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Narrative Reviews

Vaccines and vaccine resistance: Past, present and future

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ABSTRACT

Background: Edward Jenner, by any definition would be considered the father of vaccinology. His use of cow pox virus for vaccinating against small pox is the prime example of a live vaccine. Using a virus that has very low virulence for humans and therefore, fits the definition of attenuated. Hesitancy towards a vaccine of this type, much before the science of microbiology and immunology were established, would have been justifiable. In the first half of 20th century, large number of vaccines became available for childhood diseases with significant morbidity and mortality. Around the same time global travel and trade led to escalation in the widespread transmission of diseases caused by microbes.

Objective: The objective of this narrative is to offer a balanced view of science behind vaccines, their current status and advances expected in the near future. At the same time the various types of reactions from public at large towards vaccines over past decades are reviewed.

Content: This narrative provides a historical perspective of vaccine development, reviews mechanisms of vaccine induced protection, currently available vaccine technologies and vaccines. The focus is on newer vaccines including those utilizing viral vectors and gene based vaccines. Based on the times during which this narrative is being written, messenger RNA vaccines are discussed in detail.

Conclusion: The content and review of literature offered in this review makes the impact of vaccines on human life clear. It is also to be accepted that resistance and hesitation towards vaccines is nothing new or limited to vaccines being used during the ongoing pandemic of Covid 19. The continued development of science and products of vaccinology is necessary for further impact on human life. The development of a strong public health infrastructure by nations around the world is the key to improve upon current efforts at public awareness, proactive interventions and appropriate vaccine utilization during all times. Preparedness for epidemics and pandemics would then become more and more efficient than currently in existence.

Small Pox, one of the history's most feared human illnesses carried a death rate of 30% and many serious morbidities. Early attempts to intentionally infect (inoculate) people against smallpox were made in china and India [1]. The word “inoculation” comes from its use in horticulture meaning to graft a bud (or eye) from one plant to another. This term is now used interchangeably with “Immunization” since the discovery that a functional immune system is needed for inoculation to be effective. The scabs from healing smallpox pustules were ground up and blown into the nose of well people in China. In India, the method involved lancing a pustule of a patient recovering from smallpox and using the same lance to inoculate the material into the skin of a healthy person through scratches. In 1022 AD, a book called “The Correct Treatment of Small Pox” mentioned using scabs from a recovering patient and grinding them up to give to healthy people. The practice known as “Variolation” was adopted in Europe in the 18th century and received endorsement of Lady Mary Worley Montagu, wife of British ambassador to Turkey in 1721. As it became evident that variolation -induced small pox disease caused 2–3% mortality and further outbreaks were triggered, the practice became a felony in many parts of Europe. The next mile stone towards safer inoculation was the observation that dairy farmers did not catch smallpox. Edward Jenner, the 18th century English physician hypothesized that cow pox virus from cattle transmitted to dairy farmers caused no or mild illness leading to observed protection against a much serious illness caused by human small pox virus. After a series of experiments, he inoculated a small number of healthy people in 1796 with pus from the cow pox lesions from milk maid's hands and exposed them to patents with small pox. The fact that they did not develop smallpox supported his hypothesis that the protection against small pox was the result of response evoked by cow pox virus inoculation. Jenner's observations, hypothesis and early experimentation is now considered the birth of immunology, vaccine therapy and disease prevention. The origin of the term “Vaccination” is from the Latin for cow (Vacca) Vaccines over

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the centuries since have eradicated small pox, likely to eradicate poliomyelitis soon, drastically reduced childhood mortality, increased life expectancy and prevented lifelong disabilities.

Robert Koch in Germany established Koch's postulates in 1877 that formally provided proof and wide acceptance for "Germ Theory "of disease. The French biologist, Louis Pasteur (1885) prevented rabies in a young boy bitten by a rabid dog by injecting him with a weakened form of the rabies virus each day for thirteen days. Pasteur called his treatment "Rabies Vaccine "thus expanding the meaning of the term vaccine beyond its origin almost a century ago. The term has since been used to include a long list of interventions with live weakened or killed whole microbes, protein or carbohydrate components of microbial cells and most recently the genetic codes for the antigen.

The first half of 20th century saw an explosion of vaccines against whooping cough (1914), diphtheria (1926), tetanus (1938), influenza (1945) and mumps (1948). With advances in technology and technology transfer, vaccine production received a major boost in the late 1940's. This made feasible efforts at vaccine campaigns around the globe and disease eradication. By this time global travel and trade had caused a major escalation in the potential for widespread transmission of diseases caused by microbes. Vaccines against poliomyelitis (1955), measles (1963), rubella (1969) and others were added in the later part of 20th century. The first microbial disease to be prevented by vaccination in 1796 became the first to be eradicated from the globe in 1980. With the increase in world population and poverty, late 1990's saw an increasing lack of or partial initial immunization of children in developing countries. In 2000, Bill and Malinda Gates foundation and partners set up the Global Alliance for Vaccines and Immunization now called GAVI. By encouraging vaccine manufacturers to lower vaccine prices for less resourceful countries in return for high volume and long term predictable demand, thirteen million child deaths have been prevented.

Following the fundamental principle of biology, infections caused by new and emerging pathogens appeared as many from the past were being controlled by vaccination. In response to the lessons learnt from 2014/2015 Ebola Virus epidemic, the world prepared itself to handle such epidemics better. The Coalition for Epidemic Preparedness Innovation (EPI) was launched at Davos in 2017. The coalition is a partnership between public, private, philanthropic and civil society organizations working to accelerate the development of vaccines against emerging infectious diseases and to enable equitable access for affected populations during outbreaks. The first vaccine against Ebola was approved by the US FDA and EU regulators in 2019 and a second received approval in Europe in 2020. The time between the start of first phase 1 trial (October 2014) to the approval of first vaccine (Nov 2019) was five years compared to typical 10- 15-year time line for vaccine development.

1. Mechanisms of vaccine induced protection against infections

Vaccine immunology and generation of vaccine – induced protection is complex and dependent on interaction between multiple compartments of host immune system. The early protective efficacy is measured by the detection of antigen specific antibody. In general, the higher levels of antibodies correlate with better protection. Above and beyond the quantitative peak of vaccine induced antibody titers, the quality of such antibodies including specificity, affinity, avidity, bactericidal activity, neutralizing activity are the major determinants of efficacy. For long term protection, the antibody response needs to persist above a threshold level. In the absence of such a level, the vaccine needs to induce and maintain immune memory cells that can rapidly and effectively reactivate with subsequent exposure to the same or related microbe [2]. The effector mechanisms of vaccine induced immunity include both the cells and the products they secrete. The antibodies secreted by B lymphocytes bind to specific antigens on the microbe or to their toxins are the front line response and easy to measure. However, the network is completed by various types of T lymphocytes. The CD4 or T- helper cells (Th1 and Th2) produce cytokines and support the generation and maintenance of B lymphocytes. T helper cells defend against extracellular bacteria that colonize the skin and mucus membranes through recruitment of neutrophils and induction of local inflammation. Follicular T- helper (Tfh) lymphocytes have recently been identified in the lymph nodes. They support the activation and differentiation of B lymphocytes into antibody secreting cells. They have been shown to directly control antibody responses and function as adjuvants. Cytotoxic or CD8 lymphocytes contribute to the immune response by recognizing and killing infected cells and by secreting antiviral cytokines. They help limit the spread of infectious agents. Regulatory T (Tregs) lymphocytes control the effectors by maintaining immune tolerance. Most microbes, their antigens, the vaccines for them trigger both B cell and T cell responses. CD4 T cells are required for antibody responses by B cells (humoral immunity) against extracellular pathogens. In turn, antibodies significantly influence T cell (cellular Immunity) responses to intracellular pathogens. The nature of the antigen or vaccine directly influence the recruitment of various types of effectors and resulting protective efficacy. In a classically T- independent response, capsular polysaccharides of bacteria like Streptococcus pneumoniae and Neisseria meningitides elicit B cell responses. Once conjugated to a protein carrier, the peptide antigen recruits antigen – specific CD4 T cells transforming the response to T- dependent. The T-dependent responses are also elicited by protein antigens, toxoids, inactivated and live attenuated viral vaccines. T- dependent immune responses offer high affinity antibodies and immunologic memory. Memory B cells are generated only during T- dependent immune responses through germinal center and follicular T helper cells. Memory B cells are resting cells and do not produce antibodies. Upon reexposure to antigen, they rapidly differentiate into antibody- secreting plasma cells that produce higher affinity antibodies than the primary plasma cells. The induction of strong CD8 (Cytotoxic) T cell responses require live vaccines, vectors or novel delivery systems.

2. Currently available vaccine technologies and vaccines [3,4]

1. Live- attenuated Vaccine e.g.-mumps, measles, rubella
2. Killed Inactivated Vaccines e.g. poliomyelitis, hepatitis A
3. Toxoid Vaccines e.g. diphtheria, tetanus, acellular pertussis
4. Conjugated Vaccines e.g. pneumococcal, meningococcal
5. Subunit vaccines e. influenza, typhoid.
6. Recombinant Vaccines e.g. hepatitis B, human papilloma virus
7. Viral vector vaccines e.g. ebola, dengue
8. Chimeric Vaccines e.g. dengue

Routine Infant and childhood Vaccines recommended by CDC are listed at … [5].

Routine Adult Vaccines recommended by CDC by age group and underlying medical conditions and travel to endemic areas are listed at … … [5].

The first five categories of vaccines described above are made by conventional technology. All of them use a) a microbe (live attenuated or inactivated; b) a part of it e.g. capsular polysaccharide of Pneumococcus, Meningococcus, Hemophilus type B conjugated to proteins to optimize their immunogenicity; c)Toxoids modified from toxins produced by the bacteria that are involved in pathogenicity; d) Subunits of the microbial cell. In spite of major advances in technology in recent years, mass production of these vaccines remains expensive and time intensive. Virus like particles made by recombinant and viral vector technology have greatly facilitated and streamlined vaccine production.

3. Viral vector vaccines

Viral vector vaccines are a cross over between live attenuated (using replication competent or replication incompetent viruses) and gene based vaccines. The virus carries the gene encoding the antigen of interest e.g. the EBOV glycoprotein of Zaire ebolavirus that replaces the gene of the carrier Vesicular Stomatitis virus. The vector virus carrying

the code enters the cell which then transcribes and translates the gene to produce the antigen. An immune response is generated by the antigen displayed on the cell surface. The process may be amplified by slow reproduction of the vector virus with infection of more cells and production of more antigen. Preexisting immunity against any part of vaccine can limit its effectiveness. Depending on the vector used, geographic variation in preexisting immunity poses a major challenge. The DNA and RNA Vaccines do not pose this challenge. If the vector in a vaccine is cleared before it gets into cells, the immunogenic moiety never reaches its target. The low neutralizing antibody elicited in a phase 1 trial of a candidate CoVID 19 Vaccine with human Adenovirus 5 as the vector was attributed to this phenomenon [6]. The CoVID 19 Vector vaccine developed in England, uses an adenovirus that infects chimpanzees (Ch Ad OX1/A2 D1222) but not humans. However, the possibility of cross reacting preexisting immunity is a possibility. The one with emergency use authorization in the US contains a sero-group D recombinant Adenovirus 26. In spite of significant seroprevalence in certain adult populations, neutralizing antibodies against Ad26 remain much lower than against Ad5. The Vaccine developed in Russia consists of the gene for whole S protein of CoVID 19 contained in two different recombinant human adenoviruses.

4. Gene only based vaccines with focus on CoVID vaccine

The immunization method using the genetic material itself to encode for the desired antigen depends on the production of immunizing protein by the cells into which a small part of the genetic code has been introduced [7]. As has been demonstrated by CoVID 19 experience, finding the genetic code has become relatively easy and fast by currently available technologies. After this corner stone is available, gene only based vaccines are faster and cheaper to produce in large quantities compared to conventional vaccines.

5. DNA vaccines

Part of the pathogen's DNA known to code for protein/proteins responsible for eliciting a protective immune response is injected. The genetic material must enter the nucleus of the host cell, which can happen only when the cell is dividing creating an inherent inefficiency in the process. Once in the nucleus, the DNA creates mRNA which travels back into cytoplasm. This mRNA, like the mRNA in RNA Vaccines introduced into cytoplasm leads to protein/antigen synthesis. The peptides derived from the protein are presented on the cell surface and stimulate the lymphocytes responsible for generating an immune response. The breadth and depth of immune response evoked by DNA vaccines are not fully clear yet. They usually encode one protein from the pathogen. If protective immune response involves multiple proteins, multiple vaccines will need to be mixed together. Plasmids can act as a transport for the DNA vaccines. Alternatively, electroporation (electric pulses can be used to create temporary openings in the cell membrane to let the vaccine get into the nucleus. The potential value of DNA vaccines lies in their capability to get the end result of protective immunity without need for handling a virulent pathogen or to adapt the pathogen (or its parts) to manufacturing processes [8]. A biopsy from cancerous tissue can be used to make personalized antitumor DNA vaccines. Based on the information that DNA vaccines move T- helper responses to Th1 phenotype, they are under development for allergic and autoimmune disorders. Four animal health products for large animals (horses and pigs) are licensed currently. Two are prophylactic vaccines against infectious diseases, one is hormone gene for food animals and the fourth is for cancer chemotherapy. The successful use of DNA molecules in large animals compared to relatively disappointing efficacy of DNA vaccines in human clinical trials is being further investigated. Obviously that larger target mass (compared to small laboratory animals) is not the sole road block. Advances in delivery and expression technologies to increase the potency of DNA vaccines in humans are underway. Recently, regulators have granted emergency approval for the world's first DNA vaccine for human use, one of the many vaccines being used to fight the currently ongoing CoVID 19 pandemic [9].

6. Messenger RNA vaccines

Messenger RNA (mRNA) and first proteins produced by isolated mRNA in the laboratory were discovered in 1960s [9–15]. RNA in general is considered extremely unstable. mRNA was synthesized in the laboratory in mid 1980s but seen to be too unstable for use directly as a drug or vaccine. Its development into a drug or vaccine was therefore deemed to be too expensive. To be used in therapeutics, a stabilization method would be essential. In 1965, lipid molecules were synthesized into lipid envelopes called Liposomes with the potential of delivering otherwise difficult to deliver molecules to cells for treatment and/or prevention of diseases. Liposomes are made of positively charged lipids. A major mile stone happened between 1987 and 1989 when synthetic mRNA was introduced into cationic liposomes and delivered to human cells and frog embryos. This led to liposome wrapped mRNA being delivered to mice and then tested as treatment in rats. The first mRNA vaccine was tested in mice against influenza in mid 1990s. For the next ten years the lack of resources and resistance to commercialization hindered the development of mRNA as a therapeutic/preventive agent. However, a large number of scientists in various institutions continued to work at its potential independently and in collaboration. The potential use of mRNA (vaccine) as a therapeutic agent to treat cancer was received favorably by cancer immunologists. It was proposed in 1997 that introducing synthetic mRNA into immune cells from blood of the patient would allow the cells to produce tumor proteins encoded in mRNA. Once injected back, these would instruct the immune system to attack the tumor cells. A late stage cancer candidate vaccine failed in a large trial. However, the concept inspired the founders of two German companies (two of the largest mRNA companies in existence now) to do the same with administration of mRNA directly into the body. The ability of directly injected mRNA to elicit an immune response had been reported earlier in mice [12]. However, their use as a vaccine against human immunodeficiency virus had been shown to set off massive inflammatory reactions when injected into mice. In 2005, the same researchers reported that rearranging the chemical bonds on one of mRNA nucleotides, uridine, creates an analogue called pseudo uridine. This substitution allowed the mRNA to escape innate immune system. Many experts believe that pseudo uridine is an essential component of mRNA vaccine technology. Both mRNA vaccines in use currently against COVID 19 contain modified mRNA. Other approaches under investigation are a genetic modification to mRNA minimizing the amount of uridine in candidate vaccine and use of unmodified mRNA. In parallel, a scalable method for manufacturing Lipid Nano particles (LNPs) was described in 2005. The first clinical trial of a mRNA vaccine in LNPs was done against influenza in 2015. The nano- particles have a mixture of four fatty molecules. The first called an ionizable lipid converts the positively charged LNPs under laboratory conditions to a neutral charge under physiologic conditions limiting their toxicity. The ionizable lipid is the key to LNPs function while the other three contribute to structure and stability. A new method of mixing and manufacturing LNPs involves using a T- connector apparatus to combine fats (dissolved in alcohol) with nucleic acids (dissolved in acidic buffer). When the two solutions merge, the components spontaneously form densely packed LNPs. This has proven to be a more reliable technique for making mRNA-based injectables. All marketed and candidate CoVID vaccines contain closely related LNP concoctions. By the beginning of 2020, Moderna was working on nine mRNA vaccine candidates for infectious diseases without a huge success.

Within days of CoVID 19 genome sequence becoming available, Moderna created a prototypic vaccine. Collaborative work with US National Institute of Allergy and Infectious Diseases led to mouse studies and launch of clinical trials within a short period of ten weeks. BioNTech in Germany partnered with Pfizer in New York to conduct clinical trials.

It took less than eight months from first human testing to emergency authorization of two CoVID 19 mRNA vaccines. The triangle of this unprecedented success is cornered by a) availability of CoVID 19 genetic sequence, b) modified mRNA technology and c) Lipid Nano Particle technology. With unprecedented impact on human race. Both vaccines contain sequences that encode CoVID 19 spike protein as the immunogen to induce protective immunity. Other approaches to antigen use are being studied [16]. The mutated spike protein (G 614) of Delta variant renders CoVID 19 more infectious. This structural characteristic of the spike protein G 614 makes a formidable antigen also for future vaccines. The mRNA technology lends itself to use of codes for multiple corona viruses since mRNA gets into the cytoplasm with 95% of cells taking it up to make protein much more efficiently than DNA. mRNA cannot cause infection. It does not enter the nucleus and chances of integration into DNA are low. It cannot cause infection. The body breaks down mRNA and its LNPs within a few hours alleviating concerns about long term risks.

An informal comparative evaluation of mRNA, viral vector and inactivated vaccines against CoVID 19 show mRNA vaccines to have the highest efficacy (95%) compared to 75% and 50% for the other two types. As expected with any pharmacologic intervention, we have seen minor side effects and few major adverse events with all types of CoVID vaccines. There is also a question of Antibody dependent enhanced (ADE) break through infections with any of the CoVID vaccines [17] This phenomenon seen with Dengue viruses is less likely because Corona virus severe disease is not centered around infants, children or individuals with previous Corona virus infections. Vaccination of laboratory animals by SARS or MERS viruses followed by live virus challenge resulted in vaccine hypersensitivity (VAH) reactions similar to those seen in humans with inactivated measles or respiratory syncytial virus vaccines. This phenomenon will need to be entertained and avoided in future vaccination against Corona viruses.

7. Vaccine spectisism and resistance

To put current events in perspective, a quick visit to the past is necessary. Variolation, a practice to intervene in small pox transmission served as a natural precursor to the discovery of vaccination against small pox. Chinese Buddhist nuns documented the use of dried and ground scabs (from patients recovering from small pox), given by nasal insufflation to healthy people. After variolation, cases were treated as if they were infected, same as those who had acquired the disease naturally. Clearly today this would be considered immunization with a live attenuated virus followed by precautions to limit its transmission to others. Early on, the procedure was carefully performed by “experienced elderly women” resembling the concept of “birthing ladies”. The inoculation method used in India spread to other parts of Asia, parts of Africa and middle east followed by Europe and Americas. Many enlightened and self-taught physicians in various parts of Europe used the practice often with significant positive effect on the demographics of small population groups. The detailed, methodical and safe approach used by John Williamson aka Johnie Notions in 18th century was well described by Brian Smith in 1998 [18]. At the time, minor form of smallpox caused death in 1% and the major form caused death in about 30% of those infected. Some epidemics in highly susceptible, previously unexposed populations resulted in death rates as high as 50% [19]. In experienced hands, the death rate in variolated patients who developed small pox was 0.5–2%. This was enough to have detractors, oppositions and serious debates. Historically speaking, this would be the beginning of what is currently called “AntiVaxxers”.

In 1706, North American Reverend Cotton Mather of a church congregation in the colony of Massachusetts became curious about a scar on the arm of an enslaved man sold to the congregation [19]. That is how he learnt about inoculation being used against small pox. He discussed the practice with local physicians, who learnt variolation and used it in their family and servants when small pox arrived in 1721. At the end of the epidemic,14% of people with natural small pox died compared to 2% of those variolated. In 1768, Catherine the Great of Russia, variolated herself and her family followed by two million citizens. Around the same time, in the city of Norfolk in the colony of Virginia, Archibald Campbell (a physician) convinced a group of people to receive variolation. On June 27, while he and DR John Dalgleish were inoculating people at his home, a mob attacked his home. The tension between for and against groups came to a head ending in ban of the practice in 1770 by Virginia Legislature. General Washington in 1776 was suffering from losses of troops to small pox brought by British soldiers. He ordered inoculation (sometimes by force) of new recruits while they were in training which gave them the time to recover from the symptoms from inoculation or mild form of disease.

Between 1796 and 1798 Edward Jenner used material from cowpox (an animal disease) lesions to vaccinate (Vacca as in cow in Latin) people. He published evidence of protection against small pox by vaccination that was safer than variolation. Also, the vaccine could self-maintain itself by arm to arm transfer. There were detractors and resisters but science and prudence won. This was followed by decline of variolation which was made illegal in many countries, the first being Russia in 1805. But it was only during WHO's global smallpox eradication campaign (1966–1980) that the last remaining and hidden Variolation programs were ended in Afghanistan and Pakistan. In 1891, Louis Pasteur in honor of Edward Jenner widened the term Vaccine/vaccination to refer to the artificial induction of immunity against infectious diseases in general. Louis Pasteur's extension of the principle of vaccination, his work and that of his many successors has led to the development of many effective vaccines against infectious diseases including diphtheria, measles, mumps and influenza. The second disease (after small pox) targeted for global eradication by vaccination is Poliomyelitis. But for the vaccination, the world would be in the medical dark ages. During the dark ages, the human race survived without drugs and vaccines but clearly with medical theory and its prudent practice.

The concept of Variolation in essence has survived through the centuries in the form of practices like “Pox Parties” in which well children were intentionally exposed to diseases like measles, rubella and chickenpox. This practice persists in spite of strong disfavor from public health authorities [20]. It will not be a surprise to learn that the same parents who resist vaccination are the ones using the principle of variolation for their children. The facial masking to reduce the impact of CoVID 19 has benefits similar to that of variolation [21]. The hypothesis was that “Universal masking would become a form of variolation that would generate immunity and there by slow the spread in the United States and elsewhere while we await a vaccine”. Well, Vaccines, not just a vaccine arrived at an unprecedented speed. But so did the Vaccine skepticism and resistance from expected and unexpected sources. This has made an easily accomplishable goal of “mass Vaccination” in countries like the United States difficult to accomplish. As long there are unvaccinated populations even smaller than those vaccinated, the reservoir persists for ongoing transmission. So nothing under the sun is new including the very basic human characteristic of controversy about a vaccine against the virus that looks like the sun. With the mandating of smallpox vaccination in Europe in early nineteenth century for certain groups, societies of Antivaccinationists formed to protest unequal treatment and infringement of individual liberty [22]. Later that century antivaccvinism spread to the United States and persists in the form of AntiVaxxers.

The modern era of vaccination got underway in late 1950s with the arrival of vaccines to prevent poliomyelitis, measles. mumps and rubella. The poliomyelitis vaccine released in 1954 was greeted with enthusiasm. People knew Poliomyelitis as a dreaded disease and were desperate to prevent it. A few voices did speak against the vaccine but coercive policies never became necessary. The vaccines of 1960s for measles, mumps, rubella were not received with the same enthusiasm. A case in point to shed some light on this is the mumps vaccine. Mumps was seen as a mild disease n general with only some adult men suffering the most serious sequela. Some in the medical community proposed to give this vaccine only to post pubertal boys who had not yet suffered from the disease.

Deeper studies of the disease at the CDC rendered it more serious with more reasons to vaccinate all children against mumps. The federal advisory committee for immunization practices (created in 1964) recommended in 1977 that all children get mumps vaccine along with other childhood vaccines at the time. It is easy to understand why such events would cause confusion in lay public's mind leading them to questions vaccines in general.

The blossoming of social movement with the focus on questioning authority and experts coincided with the stricter approach to vaccine schedule and its enforcement. Similar to the push back against patriarchy by women, against industry by environmentalists, there was push back against doctors and public health authorities recommending vaccines. Patients, right and women's health movements led to discovery of "unexpected" problems with vaccines by mothers who shared them in resources like Mothering magazine. The additive to vaccines like aluminum, mercury and formaldehyde became topics for of scientific and public debate An hour long news report "DTP: Vaccine Roulette"aired in 1982 and ended with conflicting statements about the use of DPT in children with history of seizures from a vaccine scientist and American Academy of Pediatrics. "Dissatisfied Parents Together", an organization of parents inspired by then current events advocated safer vaccines, greater government oversight and federal compensation for the families of children harmed by vaccines. The founders of the organization co -authored a book "DPT: A Shot in the Dark" (1985) detailing the struggles of parents of children who had been harmed by vaccines. The harmful effects of DPT were compared to those of environmental chemicals like pesticides. The National Childhood Vaccine Injury Act (1986) was the result of the efforts of this organization. The vaccine schedule for children has continued to expand as has the dialogue and debate about the vaccines. The debates echo those from the nineteenth and early twentieth century in the form of a) Is it necessary? b) Is it safe? c) Can the expert advice about it be trusted?

The vaccine skepticism of today is rooted in the social movements of the post-world war II era. These movements prompted a generation of adults to question drugs, doctors, environmental contaminants and authority in general. Over time, the armamentarium of drugs and mandatory vaccine schedule for children increased while less and less of previously fatal childhood infectious diseases were being seen. Of course the later was the effect of the vaccines. It was like what was not being seen, did not happen. Smallpox was eliminated in 1980 and the eradication of poliomyelitis globally seems to be in sight. On the other hand, US declared measles eradicated in 2000. However, after a 22-year long Measles Vaccine campaign, the disease is back [23]. The role of vaccine skeptical celebrities including Jenny McCarthy and now discredited Dr. Andrew Wakefield were the products not necessarily the cause today's parenteral mistrust of public health authority and vaccines. The Lancet 1998 publication led by Wakefield on measles vaccination and autism added fuel to the fire. Jenny McCarthy, mother of a child with autism wrote and spoke about how she saw vaccines trigger her son's autism. Reassurances about new vaccines came along with new rationales for vaccination e.g. vaccinating children to protect adults and to protect economically productive time for parents. Although rational, these advances in immunology and molecular biology provided room for further controversy.

The struggle between vaccine laws, mandates and vaccine skepticism was born during the dawn of variolation and shows no signs of a final resolution. The debate has periodically quieted in the of face war, new cultural and economic preoccupations and new epidemics The current now not so new pandemic of CoVID 19 would have been expected to be one such time in human history. The arrival and uptake of multiple vaccines with scientifically proven risk benefit ratio at a warp speed would have been greeted and celebrated. Instead we are facing an unprecedented resistance from population groups of different cultures, religions, races, educational background, economic resources and demographics [24]. Events like Tuskegee Syphilis Study have been cited as medical atrocities and to a large extent explain the distrust of the US black community in the health care system [25]. Obviously not enough has been done to shed the fears of those horrendous acts of medical brutality against society.

Medical science has progressed at a much faster speed in the 20th and early 21st century than anticipated so has the communication science. Every bit of new development is used as "news" by multiple media uncountable times a day, followed by explanations and commentaries by multiple "experts" in "bite size" formats. Often, different experts use different verbiage, their own interpretation of data and sometimes down right misinformation. The multitude of "interpreters" and sources on the one hand and public's little knowledge (not better than ignorance) on the other has created a mountain out of a mole hill. What is lacking at the grass roots is public health education provided during good and bad times as honest scientifically proven information in an easily assimilable language and format. The information needs to be disseminated to the public by people on the ground who are actually providing medical care to the communities. Their recommendations are what people follow in their daily lives. The medical information collected by state public health authorities and fed to the CDC on epidemiology should go to public through this resource. The National Institutes of Health, FDA and CDC should be responsible for providing the information on drugs and vaccines to the medical providers. It is obviously good to have this information open and accessible to the public as an added resource.

What can be done in a hurry? Previous work has used two major approaches to increase vaccination rates [25,26]. The first approach focuses on those who are uncertain about vaccination and aims at boosting vaccine uptake intention. Recognizing that changing intention does not always translate into action, the second approach involves helping with follow through of vaccination intentions and overcome variables like forgetfulness, hassle costs and procrastination. Dai el published a study on the role of behavioral nudges in increasing CoVID 19 vaccine uptake [27–29]. They conducted two randomized clinical trials at the University of California, Los Angeles. Nudges, defined as interventions to alter the behavior of people in a predictable way without forbidding any options or changing economic incentives were used to improve the uptake of COVID vaccine. The starting point for the trials was Jan 20, 2021 and participants were drawn from UCLA Health primary and specialty care attributed patient list. As they became eligible for the vaccine, the UCLA Health enrolled them in two sequential large scale randomized controlled trials to study the impact of nudging followed by carefully designed reminders to reduce barriers to the vaccine uptake. The reminders were combined with additional interventions including a) behaviorally informed messaging designed to amplify the desire of individuals to get vaccinated, b) a traditional information provision intervention aimed at correcting the misconceptions involved in vaccine hesitancy. The findings of these research studies highlight that behavioral science insights and carefully designed interventions at close to zero marginal cost can increase and speed up CoVID vaccination. Combining reminders with a video based information interventions did not increase vaccination further. Of the participants who made appointment for first dose, only 10% did not show up and 90% of those who received first dose scheduled their second dose. Thus getting started i.e.; coming for the first vaccination is the biggest barrier. This has previously shown to be the case with Hepatitis B vaccination of infants.

Natural fear of unknown and organized conspiracy by government will remain. But many other things are amenable to change. It is important to recognize that modern day parents have not suffered and for the most part seen in others the diseases prevented by childhood vaccines. Raising the awareness of those diseases is of utmost importance.

Adult immunizations often are not a part of routine care in most parts of the world and suboptimal in the USA. During the pandemic, people of diverse educational backgrounds they are expected to comply with something new and unusual. Lack of public awareness that shots are not just for babies is a serious concern and can be rectified with simple and inexpensive ways. The last but definitely not the least important is to uncover for the public the myths about antimicrobial agents i.e, their lack

of for most viral diseases and their shortfalls and pitfalls for bacterial diseases. The inherently changing nature of microbes particularly under the threat of indiscriminate antibiotic use with ensuing resistance to the few still active is a more needed public health message than the often misunderstood "hype" heard everywhere these days. Incurable and/or untreatable chronic illnesses are an accepted fact. What needs to become a fact that many acute illnesses in the field of infectious diseases are not only untreatable but also transmitted to families, friends and the rest. What would be a better time than now for this lesson.

Declaration of competing interest

The author declare no conflicts of interest.

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