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Eradication of Viral Diseases, A Time to Rethink During the Covid Pandemic; Focusing on Smallpox

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ABSTRACT

Eradication of viral pathogens is an arduous task. We have all seen how Covid-19 forced the entire world into a standstill during these preceding two years. Not much success has been achieved in the past to eradicate such pathogens. The miraculous eradication of Smallpox was only possible when all of the health determinants - sociological, biological, political will, synergised together towards the elimination of one specific microorganism from the globe. This article critically takes into account every contributing factor which led to this mammoth achievement in the international public health domain and the difficulties faced in recreating it for other viral pathogens, especially for coronavirus, the current pathogen of concern.

Keywords:- (virus ; smallpox ; coronavirus ; vaccination ; antiviral drugs ; eradication ; elimination ; disease surveillance)

Introduction : -

Humankind has been fighting multiple viral diseases before the human species had even evolved into its modern shape . In some cases of viral infection , antiviral drugs & vaccination have allowed us to keep these deadly infections in check, simultaneously helping patients recover. Smallpox is the only one infectious disease, we as a society have been successful in eradicating it. Humans have come a long way , fighting viruses but the trophy is still very far, still achieving viral eradication is like a dream. In the past decades , there have been various viruses that have skipped from animals to humans and triggered large outbreaks , resulting in thousands of deaths. As smallpox is the only viral disease that has been eradicated successfully , most of the article focuses on it only . Smallpox is believed to have killed at least half a billion people in the last century, whereas all the wars on the planet during that time killed perhaps nearly 150 million. [1]

Smallpox is undoubtedly a debilitating and contagious disease. As per the National Institute Of Allergy and Infectious diseases, before 1980, the disease killed 30 out of every 100 people who became infected. The remarkable eradication of Smallpox was a monumental work by exceptional public health professionals. [22] They belonged to all geographical boundaries, came from all walks of life, from top executives at WHO, CDC or national administrators to village health workers who could not read or write but could identify smallpox faster than medical physicians practising modern medicine in even developed nations.[2]

It was only possible when multifarious determinants of health - sociological, biological & political will, each of them synergised together towards elimination of the one specific pathogen. [3] This work will critically review every factor which led to this mammoth achievement in international public health and why is it so difficult to replicate it for other pathogens. The coronavirus which the world today is suffering from is very different from smallpox. We are condemned to repeat the mistakes of the past by not learning from it. The implications for the current coronavirus and future pandemics are vital to understanding. [2]

The Determinants:-

The virus & its genome

TABLE :- Factors influencing vaccine response[4]

INTRINSIC HOST FACTORS	**PERINATAL HOST FACTORS**	**EXTRINSIC FACTORS**	**BEHAVIORAL FACTORS**
• AGE • GENDER • COMORBIDITY • GENETICS	• GESTATIONAL AGE • BIRTH WEIGHT • BREASTFEEDING • MATERNAL ANTIBODIES • MATERNAL INFECTIONS DURING PREGNANCY • OTHER MATERNAL FACTORS	• INFECTIONS • PARASITES • ANTIBIOTICS • PREBIOTICS & PROBIOTICS • PREEXISTING IMMUNITY • MICROBIOTA	• SMOKING • EXERCISE • ALCOHOL CONSUMPTION • SUBSTANCE ABUSE • ACUTE PSYCHOLOGICAL STRESS • CHRONIC PSYCHOLOGICAL STRESS • SLEEP
NUTRITIONAL FACTORS	**ENVIRONMENTAL FACTORS**	**VACCINE FACTORS**	**ADMINISTRATION FACTORS**
• BODY MASS INDEX • NUTRITIONAL STATUS • ENTEROPATHY • MICRONUTRIENTS (Zn, Vit. A, D & E)	• RURAL VS URBAN • SEASON • FAMILY SIZE • TOXINS • GEOGRAPHICAL LOCATION	• ADJUVANTS • VACCINE TYPE • VACCINE DOSES • VACCINE STRAIN • VACCINE PRODUCT	• VACCINATION SITE • VACCINATION ROUTE • VACCINATION SCHEDULE • CO-ADMINISTERED VACCINES • CO-ADMINISTERED DRUGS • NEEDLE SIZE • TIME OF DAY

Smallpox is caused by Variola major, a dsDNA virus belonging to the family of orthopoxvirus. Transmission is by respiratory droplets and somewhat through fomites — bedding and clothing.[19] While smallpox has nearly 30% mortality among unvaccinated and untreated individuals, numerous field investigations suggest that smallpox can only infect humans and does not survive for more than a few months outside the host environment, even under optimal conditions. It was perhaps the best pathogen candidate for disease eradication. [3]

The orthopoxvirus family has other three viruses which can infect humans, which includes: monkeypox, cowpox, and vaccinia, but none of these has resulted in significant epidemics. It is said that Smallpox killed poor peasants and royalty alike. [3] Smallpox in the ancient world always had a catastrophic impact on the "virgin soil" population, often introduced by invaders. As the disease progressed further, with fewer people left in the particular area to sustain the chain of transmission, the outbreak would die out until reintroduced from an infected area. As the population became large enough for the disease to circulate continually, the annual impact of an outbreak was diminished, and it gradually became an infection limited to childhood. [5]

Host factors:-

Host factors can have contributions from behavioural, environmental, and genetic factors. The known host risk factors for smallpox before eradication included physical contact with someone with smallpox infection, direct contact with infected bodily fluids, surfaces and aerosolized particles. The present risk factor is laboratory work with the virus. [7]
Whereas many factors stand out for severe COVID-19, including male sex, older age, cardiovascular disease, obesity, and diabetes. [8]

Replicability:-

FIGURE:- Major Eradication attempts in the past [26]

S.No	YEAR	PROGRAM LEADER	PROGRAM (LOCATION)
1	1801	EDWARD JENNER	SMALLPOX (GLOBAL)
2	1911	WILLIAM GORGAS	YELLOW FEVER (AMERICAS)
3	1915	ROCKEFELLER COMMISSION	YELLOW FEVER (GLOBAL)
4	1950	FRED SOPER	SMALLPOX (AMERICAS)
5	1954	WHO	YAWS (REGIONAL)
6	1955	WHO	MALARIA (GLOBAL)
7	1958	VIKTOR ZHDANOV	SMALLPOX (GLOBAL)
8	1985	PAHO	POLIO(AMERICA)
9	1986	WHO	GUINEA WORM(GLOBAL)
10	1988	WHO	POLIO(GLOBAL)
11	1994	PAHO	MEASLES(AMERICA)

Many preconditions should be met and learned from the smallpox experience for putting a break on disease transmission towards eradication.[9] Firstly fulfilment of the biological conditions of disease eradication is a cornerstone - absence of animal reservoirs. [10,17]

Other essential preconditions will be: -

- Development of an effective tool for interrupting the infection transmission chain
- Disease severity and political commitment from endemic countries.
- A clear strategy and strong management with involvement of all levels of public healthcare
- Equitable distribution of resources globally, as needed
- Continuing research being the guiding force behind policy framing.
- Optimal international coordination
- Highly motivated interdisciplinary team to see the program succeed.

A few biological factors make the potential eradicability of infectious diseases somewhat unlikely but with research efforts, effective tools of intervention — perceivable obstructions can prove to be capable in practice in the near future. [11]

Other Attempts For Viral Diseases Eradication :-

The eradication of smallpox raised hopes that the same could be accomplished for other diseases as well.

- **Yellow fever** eradication efforts didn't succeed much , primarily because it has three transmission cycles: jungle (sylvatic), inter-mediate (savannah), and urban. Hence it didn't have the biological preconditions for eradication, with viral pools re-emerging from the mosquito and primate hosts multiple times . [24,26]

- **Poliovirus** eradication program in the penultimate phase has innumerable lessons that need to be learned. Most importantly, it tells why any feedback into the program strategy is crucial; by continuous analysis of on-site information and adjustment of eradication strategies. From the methods of surveillance networking, adequacy of interventions and reporting to the reformulation of vaccines for the newly detected

strains. Only through sharp and diligent observation, the role of mopping up vaccination was understood in polio eradication. [21,26] . Polio has been either eliminated or reduced in most countries through widespread vaccination programmes , but it still continues to circulate in some parts because (among other causes) many cases do not present easily distinguishable , recognizable symptoms. As a result of which , an infected person can remain neglected and unobserved, yet still spread the virus to others.

- Considering **malaria** , its incidence has been reduced substantially in most parts of the world . It possesses a strong challenge to the old ideas and principles of eradication . It is mostly possible to fall sick with malaria multiple times , although patients may develop partial immunity after numerous attacks. Promising steps in the direction of an effective malaria vaccine has been taken but as of now no effective vaccine exists .

- **Dengue** cases first appeared in the 1950s in asian countries , Thailand and since then it has spread throughout the whole world especially in geographical regions having tropical and subtropical regions of the planet. 4 out of 10 people living on this planet are prone to this viral infection . Each year we have 50-100million dengue patients , as per WHO . Although the death rate for dengue is comparatively lesser than some other viruses . Dengue hemorrhagic fever is something which is very deadly having high mortality rates i.e. around 20% patients die. In 2019, for the age group of 9 -16 years, the US FDA approved a vaccine for dengue . In some parts of the world , an approved vaccine is currently available for those in the age group 9-45 years old, but again , the vaccine recipients must have been infected from a confirmed patient in the recent past . Those who have not been infected with the virus before could be put at a risk of developing severe dengue in the near future .

- With the introduction of the **measles** vaccine, its epidemiology changed rapidly. The frequency and severity of epidemics decreased depending on vaccine coverage and it largely became an infection amongst the susceptible children and older population. The more enormous challenges for measles eradication are twofold. For the industrialised world, measles is not a priority. Secondly, the health infrastructure and health budget among poorer nations are not adequate enough to maintain high vaccination coverage due to the enormous cost of frequent mass immunisations required for measles.[26] Measles disease results in a visible rash, a significant period of time duration elapses between exposure to the viral infection and the development of the rash. Patients become contagious before the rash appears, and it can further spread the virus before anyone realizes that they have the disease.

- Currently there are only two vaccines only to protect young children from a viral disease like **rotavirus**. Among the paediatric population it causes severe GI problems like diarrheal symptoms . This viral disease spreads very rapidly, especially through the feco-oral route . In third world countries and developing nations this viral disease has taken many lives , as rehydration treatments are not much available. As per WHO reports , around 4.5 lakhs of children younger than 5 years of life have lost their lives from this viral infection in the year 2008. With the introduction of vaccines for rotavirus , there has been a sharp decline in cases of hospitalisations and deaths due to the rotavirus.

- For pet animals , **rabies** vaccination was introduced in the 1920s , they have helped a lot in making this deadly disease extremely rare in the developed world. This condition remains a great problem in asian and african continents. Rabies is really a bad disease , it destroys the brain very badly . Currently we have a vaccine against the disease and we have immunity or antibodies that can work against this deadly viral infection. As of now whenever someone is bitten by an animal with a rabies infection , we can easily treat that patient with available immunity methods. If there is no timely treatment , there is a 100% chance that a rabies patient will die.

- The outbreaks of **ebola** struck mankind in 1786 in the african country of Sudan and Congo . Ebola spreads through blood and tissue fluids very easily. The various strains vary a lot in terms of deadliness.Ebola Reston is one strain which doesn't even make patients symptomatic. According to WHO, fatality rate varies a lot for various strains , e.g. Bundibugyo strain claims around 50% of life and sudan strain takes upto 71% of life. Till date the viral strain that created havoc in the 2014-16 period was the most lethal strain as it claimed almost 90% lives of people who got infected. As of now , no fully effective treatment has been found.

- There is no cure for **AIDS** as of 2021 , although antiretroviral treatment therapy can definitely help in controlling the virus, meaning that patients with HIV can live a longer-healthy life . “Functional cure” is something where most top researchers are currently working on . In functional cure , HIV is permanently decreased to undetectable levels in patients , but some virus residual may remain. Some of the other researchers are looking for a “sterilising cure” where HIV is removed from the patient’s body completely, but this is more risky and a bit complicated . In the 21st century era the most deadly viral disease we have is HIV . It's the disease which takes the maximum toll on human society .Quite a few HIV vaccines are going through and they are fairly -encouraging. The protection offered by them is however partial. In the recent past we have developed some good antiviral drugs which now help HIV patients to live longer with HIV . But the infection continues to prevail in large numbers in poor income countries e.g. in Asia and africa .

- **Flu** season is very common especially in the 20th and 21st century , 5 lakhs people worldwide lose lives each season due to flu only. As per WHO data . But sometimes , whenever a new viral flu strain emerges , an outbreak results with a quicker spread of the flu infection , especially with higher mortality rates. Spanish flu , which began in 1918 is thought to be the most deadly flu pandemic , especially it sickened upto 4 out of 10 of the world's population , killing around 50 million humans.

- For other viral infections for which we have effective vaccines -- influenza, mumps, varicella and hepatitis, their eradication have major challenges and limitations. The costly hepatitis A vaccine has economic restrictions. The unknown burden of rubella -- in particular that of congenital rubella syndrome, is not well known in most more impoverished countries.[26]

- The antigenic instability, frequent mutations, and regular reassortment of the influenza virus as it circulates through avian and mammalian cycles - necessitates the influenza vaccine to be redeveloped to cover newer strains. Mumps seems to be biologically eradicable but has very low priority making massive eradication programs unfeasible. The latent long term carrier states of herpes zoster suggest unlikely for eradication. Other viral zoonotic infections, yellow fever, rabies, and Japanese encephalitis are not eradicable at this time due to non-human reservoirs.[26]

Eradication Strategies & Global alignment:-

The first immunisation against smallpox was created in 1796 by Edward Jenner. Despite this, it took more than two centuries and a global vaccination program to eradicate this contagious disease. In 1980, WHO declared smallpox was eradicated. This deadly disease could be only eradicated through timely vaccination . Medically till date, we do not have any sort of treatment modalities which are tried , tested , proven.

Surveillance was a crucial part of the eradication strategy as the intervention tool gradually evolved from the primitive process of variolation to the smallpox vaccination.[23] Innovation in vaccination tools helped in gradually shifting to pedal operated jet injectors and bifid needles — an extremely economical and efficient tool for mass vaccination essential for eradication. [3]

In India, over 1.52 lakh field officials and workers were part of the eradication team in the last phases of the eradication program. With them, there were fifty international advisors and about the same number of Indian officials with thirty-three thousand district health personnel. The field workers team comprised 115,347 members to search house-to-house in 575,721 villages and 2,641 cities. Around 29,000 members were there to supervise, and 8,048 whose main responsibility was to assess the search program. For a six-day duration every month, health care workers visited every household totalling more than 100 million households. For the Indian program, WHO and innumerable health organisations supplied 348 vans and cars, 417 motorcycles, 246.7 million bifurcated needles, 210,000 needle holders, 5,000 specimen containers, 300 mega mikes and 14,000 vaccination kits. Financial logistics were the responsibility mainly of central and state governments, WHO, the Swedish International Development Agency, besides a few other national and international agencies. [18]

Smallpox eradication in most challenging terrains and limited resource countries like South Asian Countries (Indonesia, Afghanistan, India, Bangladesh) and East African countries was never purely a medical or biological issue. It required all forms of administrative, political, social and economic gymnastics, requiring months of planning and relentless pursuit of the end goal.[20] Along with the local production and adoption of several intervention tools from freeze dried vaccine to bifurcated needles, global policies needed to be tailor made depending on the local conditions and infrastructural conditions. Community partnership programmes, learning and adapting programs based on the experience of those in the field for region specific policy adaptations was critical for the success of every regional elimination program. [2]

By the year of 1959 , the governing body of WHO , World Health Assembly had passed a resolution to eradicate smallpox at the global level . "Intensified Smallpox Eradication Program " was initiated in 1966 with financial support from WHO , to increase efforts for smallpox eradication .

Conclusion & future directions:-

A global threat demanded a global synchronised effort to control SARS-CoV-2 through an international body governing health policies and practices cutting through geographical boundaries just like our common enemy. The best alternative, which we probably had in late 2019 when COVID just started getting smoke, was our World Health Organisation (WHO).
The dubious attacks by several Political leaders , prominently the USA President damaged WHO's international standing, despite the enormous role it played in eliminating Smallpox. The revival of the organisation will need WHO to mobilise the regional offices and secure support from nations across continents. [13]

A well coordinated special time-bound programme for controlling COVID-19 community transmission with clear objectives and measurable endpoints.

Time, energy and resources must be spent in strengthening management (at par with the medical aspects) consisting of a network of trained staff, allocation of sufficient financial resources, investment in logistical capabilities, and the development of a pragmatic operating strategy. Continuous research to understand the ever evolving viruses, making decisions based on evidence is quintessential and can't be compromised even in a pandemic. [17]

Gaps in the literature & further research:-

We do not know yet why some viruses like Smallpox were so selective for the human species, which is one of the most critical biological considerations to be dealt with before planning any disease control measures. [14]
Most of the research since eradication has focussed on treatment and vaccine research over the fundamental biology of the virus. More research efforts need to be put into understanding viral genome developing universal flu vaccines, effective against all the strains or subtypes emerging due to antigenic drift or antigenic shift. [15]

For smallpox, along with a very effective, efficient and a low cost vaccine, the outbreak cases could be identified with adequate confidence and timeliness. Henceforth definitive case identification through strong surveillance systems proved to be a cornerstone for the eradication. Surveillance networks and subsequent ring vaccination played a vital role in Smallpox. It is essential to understand what viral and social factors assist or hinder the success of this surveillance strategy. [3,16]
The Carter Center International Task Force for Disease Eradication has recently declared six additional diseases as indisputably eradicable potentially : lymphatic filariasis (Elephantiasis), polio, measles, mumps, rubella, and pork tapeworm. Bioterrorism is the modern war between international nations and cross-borders. International agencies like the CDC and others are now prepared to stifle any reemergence of smallpox. Future pandemics are expected , we need to accept this and prepare accordingly.
From smallpox to covid-19 , one thing that has constantly changed over time is technology, it has improved by leaps and bounds . Now we have better technology to develop vaccines , drugs and simultaneously with the help of computation , Artificial Intelligence(AI) and Machine Learning(ML) now we have a better chance of having successful predictive models as well .

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