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PAPER ID: PMC6090158

TITLE:
Position Paper on Road Map for RNA Virus Research in India

ABSTRACT:
The Indian subcontinent with its population density, climatic conditions, means of subsistence, socioeconomic factors as well as travel and tourism presents a fertile ground for thriving of RNA viruses. Despite being pathogens of huge significance, there is very little focus on research into the biology and pathogenesis of RNA viruses in India. Studies on epidemiology and disease burden, risk factors, the immune response to RNA viruses, circulating virus strains and virus evolution, animal models of disease, antivirals and vaccines are strikingly absent. Emerging RNA viruses such as Zika virus, Nipah virus and Crimean-Congo haemorrhagic fever virus are a matter of grave concern to India. Here we summarize the outcome of the India|EMBO symposium on "RNA viruses: immunology, pathogenesis and translational opportunities" organized at Faridabad, National Capital Region, India, on March 28–30, 2018. The meeting focused on RNA viruses (non-HIV), and both national and international experts on RNA viruses covered topics ranging from epidemiology, immune response, virus evolution and vaccine trials concerning RNA viruses. The aim of the symposium was to create a road map for RNA virus research in India. Both concrete and tentative ideas pointing towards short-term and long-term goals were presented with recommendations for follow-up at government level.

RNA viruses:
RNA viruses are amongst the most versatile and complicated pathogens in terms of genetic material and evolution, modes of transmission to various hosts, and persistence in the environment. The diversity of genome architecture and replication strategies by the error prone RNA polymerase drives virus evolution at an unprecedented rate as the viral genomes thrive as quasi-species continuously adapting in response to the host environment (Vignuzzi et al., 2005). Some RNA viruses can exhibit broad host tropism and are known to have the highest propensity to cross species barriers (Geoghegan et al., 2017). This further expands the host range and facilitates emergence of new virus types that cause new diseases, some with the potential to occur as outbreaks and epidemics. Vectors and animal carriers ensure persistence and endemicity of many RNA viruses in most of the tropical and sub-tropical regions of the world. Despite the high disease burden, most of the Low- and Middle-income countries (LMIC), including India, have not invested enough in research and development on RNA viruses. There is very little information on epidemiology and disease burden, risk factors, and the immune response to these viruses in diverse human and animal populations in India. A symposium on "RNA viruses: immunology, pathogenesis and translational opportunities" funded by the European Molecular Biology Organization and Wellcome Trust–Department of Biotechnology India Alliance was organized at Faridabad, National Capital Region, India, on March 28–30, 2018 (http://meetings.embo.org/event/18-rnaviruses). The symposium hosted 6 national and 11 international speakers and chairs, and the participants were from diverse research areas such as virology, bioinformatics, immunology, clinical research, cell and molecular biology, epidemiology, diagnostics and clinical research (please see meeting program in Supplementary Information). Interactive sessions and panel discussions were held to critically analyze the status of RNA virus research in India, the challenges in initiating translational research programs and to explore the way forward. This article presents the outcome of these discussions, which could act as relevant information for funding agencies, institutional leaders and policy makers in India.

Global situation ::: The public health burden of RNA viruses:
About 2/3rd of the global population lives in arbovirus-endemic zones and are under risk of exposure to dengue virus (DENV), Zika virus (ZIKV), Chikungunya virus (CHIKV), yellow fever virus (YFV) and/or Japanese encephalitis virus (JEV). DENV alone causes around 60 million apparent cases every year (Stanaway et al., 2016). ZIKV has re-merged in South America and recent reports indicate that changes in the genome have rendered the current circulating strains more virulent (Yuan et al., 2017). A single mutation in CHIKV envelope has enabled replication in a new vector Aedes albopictus, thus increasing its geographical range (Tsetsarkin et al., 2007). Enteric RNA viruses such as rotavirus and norovirus continue to be major etiological agents for childhood

diarrhea. Most cases of mild and severe respiratory illnesses are by RNA viruses. Respiratory syncytial virus (RSV) is a leading cause of severe pneumonia in children under 2 years of age with close to 33 million infections in 2015 (Shi et al., 2017). The annual epidemics of influenza and the pandemic potential of influenza viruses remain a constant threat. In addition, viruses such as Ebola virus, Crimean-Congo haemorrhagic fever virus (CCHFV) and Middle East respiratory syndrome coronavirus (MERS-CoV) have the potential to lead to outbreaks.

Indian situation ::: The public health burden of RNA viruses:
The burden of viral infections is either not estimated thoroughly and consistently, or is hugely underestimated in India. DENV alone is estimated to cost around $1 billion in terms of annual economic burden (Shepard et al., 2014) and there is no real estimate for infections caused by other RNA viruses such as Chikungunya, influenza, respiratory and enteric RNA viruses. Emerging RNA viruses such as ZIKV, Nipah virus, Chandipura virus, and CCHFV are also a matter of grave concern to India. Tropical weather conditions, poor sanitation and personal hygiene, dense population and lack of prophylactic and therapeutic options primarily contribute to year-round outbreaks and establishment of endemicity for many RNA viruses. Many reports have indicated widespread co-infections but the true impact of co-infections across age groups remains to be determined.

Strengths ::: RNA virus research in india:
India now ranks fifth in global research publication output. Vaccine research and development in India is making steady progress, which is evident in the number of product licensures in the last 7 years and the candidate vaccines that are under development (Bhandari et al., 2014; Singh et al., 2015; Dubey et al., 2017; Kulkarni et al., 2017a,b; Sutton et al., 2017; Ramasamy et al., 2018). India now produces more than 60% of the world's vaccines and is a member of the governing council of International Vaccine Institute, with a commitment of US$500,000 every year. The Biotechnology Industry Research Assistance Council (BIRAC) of the Department of Biotechnology has started many initiatives to support research programs on new vaccines and many new programs under BIRAC are nurturing industry-academia partnerships. Similarly, increasing investments by the Indian Council of Medical Research and the Department of Science and Technology have had a significant impact in this direction. The last 10–15 years have seen the establishment of a number of world class educational and research institutions such as the Indian Institute of Science Education and Research (IISERs), Translational Health Science and Technology Institute, National Institute of Biomedical Genomics and National Institute of Animal Biotechnology in addition to several new All India Institute of Medical Sciences and the Indian Institute of Technology. Therefore, the time is apt for creating a roadmap for research on infectious diseases caused by RNA viruses in India.

Challenges ::: RNA virus research in india:
The challenges for RNA virus research in India are manifold and the bottlenecks, which are further elaborated in this section, could also be relevant for other LMICs.

Enabling translational research ::: RNA virus research in india:
As compared to the western countries, developing countries like India have been sluggish in building consortia of translational researchers, establishing translational research institutes and funding translational research programs. Although some of the young Indian institutes and researchers are developing research programs with translational outcomes in mind, there is a need to build an enabling ecosystem. For example, as elucidated in Figure 1, translational research program in virology with antiviral or vaccine development as an outcome would require well-designed, sustainable partnerships for:
○ rational design, optimization and development of immunogens based on the knowledge of epitopes involved in viral entry, molecular interactions, and antigen presentation.○ generating definitive knowledge on immune responses that confer protection vs. those that do not.○ robust assay platforms that are validated with reference reagents for diagnosis, surveillance, molecular epidemiology and immune responses.○ reliable estimation of disease burden from well-designed surveillance studies.○ delivery platforms that determine the breadth and longevity of immune responses.○ robust manufacturing partners who have low-cost manufacturing capabilities complying with GMP norms and with technical know-how for scale up.○ stable clinical trial

partners who have a thorough knowledge of regulatory requirements starting from Phase I to post-licensure activities.
As a case in point, development of novel and indigenous vaccine candidate against Dengue (Ramasamy et al., 2018) began in 2009, and, assuming safety and immunogenicity, Phase III trial results are likely to be announced in 2021 or later. Similarly, work began on the structure-guided rational design of candidate influenza vaccine in 2007 and focused and steady progress has led to completion of proof-of-concept studies in animals recently (Bommakanti et al., 2010; Mallajosyula et al., 2014; Sutton et al., 2017). On the other hand, the development of the classical rotavirus vaccine started with an observation in the mid-1980s, and could only be accomplished through a large international consortium working together for over three decades (Bhandari et al., 2014). Thus, enabling translational research, in general, requires a concerted effort, sustained funding and institutional support. Therefore, institutions and funding agencies need to redesign the evaluation and input mechanisms for projects which have translational outcomes as the end point. This is a huge challenge as the investment involved is large and with no short-term outcomes or guaranteed success.

Way forward ::: RNA virus research in india:
The group of experts at the India|EMBO symposium on RNA viruses debated and recognized the challenges of running sustainable translational program in India and other LMICs. The group also felt that India has unique capabilities and resources to address these challenges and can set an example for other resource-constrained nations. The expert panel and other participants discussed various problems and suggested the following practical solutions that could be implemented as we go forward.

Conclusion:
The world today is a single tribe, and viral infections need to be viewed from a global, regional and national perspective. Examples of severe acute respiratory syndrome (SARS), chikungunya and Zika have shown us that viral infections can be local today and global tomorrow. Combating viral infections and outbreaks therefore requires a truly global effort. The community of scientists and concerned professionals must work together with single mindedness to prevent human suffering. We must build capacity and capability in LMICs that are often the most vulnerable to viral infectious diseases, outbreaks and epidemics. India has taken a positive step in partnering with the Coalition for Epidemic preparedness Innovations (CEPI) to anchor a key program for preparing India against emerging viruses. Funding agencies should believe in the philosophy of sustained investment in knowledge and should be actively involved in exchange of ideas with researchers. The leadership of institutions and funding agencies should lend more coherence to the scientific enterprise and provide better direction for utilization of existing resources. We believe these efforts will enhance India's contribution to knowledge generation and innovation in the global RNA virus research arena.

Conflict of interest statement ::: Author contributions:
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.