Vaccination: A Public Health Intervention That Changed History & Is Changing with History

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ABSTRACT

One of the most successful prophylactic interventions in the history of public health, vaccination helped control some of the deadliest and most debilitating infectious diseases. As a result of vaccination programs, smallpox was eradicated worldwide, poliomyelitis was nearly eradicated and emerges as the next eradication target, and national programs helped reduce the incidence of tuberculosis in many countries. Other, more recent vaccines have already achieved a visible impact, as revealed by the ability of the hepatitis B vaccine to decrease the number of new hepatitis infections and the incidence of hepatocellular carcinoma. While vaccination, like any other medical intervention, may have adverse effects, significant controversies gravitated, in recent years, around its supposed link to autism. One of the articles that provided substantial support for this link was recently retracted amid evidence of ample scientific and ethical misconduct. As studies from several countries found that the incidence of autism was increasing even after the removal of thimerosal from vaccines, it appears that, in all likelihood, this trend was not caused by the mercury-containing preservative, and potential causes have to be pursued somewhere else. Although many early vaccines were prepared empirically from live attenuated or inactivated pathogens, recent years have witnessed a shift toward a more rational strategy, in which concepts from disciplines including molecular biology, genomics, proteomics, and bioinformatics are increasingly incorporated into vaccine design, transforming vaccinology into a dynamic and vibrant interdisciplinary field.

Key Words: Infectious diseases; vaccination; public health.

Infectious Diseases in the Pre-Vaccination Era

Global life expectancy at birth, ~28.5 years in 1800 and ~31 years in 1900, increased over the past two centuries in the developed world, and over the past 50 years in the developing world, almost exclusively as a result of reduced mortality from infectious diseases. This became possible as a result of improved sanitation, the discovery of antibiotics, and vaccination (Bonanni, 1999; Riley, 2005).

During the second half of the 19th century, 100 to 350 infant deaths per 1000 live births occurred in the United States and Western Europe, and about 40–50% of the infant deaths between 1870 and 1900 in the United States were caused by infectious diseases (Lee, 2007). A drastic decline in infant mortality during the late 19th century and early 20th century in the United States and Western Europe resulted mostly from a decrease in infectious disease-related deaths and improved nutrition (Lee, 2007).

In the years preceding the vaccination era, between 1783 and 1800, 50% of children in Glasgow died before reaching age 10, and 40% of those deaths were caused by smallpox, which at the time was the leading cause of blindness in Europe (Henderson, 1997). National statistics from several European countries, including England, Norway, and Sweden, reveal that smallpox directly caused 8–20% of all deaths during the 18th century, in addition to increasing the risk of death from other causes (Bonanni, 1999). No treatment exists for the infection, which presented with febrile prodrugme and a generalized vesicular/pustular eruption with lesions at the same stage of development on any body part (Figure 1). When the World Health Organization (WHO) global vaccination campaign started in 1967, smallpox was still causing 10 to 15 million infections annually, and ~30% of those infected died (Bean, 2011).

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Between 1922 and 1931, ~1.7 million cases of pertussis (whooping cough) caused 73,000 deaths in the United States, as compared to a more recent 10-year period from 1983 to 1992, when slightly over 34,000 cases claimed 56 deaths (Cherry, 1999). In Japan, where the triple diphtheria, pertussis, and tetanus (DPT) vaccine was introduced in 1947, the number of whooping cough cases decreased from 100,000, and 15,000 deaths, to <300 and no deaths in 1974. After a national debate over the DPT vaccination led to its replacement with the bivalent diphtheria and tetanus (DT) vaccine, the incidence of pertussis started to increase, and a 1979 outbreak caused 13,000 infections and 41 deaths (Amanna & Slifka, 2005).
Poliomyelitis, an infectious disease that has existed since antiquity, caused annual outbreaks in the United States from the early 1900s until 1955 when the first vaccine, the inactivated poliovirus vaccine (IPV), also known as the Salk vaccine, was introduced (Salk et al., 1954; De Jesus, 2007). In 1988, approximately 1000 children worldwide were still becoming paralyzed by polio every day (WHO, Heymann & Aylward, 2006). As a result of the Global Poliomyelitis Eradication Initiative, launched in 1988 by the WHO together with Rotary International, U.S. Centers for Disease Control and Prevention (CDC), and UNICEF, the number of recorded poliomyelitis cases decreased worldwide from 350,000 in 1988 to <20,000 in 1999 and to 680 in July 2006. The number of endemic countries decreased from 125 in 1988 to 30 by late 1999, and in 2008 only four countries, Afghanistan, India, Nigeria, and Pakistan, reported the infection (Hull & Aylward, 2001; Dutta, 2008). Polio vaccination reduced the annual number of paralytic polio cases in the United States from 10,000 to approximately 10 (Nathanson & Martin, 1979). The fact that not more than 90% of the children in the United States were immunized indicates that either the vaccine spread to those unimmunized and conferred protection, or that herd immunity limited the spread of the virus through the population and eventually prevented infection even among those who were not immunized (Nathanson & Martin, 1979).

Vaccinology is thought to have started on 14 May 1796, when Edward Jenner inoculated a young boy, James Phipps, with *Vaccinia* virus that he obtained from lesions on the hands of a milkmaid, Sarah Nelmes, who was infected accidentally by a cow called Ros ebud (André, 2003). Months later, the boy was immune to infection with *Variola* virus. The concept of “variolation,” which consists of opening pustules from smallpox victims and placing dried material into the nostrils of susceptible individuals, or injecting the pustular fluid subcutaneously to induce a milder form of the disease and confer subsequent immunity, was applied before Jenner, and was reported by Lady Mary Wortley Montagu, who in 1721 learned it from Greek women in Constantinople and brought it to England. The method appears to have been used in China during the 10th century A.D. and was also practiced in India and Africa (Dinc & Ulman, 2007). The worldwide implementation of smallpox vaccination was one of the greatest success stories in medicine and public health, and on 9 December 1979, the WHO declared smallpox eradicated. Another defining moment in vaccinology was in 1885, when Louis Pasteur developed the rabies vaccine, which was the first vaccine created in the laboratory (Bagnoli et al., 2011). Vaccines currently save 3 million children annually, but an additional 2 million children die every year from vaccine-preventable infectious diseases (Bonanni, 1999).

**Vaccine Safety Monitoring**

Vaccination is one of the most effective tools in preventing infectious diseases, and one of the most significant and successful public health interventions in history (Omer et al., 2009). Like any medical intervention, adverse effects have been reported after vaccinations, and these include local reactions such as redness, swelling, tenderness, or pain, and systemic effects such as headaches, fever, nausea, allergic reactions, or seizures. In 1990, the CDC and the Food and Drug Administration jointly established the Vaccine Adverse Event Reporting System (VAERS) to collect information about adverse effects developed to vaccines licensed in the United States (Zhou et al., 2003). Between 1 January 1991 and 31 December 2001, for > 1.9 billion vaccine doses distributed in the United States, VAERS received 128,717 reports (Zhou et al., 2003).

This initiative helped implement changes for several vaccines. Between September 1998 and December 1999, VAERS received 121 reports of adverse effects after infants who received the rhesus rotavirus tetravalent (RRV-TV) vaccine developed intussusception. In mid-July 1999, the manufacturer voluntarily stopped distributing this vaccine, and after concluding in an October 1999 review that a higher risk for intussusception exists 1 to 2 weeks after vaccination, the Advisory Committee on Immunization Practices (ACIP) withdrew its recommendation for using this vaccine (Zhou et al., 2003).

VAERS was also valuable in guiding decisions during the polio vaccination campaigns. The oral polio vaccine (OPV) has been used in the United States since 1963 to prevent poliomyelitis, and this vaccine helped eliminate the disease. One of its adverse effects was vaccine-associated paralytic poliomyelitis (VAPP), a neurological complication thought to occur approximately once every 2.4 million vaccine doses, or once in every 750,000 first vaccine doses. VAPP occurs when a mutation is introduced into the live attenuated vaccine virus, by a process known as reversion, and generates a viral strain that is more neurovirulent. In an attempt to reduce the incidence of the VAPP, in September 1996 the ACIP recommended a sequential vaccination schedule in which IPV is followed by OPV. No VAPP reports were received after 1997 and, on the basis of this positive result, in July 1999 the ACIP recommended that IPV be used exclusively in the United States, to prevent polio and, at the same time, to prevent the rare adverse effects caused by OPV (Zhou et al., 2003).

**Vaccines & Autism**

One of the most fervent public health debates, the connection between vaccines and autism, was fueled by a study published on 28 February 1998 in the *Lancet* that proposed a link between mumps-measles-rubella (MMR) vaccination and autism (Wakefield et al., 1998; Poland & Spier, 2010). Several concerns were raised in the years after the study was published, and multiple discrepancies emerged upon investigation. Only one of the 12 children described in the study had clear regressive autism, and several participants described as having autism did not have this condition (Deer, 2011). Even though the study indicated that the 12 children were “physically normal,” several of them exhibited developmental delay prior to being vaccinated (Deer, 2011).
Although the original study described the children as a “consecutive series,” it later emerged that they were highly selected (Wakefield et al., 1998; Deer, 2011). In addition, the study did not include control subjects, relied heavily on parental recollection and beliefs, and was conducted for the purpose of litigation (Payne & Mason, 1998; Deer, 2011; Godlee et al., 2011). The article was eventually retracted 12 years later, on 2 February 2010 (Editors of the Lancet, 2010).

Nevertheless, this study significantly contributed to widespread fear of vaccination, resulted in many unvaccinated children, and diverted substantial resources from pursuing the real causes of autism (Oakley & Johnstone, 2004). With many parents reluctant to vaccinate their children, MMR immunization rates in the United Kingdom dropped from >90% before 1998 to ~80% in 2003–2004 (Miller & Reynolds, 2009). A measles outbreak occurred in Ireland between December 1999 and July 2000, leading to the death of three children, and in the United States, the first half of 2008 saw the largest measles outbreak since 2000, when the disease was declared eliminated (McBrien et al., 2003; Gross, 2009).

Honda et al. (2005) examined the cumulative incidence of autism-spectrum disorders between 1988 and 1996 in the Kohoku Ward, the city of Yokohama, Japan, where MMR vaccination declined between 1988 and 1992, when the vaccine was discontinued. The authors found a significant increase in the cumulative incidence of autism-spectrum disorders until age 7, from 47.6/10,000 in children born in 1988 to 117.2/10,000 in children born in 1996, and this increase was most dramatic after 1993, which indicates that the vaccine was unlikely to be the cause of autism.

Thimerosal & Vaccines

Thimerosal has been, for >50 years, one of the most widely used preservatives in vaccines (Baker, 2008; Miller & Reynolds, 2009). One of its metabolites, ethylmercury, does not accumulate in the body or in the brain but is metabolized and cleared from the organism (Miller & Reynolds, 2009). Thimerosal use is rooted in vaccine safety, which historically represented a major concern, particularly because of the dangers of bacterial contamination. The severe consequences of vaccine contamination are illustrated by multiple examples; for instance, 68 severe adverse reactions and four deaths occurred in 1916, when a batch of typhoid vaccine stored at room temperature became contaminated in Columbia, South Carolina, and 12 of 21 children inoculated with contaminated diphtheria vaccine died of staphylococcal infection in 1928 in Queensland, Australia (Baker, 2008). Since 1968, the U.S. Code of Federal Regulations has required the use of preservatives for multidose vaccines, to reduce bacterial contamination (Amanna & Silika, 2005). In 1999, the American Academy of Pediatrics and U.S. Public Health Service (CDC, 1999) recommended removing thimerosal from vaccines as soon as possible to avoid any potential risks while, at the same time, ensuring high vaccination coverage and low disease levels in the pediatric population. Subsequently, thimerosal was progressively removed from childhood vaccines, and by March 2001 all vaccines for infant use in the United States contained, at most, trace amounts of thimerosal (Schechter & Grether, 2008).

Fombonne et al. (2006) examined a group of >27,000 children attending 55 schools in Montreal who were born between 1987 and 1998. They reported that the incidence of developmental disorders was increasing, but thimerosal exposure was not related to this trend. Children vaccinated with thimerosal-free formulations had a higher incidence of developmental disorders than those who received thimerosal-containing vaccines (82.7/10,000 vs. 59.5/10,000). Most importantly, this upward trend continued even after 1996, when thimerosal was completely removed from childhood vaccines. Schechter and Grether (2008) examined data from the California Department of Developmental Services and found that autism showed a consistent increase in prevalence among children born between 1989 and 2003, an interval that included a period when exposure to thimerosal-containing vaccines declined. Stehr-Green et al. (2003) compared thimerosal exposure from vaccines with the prevalence of autism in children from Sweden and Denmark, where autism-like disorders started to increase in incidence between 1985 and 1989, a trend that accelerated in the early 1990s. This analysis revealed that the increased number of autism diagnoses occurred at a time of decreasing use and eventual elimination of thimerosal from vaccines. Hviid et al. (2003) conducted a population-based study on all children born in Denmark between 1 January 1990 and 31 December 1996. In Denmark, only the whole-cell pertussis vaccine contained thimerosal after 1970, but the last batch was distributed in March 1992, and the vaccine was subsequently manufactured without thimerosal until 1997, when it was replaced with an acellular pertussis vaccine. This unique set of circumstances opened the possibility to compare children who received the same vaccine with and without thimerosal, and the analysis revealed that the risk of autism-spectrum disorders did not differ between the two groups.

Some studies found associations between mercury exposure in pregnant women and autism-spectrum disorders. For example, in a prospective blinded analysis that enrolled 100 participants, Geier et al. (2009) found that infants of mothers with six or more amalgam dental fillings were more likely to be diagnosed with autism than infants born to mothers with less than five amalgam fillings. Interestingly, in a recent analysis that examined the relationship between the proportion of vaccinated children and the prevalence of autism and speech language impairment in the United States between 2001 and 2007, Delong (2011) found a statistically significant positive correlation, with an additional 680 children with autism or speech language impairment for every 1% increase in vaccination. Although the study had several limitations, it opens the intriguing possibility that other compounds from vaccines could link them to autism.

Vaccine Refusal & Opposition to Vaccination

Opposition to vaccination has existed worldwide since the introduction of the first vaccines and can have serious medical and public health consequences (Poland & Jacobson, 2011). Warrain (2009) reported that during the polio vaccination campaigns, religious opposition in Nigeria, Pakistan, and Afghanistan represented a major factor in the failure of immunization programs, and pointed to tribal conflicts in Pakistan as some of the biggest challenges. In 2003, political and religious leaders in three northern Nigerian states urged parents not to have their children vaccinated, telling locals that vaccines contained “corrupted and tainted” by western “evildoers.” Some vaccinators were kidnapped and beaten, and the Taliban issued fatwas to denounce vaccination campaigns as a western ploy. As a response to the vaccination boycott that ensued, the federal government in Nigeria set up a committee in October 2003 to study the safety of the vaccine, but several controversies followed, and the impasse was not resolved until July 2004, through a dialogue in which the WHO and UNICEF, along with local religious leaders, played significant roles (Jegede, 2007). However, this opposition resulted in polio cases in locations that previously had been declared disease-free.
As a result of recent concerns, most of them unfounded, parents in many locations worldwide refused to vaccinate their children, a practice that opened fervent public health debates (Omer et al., 2009). The implications become even more significant if we consider that the benefits of vaccination extend beyond the vaccinated individual and impact the community. One of the important concepts in vaccination is "herd immunity," which refers to the fact that vaccinating a large percentage of the population slows down the circulation of the pathogen in the entire population (André, 2003). Herd immunity explains why even if not everyone in a population is vaccinated, the efficient transmission of the pathogen slows down when most individuals in the community are immunized, and the pathogen cannot sustain itself and disappears (Anderson & May, 1990; John & Samuel, 2000; Garnett, 2005). There is also evidence that vaccination in children protects adults by herd immunity, as revealed in the case of the protein-polysaccharide conjugate Streptococcus pneumoniae vaccine that was licensed in 2000 for use in small children and, in addition to protecting children, also appeared to reduce disease incidence among adults (Whitney et al., 2003).

In the United States, various states allow opt-outs from vaccination based on medical, religious, or philosophical reasons. As a result, pockets of low vaccination coverage were described in various states, and these appear to overlap with local outbreaks of vaccine-preventable infectious diseases (Bean, 2011). Between 1991 and 2004, the mean state-level nonmedical exemption rate for vaccination increased from 0.98% to 1.48%, and children with nonmedical exemption have a higher risk of acquiring and transmitting infectious diseases that are otherwise preventable by vaccination (Omer et al., 2009).

In 2008, five cases of Haemophilus influenzae type B were reported in Minnesota, in children under age 5 who resided in different counties and had no relationship to one another. One of them died from meningitis (CDC, 2009; Gross, 2009). Of the five children, three were not vaccinated because the parents or guardians refused or delayed vaccination. These were the largest number of cases reported in one year since 1992, when 10 cases were reported in Minnesota (CDC, 2009). In California, 10 deaths from pertussis that were reported during 2010 constituted the worst outbreak since 1958, and 9 of the 10 children had not received the vaccine (California Department of Public Health, 2010).

Rogers et al. (1993) reported that between 4 November 1990 and 24 March 1991, 486 of 892 individuals from two Philadelphia church communities that did not accept vaccination developed measles. These outbreaks caused six deaths, with an overall case-fatality rate of 1.2% (2% for females), indicating a potentially high risk of disease and sometimes death among individuals who refuse vaccination on religious grounds.

Feikin et al. (2000) conducted a population-based retrospective cohort study in Colorado, between 1987 and 1998, to examine whether personal exemption from vaccination increases the personal and community risk for infectious diseases. The authors found that individuals who received exemptions were 22× more likely to contract measles and 6× more likely to contract pertussis than vaccinated children. The risk was even higher for children in day-care and primary schools, who had a 62× higher risk for measles and a 16× higher risk for pertussis. This was the first study to find an excess risk of pertussis among exemptors, and it also revealed that exemptors place vaccinated children at risk for measles and pertussis infections.

Between 1991 and 2004, Omer et al. (2008) analyzed the nonmedical school exemptions for vaccination in Michigan and reported considerable overlap with the foci of pertussis outbreaks. In addition to the increased individual risk, the authors also revealed an increased infection risk at the community level.

Education about Vaccines

Although vaccination, like any other medical intervention, may have risks, the benefits to the individual and to society outweigh, by far, the adverse effects (Poland & Jacobson, 2000). In analyzing how the 1998 Lancet article made headlines, Poland and Spier (2010) emphasize that its results were widely reported and sensationalized in the press, and many in the public received the idea of a link between vaccines and autism without criticism. This was compounded by a response from public health authorities that, in addition to being delayed, did not contain clear and actionable messages for the public. One of the consequences was that many parents did not vaccinate their children, or discontinued vaccination schedules that had already been initiated. As a result, many children became sick or died, creating a public health tragedy that should have been avoided.

Communicating the benefits and the potential adverse effects associated with vaccination, and ensuring that the public receives accurate information, is an important topic that needs to be addressed at several levels. This aspect becomes challenging, particularly when information from many sources can easily be disseminated online. After examining 772 Internet links, Wolfe et al. (2002) focused on 22 sites that provided antivaccination information, and revealed that three major themes presented on these websites revolve around vaccine safety, concerns about governmental abuse, and a preference for alternative health practices. The sites surveyed relied heavily on emotions. Over half of them provided written testimonies by parents who believed that vaccination harmed their children, and almost one-fourth included pictures of affected children. Diseases including autism, asthma, diabetes, learning disabilities, decreased immunity, and underreporting of the adverse effects were some of the claims found on these websites, and underreporting was frequently explained as being part of a deliberate cover-up. Violations of civil liberties were mentioned on 77% of the sites as a concern surrounding mandatory vaccination, despite the fact that vaccination has represented one of the most successful public health interventions in history.

Bean (2011) revealed that online materials were more likely to convey antivaccination messages, and to contain unverified information, than printed resources. The author emphasized that even though health-care providers used to be the primary source of medical advice, consumers and patients increasingly receive information though the Internet, where information can be provided indiscriminately by anyone and vaccination objections and adverse effects can be sensationalized.

In 2006, during the first 120 days after the human papilloma virus (HPV) vaccine was licensed, Habel et al. (2009) examined 250 online articles and reported that even though most of them explained the link between HPV and cancer, information about safety, adverse effects, and the duration of protection were frequently missing. The authors underscored the need to monitor the content of online stories by public-health educators and respond to inaccurate information.

Silberg et al. (1997) emphasized that the vast amount of incomplete, inaccurate, and misleading information found online represents a significant problem not only in medicine but also in other fields, and it is especially challenging when anyone can become, simultaneously and anonymously, an author, an editor, and a publisher, making it particularly difficult to distinguish “the useful from the harmful.”
Vaccination in the “-omics” Era

The vast majority of human vaccines were developed empirically, before the field of immunology was established. Bagnoli et al. (2011) described three generations of vaccines. The first generation, based on the principles developed by Pasteur, included whole-organism vaccines that used inactivated or live attenuated pathogens, such as the smallpox vaccine or the Bacillus Calmette Guerin (BCG) vaccine for tuberculosis. The second-generation vaccines, known as subunit vaccines, used purified or recombinant microbial components, and their development was greatly facilitated by the recombinant DNA technologies, which opened the possibility to generate highly purified components (Bambini & Rappuoli, 2009).

Recent developments in immunology, genomics, proteomics, and bioinformatics, together with the Human Genome Project, which unveiled the extent of inter-individual genetic variability, opened a new era in vaccination. The possibility of applying structural and functional genomics to the field of vaccinology enabled the rational development to be greatly facilitated by the recombinant DNA technologies, which allow the sequencing and assembly of entire microbial genomes within days, at lower costs and with higher accuracy than before, greatly facilitated this process.

The first approach that applied the “-omics” sciences to vaccine design was reverse vaccinology, first used for Neisseria meningitidis serogroup B, for which conventional strategies failed to provide an efficient vaccine. After sequencing the genome of a virulent meningococcal isolate, bioinformatics algorithms were used to identify the genes that encode putative surface proteins, which are promising vaccine candidates. Of the putative genes that were identified and cloned, 350 candidate antigens were successfully expressed in E. coli and purified, and after immunizing mice, the sera were used to explore the surface localization of the antigens and their ability to induce bactericidal antibodies, which correlate with protection. This approach led to the identification of 28 surface-exposed antigens, 5 of which were selected on the basis of their ability to provide broad strain coverage and introduced into a multicomponent vaccine (Pizza et al., 2000; Serruto et al., 2009).

One of the shortcomings of reverse vaccinology is that only one strain is used and the genetic variability that exists among strains within a bacterial species is, therefore, not represented in the vaccine. Streptococcus agalactiae, a group B streptococcus that is a major cause of infections in newborns, provides an interesting example. Although clinical isolates from Europe and the United States mostly belong to five serotypes, several additional serotypes were described, and comparative genomics revealed significant differences between them (Serruto et al., 2009). This indicated that a vaccine, when based on the sequence of a single strain, does not capture the extensive variability among strains, and including genomes from several strains may be necessary. Tettelin et al. (2005) developed the concept of a pan-genome, which represents the total gene repertoire of a bacterial species and consists of three components: a “core genome” shared by all isolates, a “dispensable genome” present in some strains, and strain-specific genes that exist only in certain strains. When Maione et al. (2005) applied this concept to vaccine discovery, from four bacterial antigens identified through bioinformatics approaches and subsequent animal testing, the authors revealed that only one was part of the core genome, and the other three were part of the dispensable genome. This underscored the need to sequence multiple bacterial isolates to ensure that several genomes are included and increase the likelihood that more of the relevant virulence factors are captured during vaccine development.

A third approach, comparative reverse vaccinology or subtractive reverse vaccinology, relies on comparing pathogenic genomes with nonpathogenic ones to identify genes that are relevant for pathogenesis (Serruto et al., 2009; Moriel et al., 2010). Moriel et al. (2010) sequenced an E. coli strain involved in neonatal meningitis and, after comparing its genome with that of other pathogenic and nonpathogenic E. coli strains, reported a marked diversity that exists not only between pathogenic and nonpathogenic strains, but also among pathogenic strains that cause similar diseases. This strategy helped identify several protective antigens that emerge as promising vaccine candidates.

In 2007, Poland et al. (2007) introduced a new term, “vaccinomics,” which incorporates immunogenetics and immunogenomics concepts, and the authors later broadened this definition to include heterogeneities in the host response during vaccination. This has opened avenues toward generating personalized vaccines that are tailored to the subpopulational and individual level. After more than 200 years, vaccinology emerges as a vibrant and dynamic field that is actively reshaped by advances in other biomedical areas, which help not only to generate safer and more efficient vaccines, but also to understand the complexity of the immune response during vaccination, still an elusive topic.

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