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Significance of Insilco Approaches in Finding Novel Biomolecules Challenging Newly Emerging, Resurging, Deliberately Emerging Global Outbreaks

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Abstract: Pandemics are large-scale outbreaks of contagious disease that can significantly raise ill health and promote death. Pandemics can spread through, wide range of geographical areas across the globe and capable of disrupting social and economic status of the countries affected. With the scientific testimony available it is evidenced that the rate of occurrence of pandemics has been drastically increased over the last two decades and presently witnessing the impact of COVID-19 disease globally. Anthropogenic activities such as urbanization conditions, increased global travel, abnormal land usage, exploitation of natural environment, are some of the significant causative factors that promote the rate of occurrence of pandemics. Rapid spread of SARS-CoV-2 virus highlighted the importance such as, be ready for any imminent event, need of detecting new bacterial & viral pathogens at initial stages of contagion and focus on the risk elements that promote the occurrence & spread of the outbreaks to humankind. It is evidenced from the literature that, there is a great demand to institute the methodological process using smart approaches such as Insilco based studies to investigate the emergence of future pandemics. Globally there is a great demand for the robust and efficient procedures to develop novel biomolecule in quick period. With this significance, the present paper aimed to survey the occurrence of global pandemics and the applications of Insilco methods in identifying newer routes to develop novel biomolecules in challenge the existing, newly emerging, resurging, deliberately emerging global outbreaks.

Keywords: Global outbreaks, Emerging, Resurging, Deliberately emerging pandemics, Insilco approaches, Novel biomolecules.

Introduction

Humankind witnessed fighting against numerous diseases caused by the deadliest pathogenic microorganisms from the centuries. Pandemics question not only the health but also the economics of the affected countries at exceptionally large scale. Noticeable number of pandemics are re-emerging after a certain period, different countries at global level owing the history of occurrence and spread of more than two pandemics at similar time period. Certain number of Pandemics that have occurred in past few centuries globally have been mentioned in the Fig 1 (Piret and Boivin, 2021). COVID-19 disease is caused by the virus severe acute respiratory syndrome–corona virus 2 (SARS-CoV2) (WHO). The disease found to be transmitted from the person-to-person in the form of droplet aerosols. COVID-19 disease has enormous impact on the global economy. In the year 2019 GDP of the globe was calculated as 87.55 trillion U.S. dollars, indicates a 4.5% decline in the economic growth. This causes the loss of 3.94 trillion U.S. globally. As on today more that 230 million people are tested positive and reported more than 4.7 million deaths globally against the COVID-19 pandemic. Pandemics

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influenced several people across the globe and caused the loss of their families. Existing, newly emerging, resurging and deliberately emerging global pandemics was discussed in the Table 1.

Table 1. Details about pandemics occurred in past few centuries

SL No	Continent	Newly Emerging	Resurging	Deliberately Emerging
1.	North America	Enterovirus D68, Heartland virus, Cryptosporidiosis, 3N2v Influenza, Cyclosporiasis, <i>E. coli</i> O 157:H7, Bourbon virus, H1N1 Influenza Hanta Pulmonary Syndrome	Powassan Virus, West Nile Virus, Measles, Human Monkey Pox, Listeriosis, Lyme Disease, Adeno Virus, Chikungunya, Acute Flacid myelitis, Dengue, Cholera, Tuberculosis	Anthrax Bioterrorism
2.	South America	Hanta Pulmonary Syndrome	Zika Virus, Yellow Fever, Cholera	-
3.	Asia	Cryptosporidiosis, vCJD, Akhmeta Virus, MERS Cov, SFTSV bunyavirus, <i>E. coli</i> O 157:H7, H5N6 Influenza, H10N8 Influenza, H5N1 Influenza	Enteno Virus, Cholera, Plague, Tuberculosis	-
4.	Australia	Hendra Virus	Yellow fever, Human, African Trypanosomiasis, Marburg Virus	-
5.	Africa	Hepatitis C, HIV, Human Monkey pox Ebola Virus	Rift Valley Fever, Typhoid Fever, Cholera, Tuberculosis	-

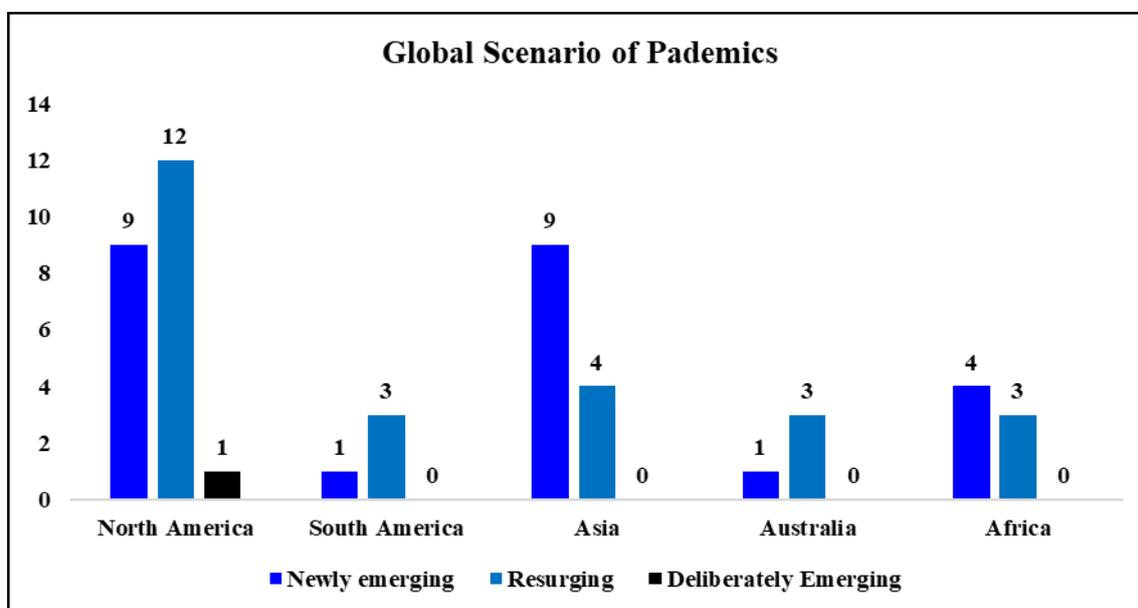


Figure 1. Distribution of pandemics on a global scale

Pandemics are also responsible for the economic loss caused due to the preventive measures such as lockdown. The total estimated economics of earlier outbreaks was mentioned in the literature (Jones et al., 2008; Jing et al., 2021)

- SARS has caused a loss of more than \$40 billion US dollars connected to productivity.
- Influenza pandemic (H1N1) has Caused \$45-55 billion dollars' loss
- Ebola outbreak has caused \$53 billion loss from the economic and social impact of West Africa.

Earliest Pandemics that terrorized people was recorded during 540BC. After 540BC, many pandemics have been recorded. Vector is the medium that plays an important role in transmitting diseases. The vectors that are responsible for spreading different pandemic was represented in the Figure 2. Duration of pandemic depends on pathogen and vector type responsible for causing and spreading disease. Some pandemics such as third cholera pandemic lasted for 17 years while pandemic such as Swine Flu lasted only for 1 year. Details regarding the

duration, of pandemic along with the pathogen responsible for causing the pandemics were shown in the Figure 2.

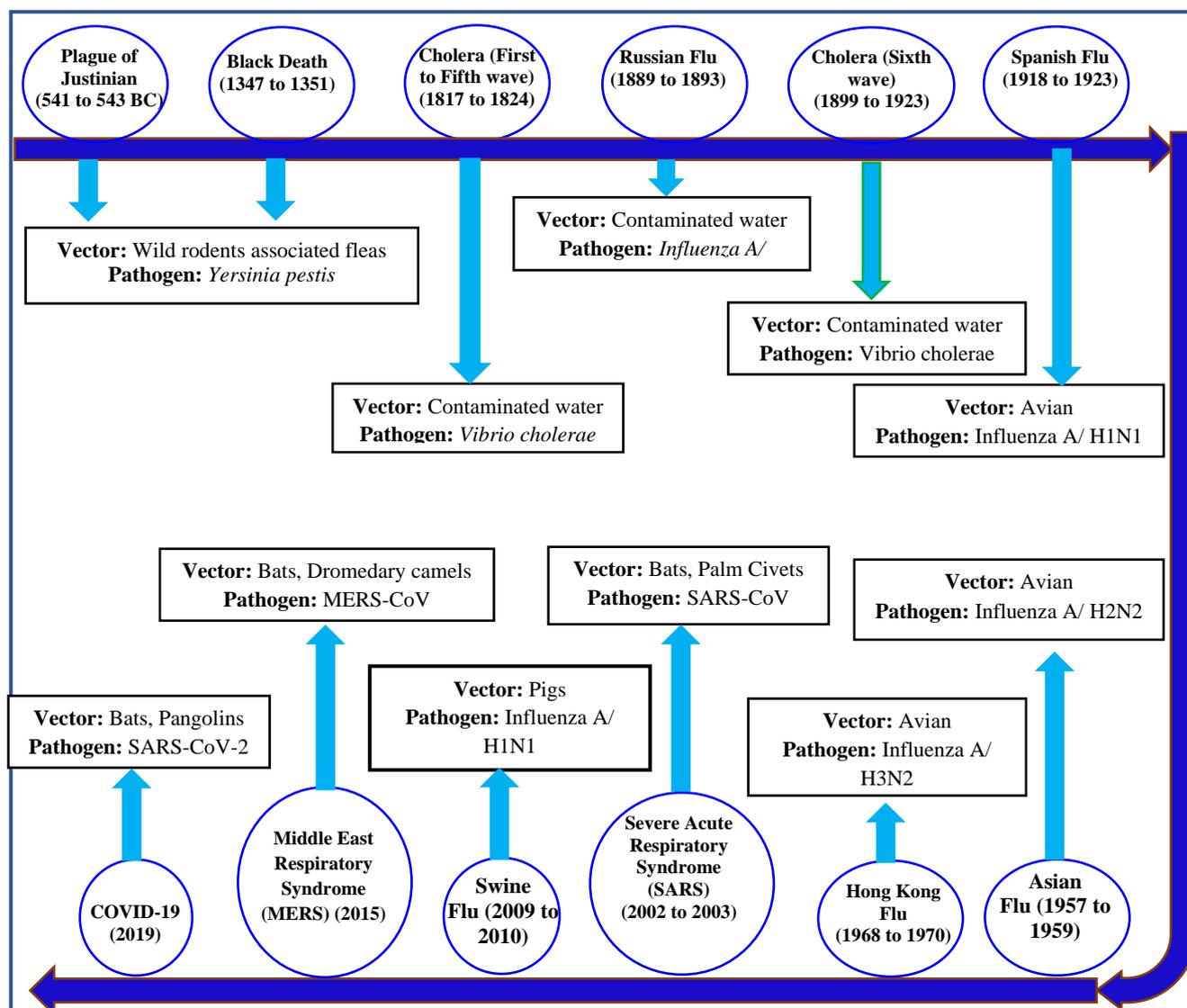


Figure 2. List of pandemics showing period of outbreak, causative pathogens, and vectors

Insilco Approaches to Develop Novel Biomolecules against Pandemics

Epidemiology is essential study to fight against any pandemic, locking down the countries, imposing quarantine and maintaining social distancing and wearing mask some of the very significant preventive measures that are learn from the epidemiological studies (Queralt-Rosinach et al., 2021). The novel coronavirus that became a global pandemic was named COVID-19 by WHO. COVID-19 was one of the potential Zoonotic diseases with a low mortality rate. Transmission of disease from infected to healthy via droplet or contact because of the absence of precautionary measures was indicated as a major health threat to the medical workers. Drugs with the potential to treat COVID-19 were still in the process of being tested for efficacy and safety. Data regarding the travel history of patients with COVID-19 symptoms was a great tool for physicians to control the spread of the disease (Wu Y C et al., 2020). IoT connected sensor technology played prominent role in controlling COVID-19 pandemic providing detailed information on breakdown of the outbreak, tracking of positive cases, quarantining positive cases and in the prevention of viral spread to others. Sensors connected through IoT helped efficiently in the summarization and assessment of data representing the most recent COVID-19 pandemic situation. IoT-connected sensor-based assessment studies of the COVID-19 pandemic data played a major role in preventing the spread of COVID-19, by helping in the process of quarantining the positive cases using a systematic identification system (Sharma & Ahmed 2021).

Vaccines designed to fight against SARS-CoV-2 virus are responsible for the development of several SARS-CoV-2 viral strains. New SARS CoV-2 variant reported in South Africa displayed more resistance to vaccines in comparison to other strains of SARS CoV-2 virus. A research group developed a multi-epitope vaccine to fight against novel strain of SARS-CoV-2 virus. Machine learning and ABCpred tool were used to design the vaccine selecting both T and B cell epitopes that boost potential immunity against structural proteins of SARS CoV-2 virus. Selected epitopes were utilized to develop multi-epitope vaccines and the structure of vaccine was predicted through Raptor tool. Human Receptor Tool Like Receptor (TLR-3) plays a vital role in conferring immune responses against infections. Receptor TLR-3 was docked with a designed multi-epitope vaccine. A stable complex of MEV-TLR3 was formed with binding score of 363.18 kJ/mol. Molecular dynamics studies was carried out on Human Receptor TLR3 and multi-epitope vaccine complex. Results displayed the potential application of MEV against novel strains of SARS-CoV-2. Multiepitope vaccines can be the key in fighting novel strains of SARS-CoV-2 virus (Humayun et al., 2022).

After the initial COVID-19 cases, many vaccines were developed to fight against SARS-CoV-2 infection and halt spreading of COVID-19 cases. A research study aims to develop a vaccine based on a coherent immunogenic peptide from the structural proteins of the SARS-CoV-2 virus. Sequences of four structural proteins of SARS CoV-2 virus namely envelope protein (E), nucleocapsid protein (N), membrane protein (M), or spike protein (S) were obtained from databases to develop immunogenic peptides against SARS CoV-2 virus. 14,441 protein sequences collected from the database were used to design 68 epitopes of E protein, 174 epitopes of M protein, 245 epitopes of N protein, and 833 epitopes of S protein. The designed epitopes were aligned with Major Histocompatibility Complex (MHC) or B-cell receptors (BCR) and epitopes displaying highest binding probability were selected. Insilco antigenicity studies conducted on selected epitopes yielded 16 antigenic epitopes and were further subjected screened for physiochemical properties and allergenicity, one epitope for E, N, and M protein and two epitopes for S protein were selected based on the results. Molecular modelling was utilized to determine the coordinates of epitopes in the 3D protein structure. Allelic protein sequences of MHC-I and MHC-II were docked with selected epitopes. Compared to other epitope-MHC complexes, epitope-Human Leucocyte Antigen (HLA)-B*3501(MHC-I allele) and epitope-HLA-DRB1*04:01(MHC-II allele) complexes conceded better results. The selected epitope displayed conserved sequences of novel SARS CoV-2 which can be used for developing different types of the vaccine in the future (de Araújo et al., 2022).

A novel process was developed utilizing Immunoinformatic tools to design an epitope-based vaccine with spike protein as the target to fight against SARS Cov-2. viral infection. The said vaccine was safe for people with immunocompromised conditions situated globally (Chukwudozie et al., 2021). A polyvalent vaccine was developed testing multiple combinations of T and B cell epitopes against the disease COVID-19, and the vaccine developed is predicted to stimulate both humoral and cell-mediated immune responses in the human system against the virus SARS Cov2. The study reported that the multivalent vaccine developed own utmost viability due to the distinctive features like responsiveness, safety, and efficacy (Sarkar et al., 2021). In last two decades, world witnessed the frequent occurrence of viral pandemics. Pandemics such as SARS occurred in the year 2003 and the most recent COVID 19, both outbreaks emerged from the wildlife market of the country china (Daszak et al., 2020). An unsupervised feature extraction (FE) method implemented through Tensor decomposition (TD) technique was applied to screen the impact of selected drugs on the gene expression pattern of Covid-19 infected lung cancer cell lines. The therapeutic candidate i.e. Ivermectin discovered through the TD method yielded a change in the expression pattern of 163 genes that were chosen for the study. Ivermectin in comparison with other repurposed drugs screened shown very promising results as a therapeutic candidate in the treatments of the disease COVID-19 (Taguchi & Turki 2020).

The outbreak of Coronavirus was declared a pandemic by World Health Organization (WHO). The response to the virus outbreak varied from country to country. Delay in detecting and responding to pandemic cases was a burden on local paramedics in China and other countries. During the early pandemic period, some nations have maintained lower pandemic cases by following proper quarantine policies. Strategies like quarantine, city lockdown, detection of infected cases, isolation of infected cases, contact tracking, and isolating persons exposed to infection were observed to be effective measures in controlling the disease spreading rate. The different responses of various countries in controlling pandemics yielded diverse results studied in this paper. Responses provided by other countries towards the pandemic were the basis for India's response to the pandemic. The above measures were useful in preventing the spread of the pandemic. Efficient detection of disease symptoms can prevent the pandemics in future (Khanna et al., 2020). Vaccine development was required to control SARS-CoV-2 infection which led to COVID-19 pandemic. Vaccines based on T-cell epitopes were more effective against SARS-CoV-2 infection. Many strategies were analyzed to improve the prediction of T-cell epitopes. Incorporating the reaction of T-cell against SARS-CoV-2 virus in process of designing vaccine was vital to understand full potential of T-cell immunity against SARS-CoV-2 virus. Discovery of binding

motifs of HLA class I for T-cell antigens have yielded algorithm development for epitope identification. Restricted Epitopes of HLA class I molecules were predicted through in-silico method to develop vaccine against infectious pathogens. Vaccine candidates developed against SARS-CoV-2 virus through above mentioned method was in developmental stages. Apart from the development of prediction algorithms, many factors limit growth of such approaches. Overcoming the limitations of algorithms can become key of designing more efficient vaccines (Silva et al., 2020).

COVID-19 was caused by SARS-CoV-2 virus in early 2019. As a result, many vaccines were developed to fight against SARS-CoV-2 virus. Vaccines designed against SARS-CoV-2 virus initiates the production of antibodies inside human body. Immunocompromised person fails to produce sufficient antibodies; hence general vaccine is less effective against SRAS-CoV-2 infection. Immunodeficiency can be caused due to conditions such as Diabetes. Present paper discusses development of vaccine against SARS-CoV-2 virus for people with low immunity against infections. Several vaccines developed against SARS-CoV-2 virus were undergoing clinical trials (Aghbash et al., 2020).

Table 2. Review pertaining to the prediction strategies of global pandemics

Sl NO	Authors	Highlights	Prospects
1.	Sharma & Ahmed, 2021	Internet of things (IoT) and sensors have played an essential role in visualization of COVID-19 pandemic information, breakdown of the epidemic, virus spread and controlling infection in real time tracking of confirmed cases and tracking of prevention level.	Novel Drugs, & vaccine development
2.	Queralt-Rosinach et al. 2021	Epidemiology is essential to fight against any pandemic, locking down the countries, imposing quarantine and maintaining social distancing and mask wearing are learn from epidemiological studies.	Study of New strains of SARS CoV.
3.	Chukwudozie et al. 2021	Discussed novel approaches in predicting SARS-CoV-2 epitope peptide-based vaccine targeting the spike protein, utilizing immune informatics tools and immune simulation measures. The protective vaccine for immuno compromised patients globally	Limited to only SARS-CoV-2
4.	Thoradeniya and Jayasinghe, 2021	Insights on conceptualizing and understanding the generation of pandemics and addressing their determinants help for prevention strategies against occurrence of future events	Early treatment option using novel drugs
5.	Sarkar et al. 2021	Represented epitope based polyvalent vaccine containing multiple T & B-cell epitopes expected to provoke both humoral and cell mediated immune responses within the body. Developed polyvalent vaccines were quite safe, effective, and responsive.	Limited to HCoV
6.	Daszak et al. 2020	SARS emerged in 2002-2003, again SARS nCov in 2019, both disease outbreaks originating in china significantly linked to wildlife markets, an obvious target for control programme to prevent future epidemics and pandemics	Need of prediction strategies to prevent future epidemics
7.	Khana et al. 2020	A delay in detection and response leads to overspreading of the pandemic globally. Some restrictions like social distancing, lockdown, case detection, isolation, contact tracking, and diagnosis of quarantine of exposed had revealed the most efficient actions to control the disease spreading	Need of prediction strategies to prevent future epidemics
8.	Taguchi and Turki, 2020	Study applied tensor decomposition (TD) based unsupervised feature extraction (FE) method to gene expression profiles of multiple lung cancer lines infected with SARS-CoV2. They identified drug candidate compounds that significantly altered the expression of the 163 genes selected by TD-based unsupervised FE. Numerous drugs were successfully screened, Ivermectin is one of the drugs screened and identified.	Need much focus on novel vaccine development

Discussion

The frequency of occurrence of global pandemics in last two decades alarm the importance of finding novel drugs to handle particularly viral outbreaks. It is evidenced from the literature that there is a great demand to institute the methodological process using smart approaches such as ML- based data mining methodologies to study the emergence of future pandemics. Globally there is a requirement for the robust and efficient procedures to develop novel biomolecule in short period of time.

- There have been an increasing number of high threat pathogens emerging and reemerging in recent years, the latest being SARS-CoV-2,
- There is no sophisticated research to predict the frequency and occurrence of pandemics.
- There is significant need in robust surveillance and early actions for rapid detection as well as rapid drug or vaccine development.
- There is no efficient therapeutics, which can address the pandemics.
- Vaccines and drugs can be available, but the process of development is time consuming.

To address these points, it advised to focus more on applying ML based data mining methods and Insilco methods in conducting through research on

- Epidemiology studies of Pandemics
- ML based Datamining approaches to predict the occurrence of global pandemics
- Epitope mapping studies of deadliest Pandemics
- Epitope-focused vaccine design to develop novel drugs

Detailed literature study envisaged the most important points such as, epidemiology studies of pandemics (Morabia, 2020), ML based data mining approaches to predict the global pandemics (Muhammad et al. 2021, Fadhil & Jaleel, 2022), epitope mapping of viral pandemics (Sikora et al. 2021, Colitti et al. 2022), Epitope-focused vaccine design to develop novel drugs (Correia et al. 2014 & Hussein et al. 2021) is the possible approach to develop novel drugs to fight against the global pandemics

Conclusion

Present paper aimed to survey for a robust prediction method to assessment the global pandemic and further to use Insilco methods to find novel epitopes in order to identify the new routes to develop a novel biomolecules in challenging the existing, newly emerging, resurging, deliberately emerging global outbreaks

Scientific Ethics Declaration

The authors declare that the scientific ethical and legal responsibility of this article published in EPSTEM journal belongs to the authors.

Acknowledgements or Notes

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