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Commentary

Global vaccine supply. The increasing role of manufacturers from middle income countries

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ABSTRACT

Hallmarks in the remarkable evolution of vaccines and their application include the eradication of smallpox, the development and delivery of the early childhood vaccines and the emergence of recombinant vaccines initiated by the hepatitis B vaccine. Now we enter a most exciting era as vaccines are increasingly produced and delivered in less developed countries. The results are dramatic decreases in childhood morbidity and mortality around the world.

1. Introduction

As the causative agents of human infectious diseases have been discovered over the years, and approaches to their diagnosis and prevention developed, great progress for disease control has followed. A hallmark date in the history of infectious disease control using vaccines was October 1977. That was the onset of the last case of community-acquired smallpox in the world. For this disease, the protection of humans by inoculating them with cowpox had been discovered almost 200 years before. But it was the technologic advances of vaccine production, developed in the mid-1900s, which gave public health the tool that enabled the world to eradicate the disease. These advances enabled production of a low cost, heat stable vaccine that was easy to reconstitute and deliver. The supply of millions of doses of this highly effective vaccine enabled the successful eradication of this deadly disease. A second hallmark era occurred between 1950 and 1970 with the development and delivery of large numbers of additional childhood vaccines. During this period, great advances were made in growing and safely and effectively inactivating microorganisms. And a slew of safe and effective vaccines emerged. A third hallmark was the licensure in 1986 of the first recombinant protein vaccine for hepatitis B virus. Since then there has been a veritable rush of new, safe and effective vaccines that take advantage of a wide variety of new technological advancements for development, production and delivery of vaccines. These advances have led to the licensure of vaccines for meningitis, pneumonia, haemophilus influenza B, hepatitis B, typhoid, hepatitis A, rotavirus, HPV (cervical cancer), Japanese encephalitis, and more.

Importantly, the decreases in the burden of diseases resulting from the application of these vaccines have not been limited to the wealthy residing in the industrialized nations of the world. Indeed, with concerns for disease occurrence in all corners of the world, nations and wealthy, socially conscious organizations have put resources into vaccine development, purchase and delivery so that children in all corners of the world could realize the benefits. Here a forth hallmark is emerging as more and more of the world's vaccine supply is now increasingly being produced in high-tech facilities in middle income countries (MICs). Not only have many of these countries become self-sufficient in vaccine production, but also many are now supplying high quality vaccines to their neighbors.

2. Initial vaccine successes

Looking back, the inauguration of the era of vaccines started with the discovery of the vaccine to prevent smallpox. Here, English farmers and physicians in the late 1700s noted that cowpox infection, transmitted to the milk maid's hands from the teats of infected

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Table 1
Smallpox Vaccine Production in India – by national production facility 1962–1977.[a]

Period	Patwadangar	Belgaum	Guindy	Hyderabad	Total
1962–63	38,368				38,368
1963–64	87,171		609		87,780
1964–65	480,208		5418		485,626
1965–66	1,202,296		212,565		1,414,861
1966–67	858,889	172,000	380,639		1,411,528
1967–68	959,931	620,155	557,867	173,685	2,311,638
1968–69	1,188,680	1,123,031	852,667	401,827	3,566,205
1969–70	1,077,385	812,383	470,000	466,759	2,826,527
1970–71	829,054	498,337	1,114,000	244,657	2,686,048
1971–72	1,185,385	1,164,037	792,662	381,434	3,523,518
1972–73	2,765,181	1,447,573	1,204,684	442,398	5,859,836
1973–74	4,054,862	2,317,641	1,627,417	807,542	8,807,462
1974–75	3,298,075	3,174,857	1,886,277	1,065,035	9,424,244
1975–76	2,853,113	1,908,252	1,721,082	691,073	7,173,520
1976–77	1,545,918	1,888,716	1,628,057	569,657	5,632,348
Total	22,424,516	15,126,982	12,453,944	5,244,067	55,249,509

[a] Production expressed in numbers of ampoules: 1 ampoule contained 12–15 doses upon manufacturer's recommendations. However, with the introduction of the bifurcated needle, 50–70 vaccinations could be given from 1 ampoule [5].

cows, prevented them from being infected with smallpox. Derivatives of this smallpox vaccine were used extensively from that time onward. Initially, the common practice was to take scabs from a recently vaccinated person and use that material to inoculate the next person. But, this practice had clear infectious disease risks since, along with vaccinia virus, these scabs carried other infections such as syphilis and hepatitis. Recognizing this risk, in 1898, the British government outlawed the practice of person-to-person vaccination.

This decision became practical once large-scale vaccine production processes had been developed that did not rely on humans as the source of vaccine. For smallpox vaccine, such processes were first launched by the Director of Italian vaccines, Gennaro Galbiati in 1810. Here the vaccine production "factory" was the underside of a cow that was scratched and inoculated with vaccinia-containing fluid. Days later, as vaccinia-filled pustules developed on the cow's skin, the pus was harvested and vialed as vaccine.

In the end, it was further improved production systems which enabled the successful eradication of the disease. Using locally produced vaccines, many countries in the world, including China, had successfully eradicated smallpox. But many others had remained with active infection. In 1966, the United States launched a program to assist 18 West African countries using US-produced smallpox vaccine to eliminate the disease. During this effort, the crucial concept of search and containment was developed and, soon thereafter, smallpox was eradicated from all targeted countries in West Africa [1].

With these successes, discussions began about the feasibility of actual eradication of smallpox from the remaining 50 or so countries of the world where transmission continued. Despite the dramatic proof-of-concept successes in the West African program, some, including the Director General of the World Health Organization (WHO) at the time, said the concept of worldwide eradication was impossible [2]. But in an unusual joining of often opposing forces in the Cold War era, Russia and the United States spoke with a common voice [3] and, in 1966, WHO's World Health Assembly called for a global effort to eradicate smallpox.

But, without the proper tool (a safe and effective vaccine), eradication could not be possible. Indeed, it was recognized at the time that much of the vaccine used around the world to prevent smallpox was sub-standard. This weakness had to be overcome if the program was to succeed. To this end, Dr. Isao Arita from Japan joined in Geneva and took on the task of improving vaccine potency for all vaccines produced for the eradication program. Because of the frequent discovery of low potency vaccine from many countries, almost all of the vaccine initially used for smallpox eradication came from the United States and Russia. But, with focused efforts on improving production in endemic countries, a huge technology transfer effort followed. By five years into the eradication effort, 80 percent of the vaccine in use was of high quality. And it was being produced in endemic countries [4].

As the worldwide eradication effort expanded, the demands for vaccine became immense and the expansion of vaccine production became crucial for the success of eradication. Take, for example, vaccine production in India. At the beginning of smallpox eradication, India produced 1.4 million ten-dose vials of smallpox vaccine per year. By the time smallpox was eradicated a decade later, India's output had increased to almost 9 million vials per year (Table 1) [5].

3. New development

Learning from the success of smallpox vaccination, early researchers took on the quest to develop additional vaccines to prevent other diseases. Courageous European researchers, including Pasteur, Roux, Yersin and Koch, developed vaccines to prevent rabies, typhoid, cholera, plague and more [6].

Following this remarkable initial era came a second. Here, from the 1950s to the 1970s, with the discovery of more advanced viral culture systems, the modern age of vaccine production emerged. This opened a new era in the prevention of infectious diseases of humans and resulted in safe and effective vaccines for measles, mumps, rubella, varicella and Japanese encephalitis.

Up to this point, the standard *in vitro* culturing tools for microbial growth and inactivation had been used to produce vaccines. These systems relied on culturing the infectious agents in the laboratory and either inactivating them (for a "killed" vaccine) or making them less virulent (for an "attenuated" vaccine).

This remarkable era was soon to be replaced by another equally exciting one that began with the advent of recombinant technology. This third era introduced a time when vaccine developers could begin to focus their development and production systems on the exact portion of the infectious agent's structure which would stimulate protective immunity. Here, after understanding the site to which protective immunity was directed, recombinant "gene jockeys" could snip out or add in genes to make safe and effective vaccines. Then they developed production systems and commanded them to produce large quantities of subunit or live virus vaccines. These advancements have opened up vast possibilities since, in the past, many of the known infectious agents could