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A BRIEF HISTORY OF VACCINE AND VACCINATION

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ABSTRACT

Protecting against long-standing illnesses will continue to be important in the decades and centuries ahead, but the work is not complete. In order to protect the world against infectious diseases, we need a mechanism to monitor new viruses, and rapidly develop vaccines against the most dangerous emerging infections. It is no secret that vaccinations have revolutionized global health. Arguably the single most life-saving innovation in the history of medicine, vaccines have eradicated smallpox, slashed child mortality rates, and prevented lifelong disabilities. Edward Jenner developed the first vaccination to prevent smallpox. Gavi, the Vaccine Alliance, aims to lower vaccine prices for the poorest countries. The Coalition for Epidemic Preparedness Innovation (CEPI) works to accelerate the development of vaccines against emerging diseases. A global partnership between public, private, philanthropic, and civil society organizations working to accelerate the development of vaccines against emerging infectious diseases and enable equitable access to these vaccines for affected populations during outbreaks. The challenges faced in delivering lifesaving vaccines to the targeted beneficiaries need to be addressed from the existing knowledge and learning from the past. A brief historical perspective on smallpox disease and preventive efforts since antiquity is followed by an overview of 19th century efforts to replace variolation by vaccination, setting up of a few vaccine institutes, cholera vaccine trial and the discovery of plague vaccine. In the post-independence period, the BCG vaccine laboratory and other national institutes were established; a number of private vaccine manufacturers came up, besides the continuation of smallpox eradication effort till the country became smallpox free in 1977. We've come a long way since the risky and gruesome early inoculation efforts five centuries ago. Scientific innovation, widespread global health campaigns, and new public-private partnerships are literally lifesavers. Finding a vaccine to protect the world against the new coronavirus is an enormous challenge, but if there's one thing we can learn from history, it's that there is reason for hope.

KEYWORDS: Vaccine, vaccination, smallpox, cholera.

INTRODUCTION

Vaccination is a proven and one of the most cost effective child survival interventions.[1] All countries in the world have an immunization programme to deliver selected vaccines to the targeted beneficiaries, specially focusing on pregnant women, infants and children, who are at a high risk of diseases preventable by vaccines. There are at least 27 causative agents against which vaccines are available and many more agents are targeted for development of vaccines.[1,2] The number of antigens in the immunization programmes varies from country to country; however, there are a few selected antigens against diphtheria, pertussis, tetanus, poliomyelitis, measles, hepatitis B which are part of immunization programmes in most of the countries in the world. The first vaccine (small pox) was discovered in 1798. The most striking success of these efforts has been the eradication of smallpox disease from the planet.[1-3] Though a proven cost-effective preventive intervention, the benefits of immunization is not reaching too many children who are at the maximum risk of the diseases preventable by these vaccines. Majority of the children who do not receive these vaccines live in developing countries. As per the recent nation-wide survey data, of the targeted annual cohort of 26 million infants in India, only 61 per cent had received all due vaccines.[4] Understandably, the implementation of vaccination programme and ensuring that the benefits of vaccines reach to each and every possible beneficiary is a challenging task. This review documents the history of vaccines and vaccination in India and analyses the events of past to provide policy direction for the vaccination efforts in the country. The focuses is on broader events and it does not address detailed operational aspects of immunization programme in the country; however, the selected global timelines and events have been referred to provide a context and perspective.

Human vaccinology, with its primary focus on the individual, seems far removed from veterinary medicine, with its concern for the health of the herd. Yet several episodes in the past (smallpox, fowl cholera, anthrax, swine erysipelas, rabies, tuberculosis, etc.) serve to illustrate the proximity between research on veterinary and human vaccines. In some cases the human vaccine was developed first, while in other cases it was the animal vaccine. The history of vaccinology clearly demonstrates the importance of these 'two medicines' working together. Foot and mouth disease (FMD) vaccines were among the first vaccines to be developed, beginning at the end of the 19th Century. Thanks to the discoveries of several researchers, including European researchers such as Vallée (French), Waldmann (German), Frenkel (Dutch) and Capstick (British), FMD vaccines began to be produced on an industrial scale from 1950 onwards, making possible vaccination of millions of animals in Europe and beyond. Vaccination strategies against FMD have always been dependent on the properties of the vaccines being used. At the beginning of the 21st Century FMD vaccines are designed in such a way that serological tests can differentiate infected from vaccinated animals, which has affected OIE regulations on international trade in animals and animal products. The history of vaccination against rinderpest, bovine contagious pleuropneumonia, and Marek's disease will also be dealt with.[3]

History of vaccine and vaccination

Since at least the 1400s, people have looked for ways to protect themselves against infectious diseases. From the practice of "variolation" in the 15th century to today's mRNA vaccines, immunization has a long history. Integral to that history has been the World Health Organization (WHO), whose global vaccine drives through the 20th and 21st centuries have played such a crucial role in reducing serious illness. For World Immunization Week, WHO has teamed up with Google Arts & Culture and scientific institutions from around the world to bring this history vividly to life with A Brief History of Vaccination.[3]

From insufflations to vaccination

Looking back at the history of vaccination, with detailed stories drawn from medical archives, you'll discover how we arrived at the jabs that have saved lives across the world. While you'll encounter famous pioneers like Lady Mary Wortley Montagu, Edward Jenner and Louis Pasteur, you'll also learn that vaccination has a much older history. In 15th-century China, for instance, there existed the practice of "insufflation" — blowing dried smallpox scabs into the nostril with a pipe to prevent natural smallpox, which was far more dangerous. It was in the 20th century that earlier discoveries really started to bear fruit. Smallpox was eradicated globally and vaccines for polio, measles, influenza, hepatitis B, meningitis and many other diseases were developed. It was also the century that saw the inauguration of the WHO and its vital "Expanded Programme on Immunization,"which opened up a truly global front against vaccine-preventable diseases. There are also those whose stories aren't so well known, but nevertheless deserve to be told. You'll learn about the enlightened Grand Duke of Tuscany who experimented with inoculation in the 18th century. Also featured here are the Mexican authorities whose efforts to defeat smallpox in the 19th century were ahead of their time.[3,4]

Ancient times till first documented smallpox vaccination in India in 1802

The history of vaccines and vaccination starts with the first effort to prevent disease in the society.[3,5,6] Smallpox (like many other infectious diseases including measles) was well known since ancient times and believed to have originated in India or Egypt, over 3,000 years ago7-10. This was subject of observation for many learned minds and physicians such as Thucydides in 430 BC and Rhazes (also known as Abu Bakr) in 910 AD who reported that people affected by smallpox were protected from the future infections.[4] Abu Bakr also gave the initial (and probably the first) account of distinguishing measles and smallpox in 900 AD. From India, there are a few descriptions of occurrence of disease; however, one of the best recorded smallpox epidemics was reported from Goa in 1545 AD, when an estimated 8,000 children died.[7] Historians and physicians have sometimes referred smallpox as 'Indian Plague', which suggests that the disease might be widely prevalent in India in the earlier times.

Smallpox affected all races and all regions of the world, with frequent epidemics and inoculation was practiced in a number of countries in East; however, the practice reached Europe especially in the United Kingdom not before early 18th century. Knowing the severity of disease, various approaches were tried to prevent the scourge. Benjamin Jesty, an English farmer and cattle-breeder, in 1774 conducted an experiment with cowpox matter inoculation on his wife and two children and had almost discovered the first smallpox vaccine.[8] Twenty two years later, Edward Jenner made similar observation in milk-maids and noticed that a person inoculated with cow-pox virus, would develop a mild cowpox disease, with no serious risks and would be protected from future smallpox infections. Jenner's observation was his discovery of smallpox vaccine. Jenner published his observation in his seminal work titled 'An enquiry into the causes and effects of Variolae Vaccinae' in 1798. Soon after Jenner's publication, the smallpox vaccination spread to many parts of the world, especially Europe and America. The smallpox vaccine reached India in 1802 (within 4 years).[7,8]

Vaccination in India (1802-1899)

The first doses of smallpox vaccine lymph in India arrived in May 1802. Anna Dusthall, a three year old child from Bombay (now Mumbai) became the first person in India to receive smallpox vaccine on June 14, 1802.[6] From Bombay, through human chain of vaccinees, the smallpox vaccine as lymph was sent to Madras, Poona (Pune), Hyderabad and Surat. The proven benefits of smallpox vaccination had such impact that variolation was outlawed in many European countries and also in some provinces of India as early as 1804. There were special efforts done by officials of Indian Medical Services to popularise smallpox vaccination. The uptake in the general public was low due to several reasons including need to pay a small fee for vaccination, belief in the practice of inoculation and that the disease was a wrath of goddess and many other misconceptions. Another major factor was organized oppositions by erstwhile 'Tikadaars' (who were involved in variolation) to smallpox vaccination fearing that they might lose their jobs. The vaccination in the 19th century was implemented through 'vaccination and sanitary departments' and the Sanitary Commissioners were in-charge of these efforts. However, the structure and approaches adopted in each province varied slightly. The vaccination would be offered through 'dispensaries' in urban areas, which would also act as a store for vaccine lymph. There were a few variations i.e. Bombay system of vaccination, started in 1827, was largely reliant on touring/travelling vaccinators, responsible for vaccination circles or subdivisions. Later on, Bombay system became most widely used approach in other provinces of India. Nearly two third of vaccination used to be done by touring vaccinators and rest at the dispensary system in India.[10-12] The Compulsory Vaccination Act was passed in India in 1892 to ensure higher coverage with smallpox and reduce the epidemic. The 'Act' largely remained on the papers except at the times of epidemics. On records, the law was in force in approximately 80 per cent of the districts of British India in 1938.[6]

Vaccination in India (1900-1947)

The beginning of twentieth century witnessed a few socio-scientific-geopolitical events, which had lasting effect on vaccination efforts in the country. These changes were: (i) Outbreak of cholera and plague in India (1896- 1907) and the services of already limited number of vaccinators were diverted to epidemic control efforts, (ii) The First World War (1914-1918) started and with coinciding Influenza Pandemic (which reportedly killed around 17 million Indians) became a priority for the Government, (iii) New scientific understanding that two doses of smallpox vaccine would be needed for long lasting protection. It was a challenge considering that it meant convincing people to get vaccinated twice with perceived inconvenient and painful procedure.[6] (iv) Most significantly, the Government of India Act of 1919, which devolved a number of administrative powers from Centre to Provinces, by which the local self-governments were assigned the responsibilities of providing health services, including smallpox vaccination. (The health service delivery being a State subject in India has an origin in this Act). This period provides an insight as to how sociopolitical situation can adversely affect health of the people. Specially, 'The 1919 Act' originated with good intentions but the local government had limited financial capacities to fund vaccinators and often led to the variable efforts and progress on smallpox vaccination. The vaccination efforts continued with variable progress till 1939, when World War II was started. Vaccination efforts, though still a focus of local administration, became a casualty of the war. The vaccination coverage went down and in 1944-1945 in India, the highest numbers of smallpox cases in the last two decades were reported. As soon as the World War II ended, the focus was brought back on smallpox vaccination and cases decreased suddenly.[4,6] Another important milestone of this period was the typhoid vaccine trials in India between 1904 -1908. The Anti-typhoid Committee of British Army Medical Department carried out extensive trial of vaccine in 24 units of British Army, joining their operations in India and Egypt. The Committee compared the attack rate of typhoid amongst volunteers for vaccination and amongst non-volunteers in Army (and thus non-vaccinated) individuals and reported six-fold decrease in attack rate amongst vaccinated. Though the methods were not strictly scientific and received adverse criticism, the trial had decisive influence on the decision making on typhoid vaccination.[12]

Vaccination in post-independence India (1947- 1977)

At the time of independence, India was reporting maximum number of smallpox cases in the world. The cholera and plague epidemics were occurring but focus on control of these diseases was restricted and discussions were on about overall health development. Sir Joseph Bhore committee report was just out. Limited budgetary availability had curtailed majority of the efforts. Tuberculosis was perceived as a major cause of morbidity and mortality. In May 1948, the Government of India issued a press note stating that tuberculosis was "assuming epidemic proportions" in the country, and that it had "after careful consideration" decided to introduce BCG vaccination on a limited scale and under strict supervision as a measure to control the disease. A BCG Vaccine Laboratory at King Institute, Guindy, Madras (Chennai), Tamil Nadu, was set up in 194832. In August 1948, the first BCG vaccinations were conducted in India. The work on BCG had started in India as a pilot project in two centres in 1948.[11,12]

National Immunization Programme in India (1978 onwards)

Smallpox eradication left a legacy of improved health system, trained vaccinator, cold chain equipment and system and a network for surveillance of vaccine preventable diseases. Experts globally agreed to utilize this opportunity of trained workforce for better health and reduce child morbidities and mortality from other vaccine preventable diseases. The World Health Organization launched Expanded Programme on Immunization (EPI) in 1974. As soon as India was declared smallpox free in 1977, the country decided to launch National Immunization programme called Expanded Programme of Immunization (EPI) in 1978 with the introduction BCG, OPV, DPT and typhoid-paratyphoid vaccines. The target in EPI was at least 80 per cent coverage in infancy, the vaccination was offered through major hospitals and largely restricted to the urban areas and thus understandably, the coverage remained low. Typhoid-paratyphoid vaccine was dropped from EPI in 1981, reportedly due to considered higher reactogenecity and low efficacy of the vaccines and also due to perceived reduced burden of typhoid disease in the country. Tetanus toxoid vaccine for pregnant women was added in EPI in 1983. The EPI was rechristened with some major change in focus by the launch of Universal Immunization Programme (UIP) on November 19, 1985. The measles vaccine was added to the existing schedule. The objectives and major focus in UIP were: (i) rapidly increasing immunization coverage and reduction of mortality and morbidity due to six vaccine preventable diseases (VPDs), (ii) improve the quality of service, (iii), establish a reliable cold chain system till health facility level, (iv) phased implementation - all districts to be covered by 1989-1990, (v) introduce a districtwise system for monitoring and evaluation, and (vi) achieve self-sufficiency in vaccine production and manufacturing of cold chain equipment.[13]

COVID-19 vaccines

Coronavirus disease 2019(COVID-19), the enormously transmissible disease resulting due to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as the causative agent, instigated a dreadful outcome ensuing worldwide emergency with its rapid spread and greater mortality rate resulting in grievous disruptions. It arose as the greatest substantial world-wide health catastrophe ever since the period of influenza pandemic of 1918, causing more than 3.7 million deaths worldwide. The influence of this pandemic was ascertained in every arena of life on a worldwide level. COVID-19 has devastated many countries, thrashing our health care system besides having a major impact on the academic sector encompassing an enormous number of students, teachers along with staff members. With the implementation of the lock-down the offline classes were substituted for the online mode not only in India but globally.

A vaccine is designed to prevent diseases. COVID-19 vaccines tell your body how to recognize and fight the virus that causes COVID-19. COVID-19 vaccines cannot give you COVID-19. COVID-19 vaccines help protect you from COVID-19 disease. If you do get sick with COVID-19 after being vaccinated, it is less likely that you will get very sick or have to go to the hospital. Everyone age 6 months and older should get vaccinated. The COVID-19 vaccines were carefully tested in a diverse group before being authorized for emergency use. Tens of thousands of Black, Latinx, American Indian, and Asian people participated in the Pfizer, Moderna, and Johnson & Johnson vaccine studies. We know that these communities, along with our disability and LGBTQ+ communities, are often excluded from the benefits of medicine and experience ongoing and historical racism, medical trauma, and abuse. These factors worsen the impact of COVID-19 for these communities and emphasize the importance that the vaccine works and is safe for all. No safety steps were skipped in the making of the COVID-19 vaccines. The Food and Drug Administration (FDA) required safety data for the vaccines to be authorized. Additionally, medical researchers continue to monitor the vaccines for safety.[14,15]

Vaccination programme and vaccines in India

Years ahead The science of vaccine evolved across the globe in late 19th century and India was amongst a few countries to have been involved in these efforts. The cholera and typhoid vaccine trials and research and discovery of plague vaccine took place in the country. Vaccine institutes were set up in early and whole of twentieth century. Though the pattern moved from public to private vaccine manufacturing units but the country has retained self-sufficiency through indigenous production. Smallpox has been eradicated and the country has become poliomyelitis free since January 2011. In spite of all positive changes, there are ongoing challenges and shortcoming in the programme. The coverage with vaccines in National Immunization Programme is suboptimal and only 3/5th children receive all due vaccines and only 3/4th receive 3 doses of DPT vaccine.[4] There are inter- and intra-state variations in the coverage. Data recording and reporting is suboptimal and disease surveillance system desires a lot for improvement. The lack of supervision and monitoring is often cited and communication for increasing immunization coverage is limited. The system for AEFI surveillance is improving but still need to be strengthened. There have been systematic efforts in the last decade to show a hope that immunization coverage would be improved in coming months and years. The history of vaccination efforts suggests that the systematic methodological rigour is required to improve coverage with all antigens in a diverse country like India, with health being state subject. The methodological rigour of past and focus on research has a lot to guide immunization programme in India. Some of the key common areas in early vaccination efforts and current times are as follows : (i) Smallpox control efforts focused both on hygiene and sanitation measures and vaccination. This approach has to be followed for many new antigens such as Rotavirus diarrhoea etc.; (ii) There was strong opposition of vaccination by a section of experts and society. These groups derived strength from similar groups in other countries. Though time has changed, the similar groups exist in the present times, (iii) Limited and incomplete reporting of smallpox cases and deaths (disease surveillance) failed the programme managers to prove that vaccination is making any significant change.[16]

The disease surveillance scenario poses similar challenges in the current times. The programme has become more complicated with addition of new antigens and disappearing diseases (as a result of improved coverage) has raised people's expectations on the safety standards of the vaccines. During this period, stringent safety regulation has made vaccine research costly with more sophisticated technique. These factors have led to reduction in the number of vaccine manufacturers in both public and private sectors. A major challenge in vaccine production in India is sub-optimal investment by public sector for vaccine research. The vaccine manufacturing units set in India are still producing some of the traditional vaccines and there appears to be a need for more funding and research on newer antigens. Indian manufacturers are participating in the development and clinical trials of a number of other candidate vaccines which would ensure that these vaccines are accessible to Indian population, as and when these become available56. The national vaccine policy of India has suggested that 'a number of linkages need to be explored between academia, industry and international institutions such as National Institute of Health (NIH), Gates Foundation, the GAVI Alliance, PATH, World Health Organization and the International Centre for Genetic Engineering and Biotechnology (ICGEB), etc. Immunization programme needs better support and funding for conducting operational research to address programmatic issues and to improve coverage with all antigens in UIP of India. There is increasing demand for additional antigens such as mumps, rubella, and typhoid vaccine in India. The immunization programme in India is a centrally funded programme. A good proportion of children are vaccinated with available and licensed non UIP antigens. Increasing proportion of immunization is being provided by private sector and the proportion is likely to increase over coming years. The benefits of vaccination need to be extended beyond traditional childhood period and new approach of 'lifecourse immunization' for including larger age groups such as adolescent and elderly is being contemplated globally, with an argument that not offering the benefits of available safe and effective vaccines is an ethical issue14. The national technical bodies need to deliberate and come up with its advice and opinion. This would change the dynamics and government may not be able to finance all vaccination efforts and there would be increasing role of professional association in supporting vaccination efforts of the country.[17] This highlights the futuristic need for better and regular interactions in government programme managers and professional bodies to shape the vaccination efforts in the country. The systematic efforts are needed to generate evidence for making a decision to (or not to) introduce new antigens in the programme and to prove the impact of vaccine introduction on disease, once the vaccine is introduced. There have been discussions for strengthening VPD surveillance in the country since the beginning of UIP; however, surveillance for VPDs is far from optimal. The discussion should be moved from implementation and a robust VPD surveillance system, encompassing all existing and upcoming antigens, should be developed with ability to provide sufficiently representative data from all parts of the country. Implementing immunization programme cannot be segregated from the 'knowledge-base' in immunology. The number of trained people in vaccinology and immunology in India is less than what country of this size requires. Globally, the practice of immunology has slowly become part of vaccinology; however, in India there is still limited focus on training in vaccinology and immunology. The technologies for ensuring efficient and potent vaccines to the beneficiaries are becoming available and should be optimally utilized.[18]

Types of vaccines

An antigen is the active ingredient of the vaccine that generates an immune response against a specific disease-causing organism. Vaccines are broadly classified by how the antigen(s) are prepared. Vaccines may be viral (live or inactivated), viral vector, subunit (protein or polysaccharide), or nucleic acid (DNA or RNA). Combination vaccines may include inactivated, protein-based and/or protein-conjugated polysaccharide vaccine components.

Live vaccines contain pathogens, usually viruses, which have been weakened (attenuated) so that they are able to replicate enough to trigger a immune response, but not cause disease. Immunity from live vaccines is usually very long-lived. *Vaccine examples: MMR, varicella, rotavirus*. Non-live vaccines (Inactivated or whole killed): Killed vaccines contain whole bacteria that have been killed. *Vaccine example: whole-cell pertussis vaccine*. Inactivated vaccines contain viruses that have been inactivated in some way, so they are unable to replicate or cause disease.*Vaccine examples: Influenza, hepatitis A and poliovaccines*.[19,20]

Subunit vaccines contain pieces of the pathogens they protect against. There are several different types of subunit vaccines:Toxoid vaccines are produced by harvesting a bacterial toxin and changing it chemically (usually with formaldehyde), to convert the toxin to a toxoid. Toxoid vaccines induce antibodies that neutralise the harmful toxins released from these bacteria. *Vaccine examples: Diphtheria, tetanus*. Polysaccharides are strings of sugars. Some bacteria such as *Streptococcus pneumoniae* have large amounts of polysaccharide on their surface, which encapsulate the bacteria. Polysaccharide vaccines are poorly immunogenic, and can only induce a primary immune response, so no immune memory is made for protection later on. Polysaccharide conjugate vaccines contain carrier proteins that are chemically attached to the polysaccharide antigens. This addition results in the activation of a T-cell response, inducing both high-affinity antibodies against the polysaccharide antigens, and immune memory and can be used in infants.[21,22] *Vaccine examples: Hib-PRP, PCV13 and MenACWY.*

Recombinant vaccines are made using a gene from the disease-causing pathogen. The gene is inserted into a cell system capable of producing large amounts of the protein of interest. The protein produced can generate a protective immune response. *Vaccine examples: Hepatitis B vaccine and HPV vaccine*. Recent developments in vaccine technology have allowed the use of messenger ribonucleic acid (mRNA) to deliver the genetic code to our dendritic cells to make specific viral proteins. Since mRNA is easily destroyed by ubiquitous ribonuclease enzymes, it is protected inside a lipid nanoparticle that also facilitates uptake by the dendritic cells. Inside the dendritic cell, ribosomes and vaccine mRNA generate the viral protein which is then presented to the T and B cells in the lymph nodes.*Vaccine example: Pfizer COVID-19 Vaccine (mRNA-CV)*. Viral vector vaccines also use mRNA to code for a protein to be made in the body, however, the method of transport into cells is different. A viral vector will use a harmless adenovirus to introduce the protein to immune cells. The immune cell then creates the protein from the mRNA instructions and triggers an immune response.*Vaccine example: AstraZeneca COVID-19 vaccine (ChAd-CV)*. In addition to an antigen, a vaccine may contain a range of other substances; for example, an immune enhancer (adjuvant) and/or a preservative.[23]

Some people have concerns about animal-derived products such as gelatin in vaccines. This may be for faith-based reasons or concerns about the safety of animal derived products. Very rarely, vaccines provoke a serious allergic reaction called anaphylaxis. The risk of this happening varies from vaccine to vaccine. Over all the risk is between less than one to up to three times, out of every million doses of a vaccine. The components more likely to cause such a reaction are gelatin, egg proteins and antibiotics, although theoretically an allergic reaction can be triggered by almost anything.A person’s allergy history should always be assessed prior to immunisation, however there are very few occasions when vaccines should not be given. A vaccine should not be given when there is a history of anaphylaxis to an ingredient in the vaccine, except for egg anaphylaxis and influenza vaccine, or to a previous dose of the same vaccine. A vaccine can be given when past reactions were not anaphylaxis, for example, reactions which have only involved the skin.[24,25]

CONCLUSIONS

The evolution of vaccination efforts in India is far more complex than presented in this review and every single event merits a detailed analysis. Though preventive efforts from diseases were practiced in India, the reluctance, opposition and slow acceptance of vaccination have been the characteristic of vaccination history. The operational challenges keep the coverage inequitable in the country. The lessons from the past events have been analysed and interpreted to guide immunization efforts. There are many lessons learnt from the history from extending the benefits of immunization to every possible beneficiary in the country to achieve the stated policy goals.

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