Vaccine 32 (2014) 5259–5265

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Commentary

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

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ARTICLE INFO

Article history:
Received 17 April 2014
Received in revised form 27 June 2014
Accepted 18 July 2014
Available online 8 August 2014

Keywords:
Vaccine
Supply
Production
Less develop countries

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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http://dx.doi.org/10.1016/j.vaccine.2014.07.069
0264-410X/

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

not be successfully grown in culture systems that could be used for large-scale vaccine production.

In addition, along with the tools of recombinant technology, came an improved ability to understand the varied intricacies of vaccine production. This understanding, and the resulting skills, opened a remarkable opportunity to produce large quantities of low cost vaccines. This allowed national and international disease control experts to combine forces to take on international disease control programs that were just not conceivable in earlier times.

4. Expanded delivery of existing vaccines (the EPI)

The early process of moving modern quality standards for the production of smallpox vaccine into less developed country vaccine facilities had far greater ramifications than just the eradication of smallpox. Indeed, the 1980s initiated a new era for vaccines as worldwide vaccine delivery experts joined up to take on the elimination of multiple other diseases for which vaccines had already been developed. With a clear understanding of the capability of the developing country manufacturers to produce vaccines and their immunization teams to deliver them, international collaborative institutions provided funds to purchase vaccines to prevent many diseases and deliver them to the children in need. The primary focus at that time aimed at the delivery of the recommended routine immunizations to all children of the world. And, as the years progressed, many of these vaccines were produced in the affected countries.

CDC physician Rafe Henderson had worked on several international assignments, including a two year stint with smallpox in West Africa. When the director of the successful Smallpox Eradication Programme, DA Henderson, returned to the US, Rafe took over in Geneva. With smallpox gone, his role, was the Director of WHO's new Expanded Programme on Immunizations (EPI). This program was designed to markedly increase the proportion of children in the world receiving all of the recommended childhood immunizations. He described the legacy that the smallpox eradication program had on this new assignment:

> "... I went back to WHO in 1977 ... when I went back, a lot of the ... smallpox ... *workers remained* ... So suddenly I had a ... large staff of people who had that same motivation, who had that same perspective, coming ... into the Expanded Program on Immunization. They continued on to do polio eradication, the diarrheal disease program, a whole slew of very, very important public health initiatives." (Table 2) [7]

Table 2
Vaccine development initiatives.

Initiative	Founded
Viral Hepatitis Prevention Board	1992
International AIDS Vaccine Initiative	1996
Malaria Vaccine Initiative	1999
Hookworm Vaccine Initiative	2000
AERAS Global TB Vaccine Foundation	2001
Dengue Vaccine Initiative	2001
Meningitis Vaccine Project	2001

These field-experienced delivery experts understood their role as "advisors" to whatever country in which they were assigned. They understood that the success of each village, district, province and country depended on the responsible local and national workers at each of these levels. They had learned from their previous assignments that, as an international assignee, their job was to advise and support these local people. They did their jobs well. These advisors joined with experienced national teams and life-saving vaccines were delivered by the millions.

In the 40 years since the launching of the EPI, the results in protecting the world's children have been quite amazing. Fig. 1 documents the changes in routine diphtheria, tetanus and whooping cough vaccine (DTP) coverage from 1980 onward. At the beginning of the EPI, only one in five children (20%) had received the recommend three doses of DTP. By 1985 this had climbed to 49% and, by 1990, to 75%.

This huge childhood vaccination effort, extending from Geneva to Ministries of Public Health in dozens of countries and then on down to each country's rural health care workers, had an immense effect on preventing these terrible diseases that, in previous years, had so severely affected young children. Not surprisingly, the most rapid vaccine coverage took place in the American, European and Pacific Regions of WHO (Fig. 2). It took longer to reach higher childhood coverage in the South East Asia, African and Eastern Mediterranean Regions. But, as a whole, the dramatic increases in childhood vaccine coverage, in all areas between 1980 and 2000, were truly remarkable and carried huge health benefits.

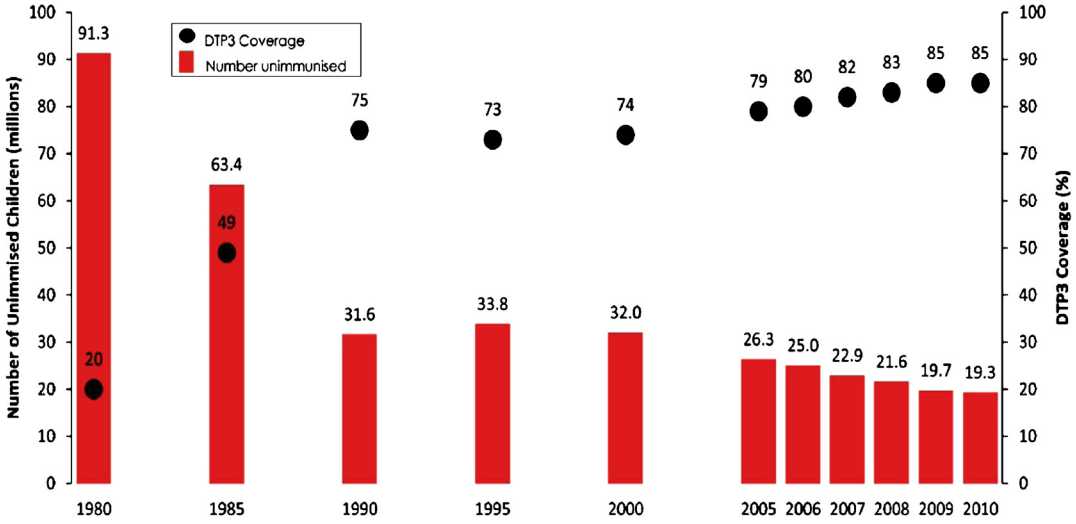

Fig. 1. Global routine immunization coverage with three doses of diphtheria and tetanus toxoid with pertussis (DTP3) vaccine.
Source: WHO and UNICEF estimates of national routine immunization coverage, 2010 data revision (July 2011); Population data for surviving infants obtained from United Nations, Department of Economic and Social Affairs, Population Division (2011). World Population Prospects: The 2010 Revision, CD-ROM Edition.

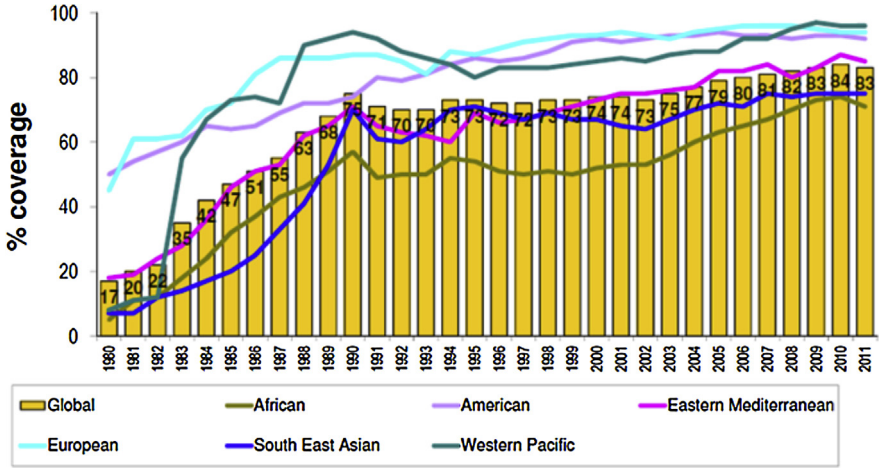

Fig. 2. Global Immunization 1980–2011, DTP3 coverage global coverage at 83% in 2011.
Source: WHO/UNICEF coverage estimates 2011 revision, July 2012. Immunization Vaccines and Biologicals, (IVB), World Health Organization. 194 WHO Member States, Date of slide: 18 July 2012.

5. Increased vaccine production

The increased effort to deliver vaccines stimulated a logical follow-up call. Recognizing the immense need for additional supplies, there was a need for increased production of all recommended childhood vaccines. To ensure the quality of these vaccines, in 1987 WHO set up its "prequalification programme" to "ensure that the vaccines supplied through (United Nations procurement agencies) are consistently safe and effective under conditions of use in national immunization programmes [8]." This has required a major, long-term, effort on the part of WHO to, first, strengthen national regulatory authorities and, subsequently, undertake site audits of the manufacturing facilities themselves.

The results have been more-than-impressive. Over the years, there has been a dramatic increase in the production of high quality vaccines from emerging market vaccine manufacturers. In 1997, these manufacturers supplied less than 10% of vaccines purchased by UNICEF. By 2012, that proportion rose to approximately 50% [9]. Parallel figures from the Global Alliance for Vaccines and Immunizations (GAVI) describe the evolution of vaccine suppliers from 2001 to 2011 [10]. GAVI reports that, of their six suppliers of vaccines in 2001, only one was located in an emerging market country with the remaining ones being from industrialized countries. This changed in 2010. By then, of the ten manufacturers that supplied vaccines to GAVI, five were in emerging market countries (Fig. 3).

6. Increased vaccine development

In parallel with this remarkable expansion of vaccine production and delivery in emerging market countries, there has been a proliferation of new organizations with the specific goal of stimulating vaccine development for diseases that are highly prevalent in less developed areas of the world. Led by the Bill and Melinda Gates Foundation, these have included PATH, the GAVI Alliance, the Sabin Vaccine Institute, the Task Force for Global Health and others.

These funders and interest groups have, in large part, stimulated disease/vaccine-specific development organizations that, over the past decade or two, have been leaders in the development of new candidate vaccines for HIV/AIDS, meningitis, hepatitis, malaria, dengue and tuberculosis (see Table 2). Important for these endeavors has been the realization that, for many of these infections, the major burden of disease was carried by less developed areas of the world. As a result, for these diseases, the financial incentives for industry to invest the considerable funds necessary to develop new vaccines were minimal. Thus, there was an obvious need for special funding to counter-balance the absence of financial market incentives.

An interesting follow-on cycle has occurred. As new vaccines were developed, it stimulated interest in vaccine production in emerging market countries. Once interest in vaccine production is stimulated, it necessitates the development of both the skills and facilities necessary to successfully produce vaccines. This has often followed by a re-stimulated interest to build expertise to develop improved vaccines for existing diseases. And with this expertise, some are exploring the development of entirely new vaccines.

7. The examples of Brazil, India and China

To better describe this evolution, we have selected three countries: Brazil, India, and the People's Republic of China (China). These have been chosen because the vaccine production organizations of each of these have evolved quite differently. Each, like most large countries, had historically relied on state-run vaccine companies to supply vaccines since the early 1900s. But, with the massive technological evolution that followed, major adjustments to vaccine production were necessary and different countries followed quite different paths.

Brazil represents a country where its Constitution includes the right to health care and, for vaccines, the government supplies vaccines for its population. The vast majority of these government supplied vaccines are provided by two vaccine producers – the Instituto Butantan in Sao Paulo and Bio-Manguinhos/Fiocruz in Rio de Janeiro (Table 3A). These two organizations supply over 80% of the vaccines for Brazil [10]. At Butantan, besides its massive production efforts, it has undertaken research on both new vaccine adjuvants, and early development of vaccines for rotavirus and dengue virus. Furthermore, Butantan has been funded by the WHO to manufacture vaccines against potential pandemic influenza viruses such as H5N1 and H7N9 [11].

India's vaccine developers followed different paths (Table 3B). Like most large countries, by the middle of the 1900s, India established government vaccine production facilities in several areas of the country. These were followed, between 1984 and 1989, by the establishment of three new public sector vaccine companies (Bengal Immunity, Ltd., Bharat Immunologicals and Biologicals Corp., Ltd., and Indian Vaccine Corporation, Ltd.) that were opened in different areas of India. Neither of these government efforts did well. Only Bharat (not to be confused with Bharat Biologicals),

Table 3
(A) Brazilian vaccine companies. (B) Indian vaccine companies. (C) Chinese vaccine companies.

No.	Name of company	Vaccines marketed	Vaccine in development	Location
(A) Brazilian vaccine companies				
1	Butantan	Tetanus toxoid DTP (peds and adult) Recombinant hep B Rabies Vero Cell Influenza	Dengue (NIH) Rotavirus (NIH) Pneumococcal Schistosomiasis (Sabin Inst.) Recombinant BCG Whole-cell pertussis with lower content of LPS	Sao Paulo
2	Fiocruz	DTP-hep B Yellow fever Hib Meningitis A and C Polio MMR	Chagas	Rio de Janeiro
(B) Indian vaccine companies				
1	Shantha	Hep B* Tetanus toxoid* Cholera O1/O139*	HPV Vi-dipth toxoid Rotavirus	Hyderabad
2	Bio E	DTwP–Hep B–Hib* Tetanus toxoid* JE inactivated* DTwP DT Td Hep B IPV Hib-DTP-hepB	Hib conjugate DtwP–HBV Mening A + C + Y + W135	Hyderabad
3	Bharat biotech	H1N1 Influenza Meningitis Rotavirus	Malaria Conguj. typhoid	Hyderabad
4	Panacea Biotec	Recomb Hep B DTP-HepB-Hib* Bivalent Inactivated whole cell oral cholera	Influenza Dengue Anthrax JE	New Delhi
5	Serum Institute	BCG* Tetanus toxoid* DT* DTP* Hib conjugate* Td* Rabies* Measles* MR* MMR* Rubella* DTP–HBV* DTP–Hib* DTP-HBV-Hib* Meningitis A conj* HepB* OPV1,3* OPV1,2,3* Rotavirus Attenuated H1N1*	Mening A conjug. Mening A + C + Y + W135 Pneumococcal Conguj.	Pune
6	Bharat Immunologicals and Biologicals Corp	Oral Polio		Bulandshahr. UP
(C) Chinese vaccine companies				
1	CNBG (China National Biotech Group), has 6 Institutes	Over 30 vaccines: HBV, BCG, OPV, Measles, MMR, Rubella, DTP, DTaP, MR, Hib, MenA + C + Y + W135, 23Pnu polysacchaide, Rotavirus, Varicella. JE* (Chengdu) TT, TD, Cholera, Typhoid Vi-polysaccharide, Hantaan virus. Anthrax, influenza, Hep A, Rabies	Rotavirus, Ev71, PCV13, New BCG, Sabin-IPV, HPV, recombinant smallpox	Beijing, Shanghai, Lanzhou, Changchun, Wuhan, Chengdu
2	Sinovac	Hep A, Hep A + B, Influenza,	EV71, PCV13, Sabin-IPV	Beijing
3	Minhai Biotech	MR, DTaP, DTaP + Hib, Hib, HBV	MMR, PCV15, HPV, BCG	Beijing/Shenzhen
4	Zhifei Biotech	HBV, Hib, Meningococcal A + C + Y + W135 Polysaccharide, MenA + C conjugate. MenA + C + Hib	PCV13, Varicella, Typhoid conjugate	Chongqing/Beijing

Table 3 (*Continued*)

No.	Name of company	Vaccines marketed	Vaccine in development	Location
5	Walvax-Biotech	Hib, Men polysaccharide A+C+Y+W135, MenA+C conjugate, Hep A. DTaP	HPV, PCV, Rotavirus, Influenza, Typhoid	Kunming
6	Forwell Biopharma	Rabies	Meningococcal A+C+Y+W135, Influenza, Ev71, DTaP. JE	Yanjiao Hebei
7	Huabei Pharma	HBV		Shijiazhuang
8	Hualan Bio	Influenza, HBV, MenA+C+Y+W135	Rabies	Xin Xiang
9	Hissen Biopharma	HBV, Rabies, influenza		Dalian
10	Chengda Biotech	Rabies, JE	Influenza	Shen Yang
11	Yisheng Biotechnology	Rabies, JE, HBV	Rotavirus	Shen Yang
12	Promise Biologicals	Rabies		Guangzhou
13	Hutchison MediPharma	Hep A, influenza		Shanghai
14	Innovax Biotech	Recombinant Hepatitis E	HPV	Xiamen
15	Shanghai United Cell Biotech	Cholera (whole cell)	HepB	Shanghai
16	Research Institute of Medical Biology, Chinese Academy of Medical Science	OPV, Hep A	Sabin-IPV	Kunming
17	Jenner Bio	Subunit influenza		Tianjin
18	Changsheng Bio	DTaP, Rabies, influenza, Varicella, Hep A		Changchun
19	Royal (Wuxi)Bio	Men A+C Conjugate Hantaan virus (HFRS)		Wuxi
20	Hengye		JE, Mumps, HPV	Qingdao
21	Cansino		Pnu protein vaccine, Men A+C+Y+W135 conjugate	Tianjin

* WHO Prequalified.

has survived, but, even its survival is in question [12]. In contrast to these public institutions, India's private vaccine manufacturers have done far better. These companies, Shantha (now part of Sanofi), Biologicals E, Bharat Biotech, Panacea Biotec and Serum Institute of India, produce a wide variety of state-of-the-art vaccines, including several for export. Indeed, all of these companies have WHO approved products – most notably, the Serum Institute, with over 20 WHO approved vaccines. Moreover, like Butantan, these companies are exploring the development of early-stage candidate vaccines including one for malaria.

China has been different from both Brazil and India. And it is still evolving (Table 3C). Here the former six central government pillars of the vaccine production located in six regions did not die off like those in India. Instead, they have joined together to form the China National Biotech Group (CNBG) owned by the central government. This group of companies produces over 30 different vaccines and one of these (Chengdu) has recently received WHO approval for their Japanese encephalitis vaccine. In addition to the CNBG, there has been a remarkable proliferation of private or semi-private vaccine companies throughout the country. At last count, there were at least 20 companies from 14 provinces. Of the non CNBG companies, two have yet to have a licensed vaccine, eight have one or two licensed vaccines and eight others have between 3 and 5 licensed products. Many of these companies have a wide variety of new products in development.

8. Looking ahead

These three examples mirror the variation that has been seen throughout the world. Each of these three countries considers vaccines to be essential tools for the health of their citizens. Each has developed companies differently and each has produced vaccines differently. But the bottom line has always been the same – lives saved, misery averted and financial burdens avoided.

The progress in worldwide vaccine production and application has resulted in disease control successes that have stimulated even more interest in both developing new vaccines and improving the delivery of existing ones. These combined successes form a remarkable story. And the story continues with ever-expanding goals. The successes of one aspect feed the successes of the next and the cycle continues to expand. We can only imagine what the next chapters will bring in this remarkable venture.

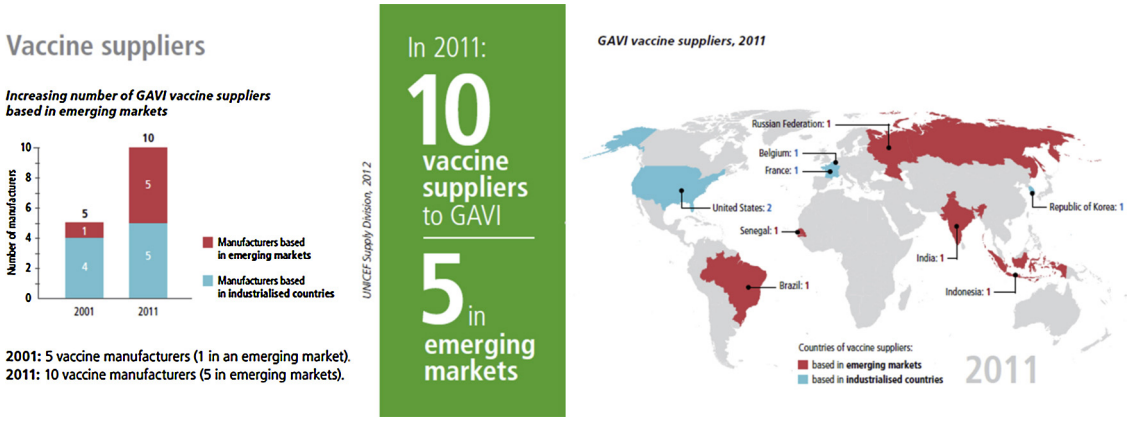

Fig. 3. Vaccine suppliers to GAVI.

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