo* and *in vitro* clinical validation is required [97]. We have strong molecular knowledge on the virus but there is no potential vaccine or remedy developed yet. By using the molecular approaches, Dash et al. attempted to develop an epitope based peptide vaccine against Ebola. It used a combination of B-cell and T-cell predictions followed by molecular docking and dynamic stimulation approach. The study reported a potential peptide region HKEGAFFLY (ranging from 186 to 220 and the sequence HKEGAFFLY from the positions of 154-162) which helps in development of potential defensive system against EBOV [98]. In many cases, Virus like particles and recombinant viral vectors provided potential vaccine candidates, with this advantage; Schwenecker et al. constructed a modified vaccinia virus Ankara-Bavarian Nordic® to generate Ebola like virus particles. Moreover, the study successfully reported that the MVA-BN-EBOV-VLP efficiently induced EBOV-specific humoral and cellular immune responses in vaccinated mice [99]. This study provides basic knowledge on development of multivalent virus like particle modified vaccine candidates. Of course, very few studies reported positive note on vaccine development; various approaches such as plant made vaccines [100], viral vector and dose dependent cell dynamic models [101], transcriptomic analysis [102], and genomic-based vaccine development [103] are under clinical trials and hopefully passed the clinical validations. In a technical point of view, approaches that are available to develop vaccines for emerging infectious diseases are not effective and sustainable; however, the advent technologies offer opportunities to develop new vaccine candidates. So far, independent researchers, private sector, national and international organizations have made several attempts to develop vaccines against emerging diseases such as Ebola, but there is a need for global governance to make attractive global approach [104].

Translational Approaches Raising the Hope

As discussed above the available techniques and methods to treat the infectious diseases are effective but not sufficient because most of the pathogens are getting resistance to the drugs and changing the genetic compositions rapidly. This clearly indicates that the need of integrated approaches to

understand the basic concepts that could convert to clinical applications to improve the patient care. Over the past two decades, we witnessed technological evolution in science after the development of high throughput technologies and next generation sequencing methods. Genomics, proteomics, metabolomics and bioinformatics tools have become predominant in analyzing and applying large data to solve the biological questions [105]. The aim of translational research strategy is to combine the basic research results with high throughput technologies by which the clinical infectious disease practice improve the disease management [106]. In recent times, the molecular genomics approaches and microRNA-based studies reported promising methodologies in infectious disease treatment more particularly in virus based infectious diseases [107,108]. The early 21st century has seen remarkable developments in infectious diseases treatment methods in combination of technology and computational methods. Genomics, bio-informatics and systems biology improved the opportunities in understanding the complex biological systems *in vivo*, *in vitro* and *in silico* models which are creating more opportunities and raising the hope for multifaceted future research [109,110].

Conclusion

Epidemic and pandemic infectious disease events have been evident throughout the known history of human succession. Progress in medical science has made us less vulnerable to their devastation now-a-days. In many countries, standard operating procedures and protocols for data exchange, during the outbreak are not settled between human and animal health services. Therefore, vaccine designing for vector transmitted diseases should be targeted through common procedures and protocols, which further will help in disease related data exchange and proper understanding of the disease. Nonetheless, human and veterinary health professionals fail to acknowledge and understand the correlation between human and animal health. The effective treatment, control and eradication of these diseases require an interactional understanding between humans, animals and the environment. By learning, threats, which are posed by emerging infectious diseases, could be reduced.

The high-end technological approaches used to combat infectious diseases are getting more improvised with time and awareness. Individual concern is playing a critical role in preventing and controlling infection. Though, therapeutic care for critical infectious diseases are providing appreciable assistance in recovery and eradication of causative agent but, self-health concern holds the key to secure life from such epidemiological issues. Medicine can only provide limited measures for a particular disease but a healthy immune system is always considered as the best defense ever.

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