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New Vaccines in the Pipeline 2019

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Before clinicians can administer a vaccine in the United States, the FDA must approve and license it. Investigators conduct extensive research leading up to this process, typically testing a vaccine in thousands of patients over 6 to 7 years or longer.[1] Even with large sample sizes and rigorous study designs, rare adverse effects may be missed. For example, RotaShield, the first vaccine for rotavirus, was withdrawn from the market in 1999, despite being tested in more than 10,000 patients. Postmarketing surveillance demonstrated that a rare, yet serious, risk of intussusception was linked to the vaccine, and the FDA determined that the vaccine's risks outweighed its benefits.[2]

Once the FDA approves a vaccine, the CDC's Advisory Committee on Immunization Practices (ACIP) can make a recommendation for its use. Although the FDA focuses on the safety and efficacy of the vaccine, the ACIP can consider more aspects, such as the epidemiology of the disease, health economic impact, and implementation challenges, when making its recommendation.[3] In addition, the US Department of Defense advocates for expedited development, review, and emergency use authorization of medical products that may benefit the US military forces or the general public.[4]

According to the World Health Organization, 240 vaccines were in development for 25 infectious diseases.[5] Topping the list for most candidate vaccines are HIV/AIDS, malaria, pneumococcal infections, tuberculosis, and Ebola.

Vaccines of interest in development include those for the following conditions listed in the table.[6-19]

TABLE. VACCINES IN THE PIPELINE[6-19]

- **Dengue virus:** Infection with dengue virus may cause internal bleeding and even death. The virus is transmitted by mosquitoes, and approximately one-third of the world's population lives in endemic areas.[6] Puerto Rico is the only commonwealth in the United States endemic for dengue. Dengvaxia, the first licensed dengue vaccine approved by the FDA in May 2019 for children aged 9 through 16 years with confirmed past dengue infection living in endemic areas was shown to effectively prevent all 4 viral serotypes.[7] Two phase 3 clinical trials in Asia and Latin America with more than 35,000 participants demonstrated a 59.2% efficacy in children aged 2 to 16 years; efficacy was even higher (65.6%) among children aged 9 to 16 years.[8]
- **Rotavirus:** Rotavirus infections cause nausea, vomiting, and diarrhea in pediatric patients, resulting in dehydration. Children 5 years or younger have an 80% chance of infection if they are unvaccinated.[9] Current vaccines are given at 2 months of age, but investigators are evaluating an oral vaccination, RV3-BB, that can be used at birth.[10] The preliminary results compare favorably with those of other licensed vaccines, such as Rotarix and RotaTeq.[10]
- **HIV:** In 2017, approximately 36.9 million people worldwide were living with HIV, with 1.8 million receiving a new diagnosis.[11,12] Challenges in creating a viable HIV vaccine include the rapid mutation of HIV strains, which would require multiple vaccines or a vaccine that can deliver immunity to multiple subtypes.[13,14] RV144, a promising HIV vaccine, demonstrated modest protection against infections, with an estimated cumulative vaccine efficacy of 60.5% after 12 months of vaccination in low-risk individuals.[15] Currently, the HIV Vaccine Trials Network is supporting 2 large-scale clinical trials to assess the safety and efficacy of a modified vaccine based on the RV144 vaccine and a novel vaccine targeting multiple HIV subtypes.[16]
- **Tuberculosis (TB):** Despite effective treatment options for TB, the disease remains one of the deadliest, with approximately 25% of the world's population infected with TB and 1.3 million TB-related deaths worldwide.[17] Although the Bacillus Calmette–Guérin vaccine has been available for decades, it is not considered effective against pulmonary TB, the most common form in the United States. Investigators are evaluating potential TB vaccines including whole-cell vaccines, adjuvanted proteins, and vectored subunit vaccines.[17,18]
- **Pneumococcal infection:** Investigators are testing a novel 20-valent pneumococcal conjugate vaccine (20vPnC) in phase 3 trials in subjects 18 years and older. This specific pneumococcal vaccine includes the 13 serotypes found in PCV13 as well as 7 additional serotypes known to be global causes of invasive pneumococcal disease and antibiotic-resistant strains. The 20vPnC vaccine has received breakthrough therapy designation by the FDA, which may provide eligibility for accelerated approval and priority review pending phase 3 trial results.[19]

New Delivery Systems

Combination vaccines are advantageous because they mitigate the burden of multiple injections, reduce the number of visits, and save on costs for storage and shipment.[20] In 2018, the FDA approved a new hexavalent vaccine, DTaP5-HB-IPV- Hib (Vaxelis, Merck) for primary and booster vaccination in infants and toddlers against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and invasive disease caused by Haemophilus influenzae type b.[21,22]

Vaccine adjuvants are important for eliciting desired protective and sustained immune responses against target pathogens.[23] In recent years, investigators have studied many novel adjuvants for clinical development, such as the oil-in-water emulsion MF59, which is currently being used in Fluad, an influenza vaccine, as well as ASO1B (eg, Shingrix, GSK) and CpG 1018 (eg, Heplisav-B, Dynavax).

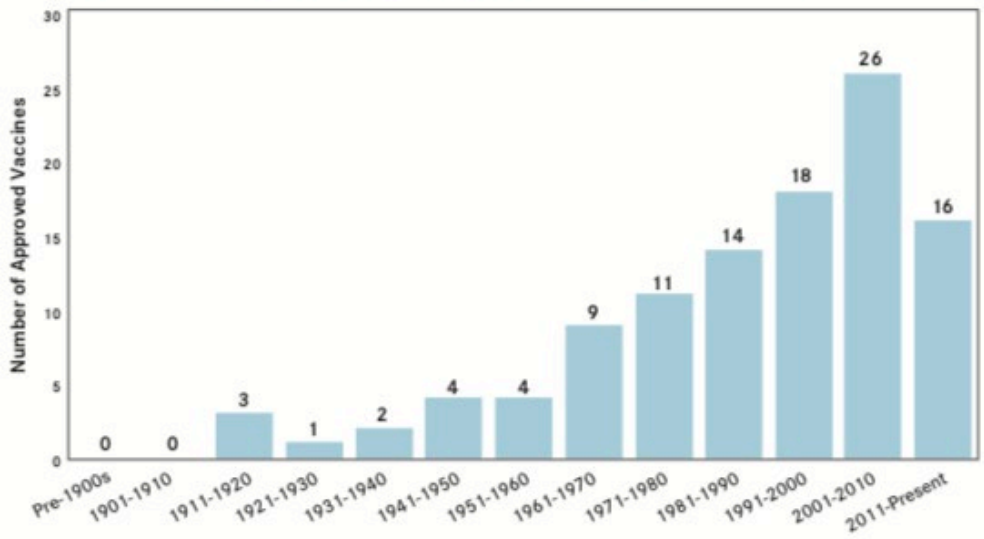
Novel Vaccines

Vaccine technology has also been applied to the treatment of noninfectious disease conditions and areas such as cancer,[24] smoking cessation,[25] and hypertension.[26] Vaccines that target tumor-associated antigens have been shown to prolong the survival of patients with metastatic melanoma with minimal toxicity.[27] An angiotensin II vaccine is also in development for hypertension.[26]

CONCLUSION

The challenges that investigators face while developing a vaccine are unique, from infectious diseases that mutate at varying rates to efforts to develop a safe vaccine that not only targets the correct strain but also elicits an adequate immunologic response. Although this article has discussed a handful of vaccines in the pipeline, investigators are evaluating many others on a global scale. Despite the obstacles for vaccine development, FDA vaccine approvals have accelerated over the past 2 decades, making the prevention of even more human diseases in the future a realizable prospect (figure).[28]

FIGURE. NUMBER OF VACCINES APPROVED BY THE FDA OVER TIME IN THE UNITED STATES*



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