The next pandemic – background research for potential pathogen

PathogenType: The family of picornaviruses (*Picornaviridae),* are well-known to cause asymptomatic to fatal disease, from rashes to encephalitis, in children less than 5 years of age (1). These viruses are non-enveloped and have small, non-segmented, positive sense, single-stranded RNA genomes and a capsid. Human picornaviruses include the genus Enterovirus which includes, the coxsackieviruses, the poliovirus, rhinoviruses (A-C) and the moniker- enteroviruses (A-D) referred to as EVs henceforth. Historically, picornaviruses were the first viruses studied, the quintessential Salk's inactivated and Sabin's attenuated vaccines were developed based on culturing the poliovirus. Perhaps the complacency ensuing the near-eradication of poliomyelitis following a successful vaccination program has relegated the picornaviruses to a ‘manageable’ status. There are several reasons to accommodate picornaviruses, specifically EVs, at the top of the list of serious threats.

EVs have a very high mutation rate, one of the highest among RNA viruses as the enzyme, RNA-dependent RNA polymerase (RdRp), lacks proofreading leading to error-prone replication (2). Additional variability is afforded by RNA recombination that allows for the exchange of genetic information between viral genera and even families, this is believed to have caused the emergence of pathogenic vaccine-derived poliovirus and increases the probability of expansion of its viral host range(3).

EVs are very common in developed and developing countries and have caused several outbreaks. We envisage the coming together of several factors in fomenting an EV outbreak, which utilizes the versatility of the various modes of transmission they employ, including faecal-oral, oral-oral and respiratory droplets(4). While rhinoviruses are most successful airborne, some enteroviruses like EV-A71 and EV-D68 can use multiple modes of transmission (5-6).

Origin&EmergenceDetails: There is limited surveillance and medical facilities in illegal, poorly managed factories like the cattle ranches that have cropped up to replace large areas of the Amazon forests. EV-D73 would develop different modes of transmission circulating in a vulnerable population living in congested spaces, accumulating mutations, while remaining undetected. These mutations could change modes of transmission or virulence.

Since EVs are known to be able to infect humans and animals(10), it is likely that feral or pet animals act as repositories of the virus. It has been noted that seasonally EVs may have a higher transmission rate(11) and they survive longer on surfaces(12) there is the possibility of increased transmission during hot and humid months, often peak times of travel to the tropics in the southern hemisphere.

PathogenCharacteristics:

EV-A71 would be a close prototype of the EV-D73 we propose could cause the next pandemic. EV-A71 infection can be asymptomatic or manifest flu-like symptoms and is one of the most common causes of hand foot and mouth disease (HFMD)(5,7) . However, it can also cause serious neurological and cardiopulmonary complications, including meningitis, acute flaccid paralysis, brainstem encephalitis, and fatal myocarditis in children (8). A study revealed that non-vector-borne, non-enveloped, non-segmented viruses have the highest probability of sustained human–human transmission, irrespective of the mortality rate caused by the infection(9) . EVs check all of these boxes and we envision EV-D73 to behave as is predicted based on these characteristics, with complex neurotropism.

EVs have various methods through which they can infect the brain, the most intelligent is what is the ‘Trojan Horse’ route. In this, the virus first infects immune cells circulating in the periphery and crosses the blood-brain barrier (BBB) undeterred by the barrier. This immune surveillance system uses leukocytes to patrol the cerebrospinal fluid and the meninges, and provides passage to some viruses like EV-A71, which can bind

receptors on these cells and get engulfed (through receptor-mediated endocytosis). Once inside the cell, it hijacks host cell machinery to make more copies of itself(4,7). Postulating a similar mechanism for EV-D73, invasion of neurons in the developing CNS could lead to neural death and neuronal degeneration, causing inflammatory damage via cytokine release, eventually pulmonary edema and cardiac failure. Generally, viral infections take a severe turn because of cascade reactions following high inflammatory response, leading to fatal tissue damage. EV-A71 and some coxsackieviruses are known to have a propensity to target neural progenitor cells and astrocytes in infants and a similar propensity in EV-D73 could lead to long-term neurological sequelae and delayed development(8).

Concomitant to neuropathy and fatality in young children, EV-D73 would have the potential of causing neurological symptoms in adults with its ability to infect CNS via the Trojan route. Recently, the picornavirus parechovirus or the Ljungan virus was detected in the brain tissue of patients with Parkinson's in dopamine-producing neurons of the substantia nigra(13). Additionally, CNS infection by enterovirus has been linked to depression(14).

OtherImpactingFactors:

While mental health awareness and avenues of treatment have risen internationally, the causes of the various spectrum of disorders are far from understood and treatments focus on symptomatic relief. Ranging from socioeconomic stress to migrations and instability caused by climate change depression has a wide range of environmental risk-factors.The question remains about how much importance is given to treating the root, molecular causes in addition to these stressors and treatment directed towards them. As its effect on productivity and the bottom line are felt(15), there is the possibility of mental non-conformities, following pandemics like COVID-19, being labelled as disorders and large-scale corporatization of the mental health field(16).