

Review Article

Human vaccines industry in China, 2019: Part—I

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Abstract

China is presently the most populous country; the annual birth rate is estimated at above 18 million each year over the next 5 years. The number of the aged population is also increasing. Continuous in-country demand for vaccines will, therefore, be maintained, providing opportunities for the manufacturers. China produces a large number of vaccines, presently estimated at 55 different types, which are used to protect against 28 types of individual infectious microbial diseases. The country has presently a total of 41 vaccine manufacturing companies, of which 21 are the major ones. The manufacturing capacity appears to be over 1000 a million doses per annum and the annual production in 2019 was over 700 million doses. Chinese imports of vaccines have remained low. The major government establishment, the China National Biotec Group (CNBG) companies are the leading manufacturer of vaccines in China and supply more than 50% of all the vaccines consumed in the country. CNBG is a research-driven biotech establishment and is engaged in R&D, manufacturing, marketing, and distribution of vaccines and blood products. CNBG has six institutes of biological products besides other assets; the six institutes are also engaged in the manufacture, distribution, and sale of vaccines through their manufacturing companies and establishments in China. CNBG has seven vaccine manufacturing units. CNBG is a subsidiary of China National Pharmaceutical Group Corporation (Sinopharm). Sinopharm infrastructure shoulders the social responsibility of Chinese national medical and pharmaceutical reserve on a sustainable long-term basis, including handling of emergency situations. Sinopharm is under the State-owned Assets Supervision and Administration Commission (SASAC) of the State Council of China and is engaged in 10 core business activities that cover biopharmaceutical products, including vaccines.

Keywords: Vaccines, Chinese EPI, Sinopharm

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INTRODUCTION

The People's Republic of China (PRC or simply China) is spread over approximately 9,600,000 square kilometers (3,700,000 sq. miles). The country is governed by the Communist Party of China. The government exercises

jurisdiction over its 22 provinces, five autonomous regions, and four direct-controlled municipalities, namely Beijing, Tianjin, Shanghai, and Chongqing. China with a population of 1.404 billion in 2017,^[1] estimated at 1.435 billion by the end of 2019 and anticipated to reach 1.464 billion in 2030,^[2] is presently the most populous country in the world.

China has also two special administrative regions of Hong Kong and Macau. The population referred above excludes the population of Hong Kong (7.39 million in 2018)^[3] and

Received: 16-04-2020

Accepted: 16-04-2020

Published: 06-06-2020

| Access this article online | |
|---|--|
| Quick Response Code: | Website: www.mgmjms.com |
|  | DOI: 10.4103/mgmj.mgmj_27_20 |

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How to cite this article: Ghosh PK. Human vaccines industry in China, 2019: Part-I. *MGM J Med Sci* 2020;7:35-45.

Macau (0.63 million in 2018).^[4] It also excludes the population of “Taiwan”; people living in Taiwan (23.73 million in 2018)^[5] are more than those in Hong Kong and Macau. The relationship between the PRC, commonly known as “China” and “Taiwan” known as the Republic of China (ROC), is complex;^[6] the two regions are separated geographically by the Taiwan Strait in the Western Pacific Ocean. There exists considerable cultural and social bondage and commonality among the people in these regions.

There were 17,230,000 births in China in 2017, which was slightly lower than those in 2016. According to the prediction by certain groups on birth rates for the future years, a bleaker picture has been projected; these predictions indicate that the birth rate would have continued to decline from 2018 onward, and by the next 10 years, there will be approximately 8 million births per year.^[7] The predictions are based on the projection of a decrease in the number of Chinese women aged 23–30 years by 40% in another 10 years, which is substantial. The above projection of approximately 8 million annual birth rates seem to be much on the lower side; it is probable that the predicted decline shall stabilize at around 12 million births by the next 10 years from the present annual birthrate of around 18 million. China had introduced in 1979 its one-child rule, enforcing people to adopt the policy; noncompliance was linked with fines, loss of jobs, or to face forced sterilization and abortions. This policy was withdrawn and was replaced by the introduction of the universal two-child policy in October 2015, with a view to promote a faster population increase to meet the future needs of the workforce of China. The new policy had stimulated the additional annual birth rates. During the period from July 2016 to December 2017, there had been additional births^[8] of 5.40 million. However, it was revealed that the birth rates from nulliparous mothers decreased by 3%, whereas there was an increase in the birth from multiparous mothers during the same period. The additional births could not catch up the expected 20 million births^[9] in the highest year. It is however perceived that as the annual birth was 17.86 million in 2016 following the introduction of the two-child policy, the annual birth rate would remain above this figure and is surmised to be above 18 million each year at least over the next 5 years. Further, it has been found that the population of elderly Chinese is increasing fast, and that the country had in 2017, citizens above 60 years of age at approximately 241 million, which was approximately 17.3% of the total population; this number is anticipated to increase to 487 million or nearly 35% of the total^[10] in 2050. For better health, this aging population shall also need a number of vaccines. Therefore, the two-prong demand generation factors for vaccines, one from the increase of

newborn infants and the other from the aged population shall provide newer opportunities for the manufacturers.

It is anticipated that although there would be a continuous increase in the demand for various kinds of childhood disease-preventable vaccines in China over the years during the next one decade, the extent of increase in the annual consumption will depend much on the national policy of the government of China on their Expanded Program of Immunization (EPI). The policy to provide better health to the senior citizens is also likely to push the demand further, especially in the areas of lungs infection and certain chronic diseases linked to specific viruses. The local vaccine-manufacturing companies will have to be alert on these aspects while planning for future production schedules. It is anticipated however that during the next decade, both demand and production will continue to grow, especially because of China's growing interest in increasing health-care activities and health-care costs, which include vaccination of eligible recipients.

The intention of this paper is to assess the emerging strength of the human vaccines industry in China and its impact and competitiveness in serving the humankind not only in China but also to the other parts of the world, especially the regions of poor economic settings. The paper is in three parts: in the first part (**Part I**), the aspects of demand for vaccines in China and the factors driving the demand along with the annual production estimate of doses of vaccines annually manufactured in the country and the major Chinese Government establishments producing these vaccines are described. In the second part (**Part II**), the major Chinese private company-wise information on vaccines production, R&D carried out in these companies and the size of the Chinese vaccine industry in the global context has been described. In the third and final part (**Part III**) of the article, the status of multinational companies (MNCs) manufacturing and selling vaccines in China has been elaborated.

STUDY METHODOLOGY

The study on the Chinese vaccine industry was carried out using data and information collected from the Internet, the certain Chinese government publications, industry publications on websites, and scientific publications by the Chinese scholars, which are available on the web. The sources of information have been cited in the text.

VACCINATION PROCESS IN A NUTSHELL

Vaccination is a process of enabling to acquire capabilities in recipients to protect them from diseases against which

vaccines are used. Vaccination imparts such capabilities in the recipients through the generation of clonal B cells and clonal T cells that have memories to remember the pathogen or its parts; the clonal B cells have, in addition, incessant capabilities of producing clonal immunoglobulins (Igs) that bind and neutralize the pathogens or their parts; further, the clonal T cells produce cytotoxic T lymphocytes, which are capable of lysing the infected cells. The complex formed by the binding of clonal Ig to the pathogens (or their parts) as also, the lysed cells, and the components are cleared by the macrophages continuously from the system, keeping the vaccinated individuals protected from the pathogens. Generation of clonal B cells and clonal T cells are complex cellular processes. In brief, these processes are initiated through the activation of mature but resting T-helper cells. Matured T cells are classified based on the cluster differentiation (CD) proteins (identified by numbers) that the cells acquire on their outer membrane while maturing in the thymus (a lymphoid organ of the immune system). The CD4⁺ T cells of two types designated as CD4⁺ T-helper cell 1 (Th1) and CD4⁺ T-helper cell 2 (Th2) are mainly involved in the immunization process. In one pathway, the antigens from a vaccination process are picked up by the dendritic cells, internalized, processed, and presented to the lymphocytes through a ligand–receptor binding process involving major histocompatibility complex (MHC) molecules classified as MHC class-II, which are encoded by a cluster of genes collectively called the MHC locus, and are present on both the antigen-presenting lymphocytes and the T-helper cells; both of which in turn get activated, process and present the antigens to the resting CD4⁺ Th1 and CD4⁺ Th2. In the Th2 pathway, the activated CD4⁺ Th-2 bind and activate the resting but matured B cells, which in turn get activated and produce clonal B cells; two major types of clonal B cells are thereby produced, one type is clonal B-memory cells and the other type is the clonal B-plasma cells. The B-memory cells remain in circulation and get activated for combating the pathogen in future infection. The plasma B cells incessantly produce clonal Igs, primarily the IgG types that have the capacity to bind to the antigens or their parts. Once bound, the complex is recognized by the circulating macrophage, which engulfs the complex and lyses it, thereby clearing the antigen and preventing the infection. In the Th1 pathway, the lymphocytes present the processed antigen to the resting CD4⁺ T cells subtypes designated as Th1, the latter cells get activated through the ligand–receptor binding process involving MHC-class I molecules, also present on both the cells and in turn multiply and differentiate into multiple activated subtypes, some of which bind on the resting CD8⁺ T cells, activating the latter into cytotoxic CD8⁺ lymphocytes. These activated cells have the capacity

to recognize the infected cells where the pathogens are multiplying, again through a ligand–receptor pathway involving MHC-class I molecules. These cells bind on the infected cells and secrete certain proteins such as granzyme and perforin, which bind on the infected cells and create holes therein, whereby the contents come out. The activated CD8⁺ T cells also secrete larger quantities of tumor necrosis factor alpha (TNF- α) and interferon gamma (IFN- γ) that further facilitates the killing of the infected cells. The macrophages floating around engulf the debris and keep the system clean. These complex processes of vaccination are presented in the form of two cartoons [Figures 1 and 2] for better understanding the immunization process.

HUMAN VACCINES MANUFACTURED AND USED IN CHINA

According to a recent estimate, nearly 700 million doses of various kinds of human vaccines are manufactured at present in China. The eligible children get certain categories of vaccines free of cost through the Chinese EPI up to the age of 14 years. These vaccines are classified as Category-1 vaccines under the Chinese “Regulations on the Administration of Vaccines and Vaccination.” Some of these vaccines such as anthrax vaccines, leptospirosis vaccine, and pandemic H1N1 vaccine is a special, need-based one. All these Category-1 vaccines cited in alphabetical order are: the anthrax vaccines (Anthrax), Bacillus Calmette–Guerin vaccine (BCG), diphtheria-tetanus-pertussis whole-cell vaccine (D Tw P), diphtheria-tetanus-pertussis acellular vaccine (D Ta P), diphtheria and tetanus combined vaccine (DT), Group A meningococcal polysaccharide vaccine (Men A), Group A and C meningococcal polysaccharide vaccine (Men AC), hepatitis A alive attenuated (Hep A-L), hepatitis B vaccine (Hep B), hemorrhagic fever with renal syndrome (HFRS), Japanese encephalitis vaccine (inactivated) (JEV-I), Japanese encephalitis vaccine (live attenuated) (JEV-L), leptospirosis vaccine (Leptospira), measles-rubella vaccine (MR), measles, mumps combined vaccine (MM), measles-mumps-rubella vaccine (MMR), measles vaccine (live attenuated) (MV-L), mumps vaccine (Mumps), poliovirus vaccine-oral (OPV), polio vaccine-injectable (IPV), pandemic influenzae H1N1 vaccine (H1N1), rubella vaccine (Rubella), and tetanus toxoid vaccine (TT).^[11] These vaccines target protection from 17 individual infectious microbial diseases. Various combinations are also manufactured to ease consecutive vaccination against multiple microbial diseases such as DPT (DP wT and DP aT), MMR, MR, and others.

From May 2016, China had adopted the strategy of using at least one dose of IPV in the childhood immunization

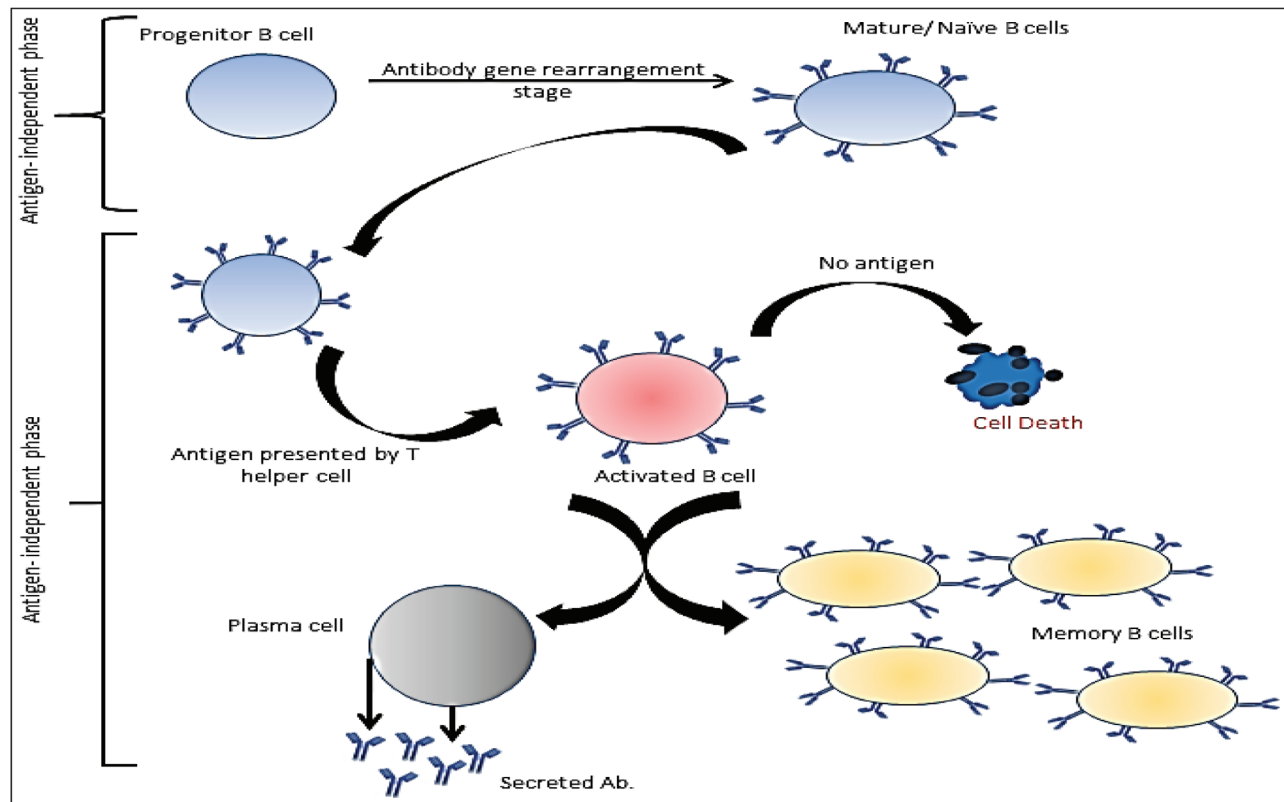


Figure 1: B cell activation process

program, which is a strategy in accordance with the Global Polio Eradication Initiative (GPEI), and which is served to decrease both the incidence of vaccine-derived poliovirus infection and to reduce the risk of infection from wild poliovirus that may enter the country. Since 2000, China has been able to maintain poliomyelitis-free status in the country. A National Immunization Advisory Committee (NIAC) had been created in October 2017 to assess the disease burden of vaccine-preventable diseases and to advise the inclusion of newer vaccines such as vaccines against pneumococcal diseases, *Haemophilus influenzae*, and rotavirus diarrhea, in the National Immunization Program (NIP). China's praiseworthy achievement of protecting their children from infectious microbial diseases through its EPI and NIP requires supplementation and strengthening through the addition of more number of vaccine-preventable diseases such as multiple isolates of *H. influenzae* responsible for meningitis, especially the type b, pneumococcal infections, *influenzae*, rotaviral diarrhea, and some more, which are presently available in China for purchase from the open market, which everyone cannot afford. There are certain other vaccine-preventable diseases, especially like the human papillomavirus (HPV) vaccine. HPV vaccines of multiple types are to be developed and deployed to protect against multiple types of diseases; vaccines against types 16 and 18 for substantial protection

against cervical cancer, against types 6 and 11 for protection of genital warts, and against types 31, 33, 45, 52, and 58 for protection of cervix, anus, vulva/vagina, penis, or throat, respectively. People of both sexes of ages, 9–45 years can receive specific types of HPV vaccines. China has developed considerable expertise in the manufacture of multiple of these vaccines locally. Therefore, the inclusion of these vaccines produced in China in their NIP is feasible if funds are available. Even realizing that this might cause increased strain on health-care budgets, the societal contributions of such endeavor toward better public health is more assured, and therefore it is thought that every effort should be made for allocating funds toward such national efforts rather than resorting to cost-effectiveness analysis-based methods for fund allocation practiced presently.^[12]

All other vaccines used in China, which are either produced by the Chinese government companies or by the Chinese private companies or obtained through imports are classified as Category 2 vaccines. Recipients of these vaccines would have to pay for these vaccines from their own resources. In another study, China has presented a total of 41 vaccine manufacturing companies. These companies have acquired the capacity of manufacturing 55 different types of vaccines, which are used to protect against 28 types of infectious microbial diseases. The vaccines against infectious individual microbial diseases other than those

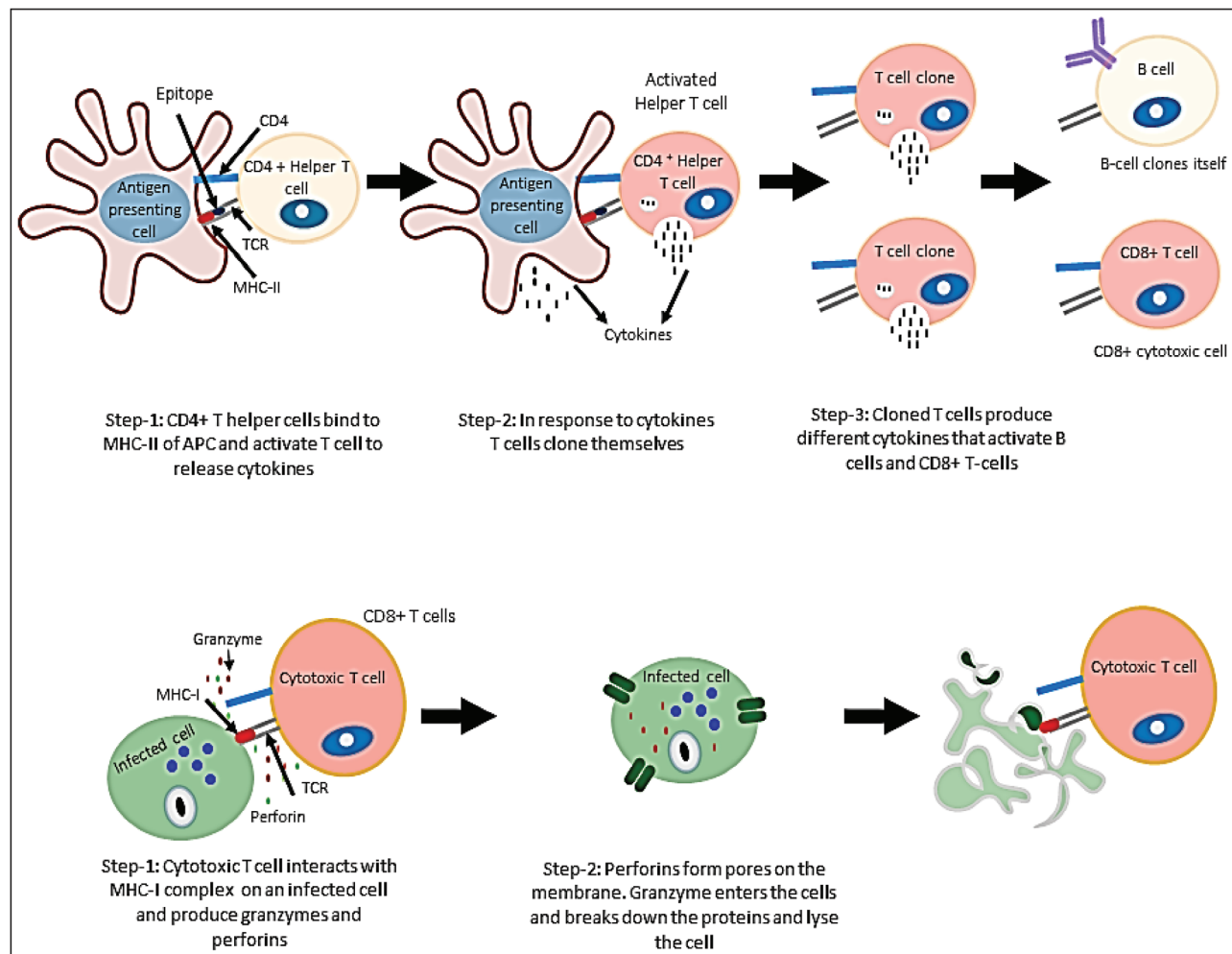


Figure 2: T cell activation process

17 mentioned above under Category-1 vaccines are those for prevention against typhoid fever, rabies, varicella, papillomavirus, plague, shigella, enterovirus 71, herpes, tick-borne encephalitis, *Haemophilus influenzae* responsible for meningitis, and 23-valent pneumococcal polysaccharide vaccine. The Category 2 vaccines are for protection against 11 individual infectious microbial diseases. The use of these vaccines and their extent of use have been instrumental to the substantial reduction of infectious diseases in China.^[13] Several other new vaccines are in the developmental stage.

VACCINES MANUFACTURING MAJOR GOVERNMENT COMPANIES IN CHINA

To understand the nitty-gritty of the manufacturing of human vaccines in China, the federal structure responsible for the manufacture of vaccines needs to be understood. Vaccines are manufactured in China both in the public sector units, owned by the government as also by the Chinese private companies and a few multinational

companies. The Chinese public sector companies presently dominate in the production of vaccines, which are required by the country in the government's National Immunization Program;^[14] the vaccines are made available free of costs to children up to the age of 14 years through the aforementioned Program. The public sector units in China manufacturing human vaccines are operated through a well-need government system. In this paper, the Chinese government infrastructures used for the manufacture of human vaccines are briefly described.

The major government company by the name China National Biotech Corporation (CNBC), renamed later as China National Biotech Group (CNBG),^[15,16] Beijing, China, was established as a research-driven biotech company. CNBG is a subsidiary of China National Pharmaceutical Group Corporation (Sinopharm). CNBG is engaged in R&D, manufacturing, marketing, and distribution of vaccines and blood products in China. The establishment was set up as early as in 1919. Over the years, the

developments in biological products in China have its history of pride and accolades embedded in the roots of CNBG.

Sinopharm,^[17] China, of which CNBG is a subsidiary is a large and the enormous group in China mandated to work on health-care issues of the country. The establishment is guided by its core values of “all for health, health for all,” shouldering the social responsibility of Chinese national medical and pharmaceutical reserves on a sustainable long-term basis. Sinopharm infrastructure promptly gets into action at times of emergency emanating from epidemics and disaster such as the present time of Coronavirus disaster (epidemic of late 2019 caused by a novel coronavirus, now called SARS-CoV-2, causing the COVID-19 outbreak), supplying and providing diagnostic devices, medicines, all kinds of necessary bioproducts, other medical devices, and Chinese traditional medicines promptly at the affected and stricken areas to ascertain, assure, and ensure sound public health conditions for the people. Sinopharm is a large organization and it employs over 128,000 people. It deals with a full chain of activities in health care, including R&D, manufacturing, marketing, and distribution, retail chain activities, engineering services relating to health care, conducting seminars, exhibitions, international services, and financial services through its various arms. It owns over 1,100 subsidiaries and six listed companies in China, which are Beijing Tiantan Biological Products, China National Accord Medicines, China National Medicines, China Traditional Chinese Medicine Holdings, Shanghai Shyndec Pharmaceutical, and Sinopharm Group (Sinopharm Holding). Sinopharm is under the State-owned Assets Supervision and Administration Commission (SASAC) of the State Council of China. Of its 10 core businesses, the biopharma units with six institutes of biological products as the core are included.

Coming back to CNBG, the establishment is engaged in the discovery, development, manufacturing, and marketing of a wide range of human health products, including vaccines, biopharmaceuticals, blood products and derivatives, diagnostic reagents, and others. Under the CNBG, there are presently six renowned institutes of biological products, namely the Changchun Institute of Biological Products (CIBP), Chengdu Institute of Biological Products (CDIBP), Lanzhou Institute of Biological Products (LIBP), National Vaccine and Serum Institute (NVSI), Shanghai Institute of Biological Products (SIBP), and Wuhan Institute of Biological Products (WIBP). Besides, CNBG owns two international trading companies in Beijing, namely China National Scientific Instrument and Materials Import and Export Corporation (CSIMC) and China National Medical

Equipment and Supplies Import and Export Corporation (CNMC). The CNBG Institutes of Biological Products are also engaged in the manufacturing, distribution, and sale of vaccines through their manufacturing companies of different names, established and situated at various parts of China.

The CNBG companies supply more than 50% of all the vaccines consumed locally in the mainland of China in both the government-sponsored free supplies as also the country's trade market. The CNBG companies are the leading manufacturers of vaccines in China. The CNBG as an establishment can be considered to be the prime biological product segment and the arm of Sinopharm. The vaccine-manufacturing units under CNBG have their manufacturing establishments in eight Chinese cities. The vaccines manufactured by these companies meet a substantial part (more than 80%) of the domestic government-sponsored free vaccines, which are required and consumed in the Chinese government's Expanded Program of Immunization (EPI). Chinese EPI vaccines include one dose of BCG, three doses of Hep B, four doses of D Ta P, OPV four doses, live-attenuated measles-containing vaccine (MCV) two doses, two doses of group A meningococcal polysaccharide vaccine (MPSV-A), one dose of live-attenuated Japanese encephalitis vaccine (JE), one dose of live-attenuated hepatitis A vaccine (Hep A-Live), one dose of DT, and two doses of meningococcal A + C polysaccharide vaccine (MPSV-AC).^[18] These six companies continue to supply the maximum quality of vaccines needed by the country. Interestingly, it can be seen that the Chinese EPI does not include any vaccine against *H. influenzae*, an infectious bacterial disease, which is responsible for meningitis in children.

In this context, it is worthwhile to mention that on one hand, although the efforts of the national vaccination program over the years had contributed substantially to containing infectious diseases among the Chinese children, on the other hand, occasional faults or misdeeds practiced by a few individuals at various levels in the huge chain of vaccines manufactured and supplied by the CNBG companies had contributed to mistrust among the Chinese about the usefulness and quality of vaccines supplied by the government free of costs. The latest vaccine scandal in China, which was revealed through an article that appeared in *South China Morning Post*^[19] print edition on July 22, 2018, reported by Leng S and Huang K was about the Jilin Food and Drug Administration's revealing of the sale of some 252,600 substandard DPT vaccines to the Shandong Centre for Disease Control and

Prevention (the agency responsible for providing public health in the Jilin province of about 100 million people) by the Chinese major vaccine manufacturing company Changchun Changsheng Biotechnology, Changchun, Jilin, China. This company was also embroiled and involved in a scandal over falsifying data on the production and sale of approximately 113,000 rabies vaccines, manufactured by it; this information was revealed by China's national drug watchdog on July 15, 2018, after a surprise visit by them to the facilities at the Jilin factory. Before these incidents, the Wuhan Institute of Biological Products, Wuhan, China, was caught by the state drug watchdog, revealing that the company had sold 400,520 inferior DPT vaccines in China.^[20] Wuhan Institute is a Chinese government-owned company. In earlier years also, there had been issues regarding the supply of quality vaccines in China and that this scandal was the third^[21] one during the last 8 years. Distrust in the supplies of government supply of vaccines was brewing among the public. The aforementioned news published in the *South China Morning Post* in July 2018 sparked nationwide anger against the government companies and resulted in fuelling further distrust for vaccines manufactured and supplied by the government companies. The news was widely circulating the world over. It was reported in the *Lancet*^[22] that it was the Chinese government's responsibility that vaccines produced and used in China, need to be effective and safe. Undoubtedly hesitancy for taking vaccines had considerably increased among the Chinese people, and this issue needed to be adequately addressed^[23] in its broader and wider perspectives.

As the Chinese government had done considerable work for improving the health of the Chinese citizens over the years and continues to do so, and further, as it has been well established in China about the benefits of vaccination, for which the country through its public-friendly government policies and the campaign has been promoting immunization of children for years, which has resulted, for example, in the vaccination of 99% of the Chinese infants with three doses of DPT, the brewed public distrust in the use of vaccines manufactured by the Chinese government companies would sooner be melted away.^[24] Moreover, the higher vaccine literacy levels in China would also work in waning the exaggerated and misleading information on vaccination.

After this vaccine scandal, the Chinese President Xi Jinping had ordered an investigation of the vaccine production chain, as a consequence of which the Chinese authorities instituted a detailed investigation and had taken corrective steps in iron-hands, which included among others, the imposition of fines on Changchun to the tune of US\$500,000 for the DPT

problems, and dismissal of a large number of companies' senior executives, including the chairperson.

China also took steps to revise its regulation deficits in the earlier law by the enactment of a new Vaccine Administration Law.^[25] The new Vaccine Administration Law is designed to enforce the adherence and practice of most stringent management rules and procedures to adhere to safety, risk management, process control, science-based supervision, and social co-governance to ensure the delivery of safe and effective vaccines to the users.^[26] It is anticipated that this law shall act as a deterrent toward the circulation of unsafe and infective vaccines in China and would restore public confidence.

The CNBG companies had resumed production and supply of quality vaccines after tightening their systems to be able to supply safe and effective vaccines to the users and had supplied during the period from January to July 2019, over 43% of the total vaccine that was approved for release by the National Institutes for Food and Drug Control (NIFDC) of China. The NIFDC had approved during the period the release of 276.6 million doses of vaccines for use.^[27]

The present annual output of the Chinese vaccines industry is 25 billion yuan (about US\$3.5 billion).^[28] Brief information about the individual CNBG companies specializing in the manufacture of human vaccines are stated as following, in alphabetical order:

Changchun Institute of Biological Products (CCIBPCL),^[29] Changchun, China, is a large state-owned medical and a biotechnology-based enterprise, which is affiliated to the China National Biotech Group (CNBG). The company was founded in 1946. It has nearly 212,000 m² of area and it employs over 1000 people. CCIBPCL has established a culture of high-class R&D, manufacture, and sale through high-class management skills. Through its vaccine manufacturing establishments, the vaccines manufactured and marketed include influenzae vaccine (split virion), H1N1 influenzae vaccine (split virion), influenzae vaccine (split virion quadrivalent), hepatitis A vaccine (freeze-dried live attenuated), tick-borne encephalitis vaccine (inactivated), and hamster kidney cell-based hemorrhagic fever with renal syndrome bivalent vaccine. Vaccines under development include hepatitis E vaccine, Vero cell-based rabies vaccine for human, inactivated hepatitis A vaccine, Vero cell-based tick-borne encephalitis inactivated vaccine, and Vero cell-based hemorrhagic fever with renal syndrome bivalent vaccine. They also manufacture a large number of other biologicals, including recombinant DNA-based products. The company produced for the first time the recombinant DNA-based

hepatitis B vaccine in China. CCIBPCL is one of the most important Chinese biotech enterprises, which have made noteworthy contributions in the biotech area in the country.

Changchun Qijian Biological Products^[30] (Qijian Bio), Changchun, China is a wholly owned subsidiary of China National Biotechnology, a subsidiary of China National Pharmaceutical Group Corporation. It is a key enterprise of biological products in the Jilin Province of China. The company was established in December 2003. The company is established in an area of 30,000 m² and is stated to have total assets of 42,295.66 million yuan. The main vaccine product of the company is the attenuated live varicella vaccine. The company is the largest manufacturer of varicella vaccine in China. The company has established European Union standards in its lab, which is built in an area of 18,000 m² and which is a current good manufacturing practices compliant facility. The whole production area is spread in the built-in area of 23,732 m². Qijian Bio is engaged in high-class R&D, manufacture, and sale of biological preparations, including handling of the disease-producing varicella virus.

Chengdu Institute of Biological Products (CIBPCL),^[31] Chengdu, China is a part of CNBC. CNBC is now named as CNBG. CIBPCL was established in 1958. CIBPCL is one of the largest R&D and manufacturing entities in biological products in China. The facilities are established in the city of Chengdu over an area of 480,000 m². The company employs over 1,400 people, of which more than 50% are scientific and technical people. CIBPCL in collaboration with the National Institute of Control for Pharmaceuticals and Biological Products, China, had developed the process for the manufacture of JE (live vaccine SA14-14-2). CIBPCL currently produces and supplies this vaccine.

Lanzhou Institute of Biological Products (LIBPCL), Lanzhou, Gansu Province, China, is a part of the CNBG. The company produces a large number of vaccines besides a wide range of biologicals, including anti-sera. The vaccines manufactured and supplied include^[32] in alphabetical order, anthrax vaccine (live), brucella vaccine, diphtheria vaccine (adsorbed), diphtheria and pertussis combined vaccine (adsorbed), *H. influenzae* type b conjugate vaccine, hepatitis B recombinant vaccine (CHO cell-based), influenzae vaccine (split virion based and whole virion based), JE purified vaccine (PHK cell line based), measles vaccine (live), meningococcal Group A polysaccharide vaccine, meningococcal Group A and C polysaccharide vaccine, plague vaccine (live), pertussis (whole-cell inactivated) vaccine, pertussis acellular vaccine (adsorbed), rabies vaccine (hamster kidney cell based) for human use, rubella

vaccine (rabbit kidney cell based), R hemorrhagic fever with renal syndrome bivalent purified vaccine (Vero cell based), *Shigella sonnei* vaccine freeze-dried oral bivalent (live), tetanus vaccine (adsorbed), and typhoid and paratyphoid A and B combined vaccine. LIBPCL was established in 1934. Situated in the northwestern region of the country, the company is mainly engaged in the development and manufacturing of biological products,^[33] which include vaccines, toxins, antitoxins, blood products, and human *in vitro* diagnostic reagents. LIBPCL is a key enterprise in the country in the field of biological products and specializes in medical microbiology, immunology, and molecular biology. The company has a total land area of 430,000 m².

National Vaccine and Serum Institute (NVS),^[34] Beijing, China, is involved in the production of bacterial and viral vaccines, toxoids, and analogous biological products. NVS belongs to the CNBG. It inherits the culture of a 100-year scientific research undertaking that was being carried out in Beijing. Presently, NVS focuses on the national disease prevention strategy and modern vaccine development research with a sharp focus on the evolving of key technologies and processes. At present, the company is involved in the development of an 11-valent recombinant HPV vaccine.^[35]

Shanghai Institute^[36] of Biological Products (SIBP), Shanghai, China is a subsidiary of China National Biotech Group, National Pharmaceutical Group Corporation; it is a state-owned enterprise engaged in research, development, manufacturing, and marketing of biological products. SIBP was founded in 1949. The organization also confers master's degree in biochemistry and molecular biology, and pathogenic biology as an authorized entity. Several postdoctoral research works are carried out at the organization. The name of the organization is presently changed to Shanghai Biological Products Research Institute (SBPRI); the organization is under the Ministry of Health, China. Among the vaccines manufactured by the organization include the varicella vaccine (attenuated live), measles, mumps, and rubella combined vaccine (attenuated live), rubella vaccine (human diploid cell-based attenuated live), measles and mumps combined vaccine (attenuated live), inactivated H1N1 influenzae A vaccine (split virion), inactivated influenzae vaccine (split virion), measles vaccine (attenuated live), intradermal BCG vaccine, adsorbed diphtheria, tetanus, and pertussis combined vaccine, adsorbed diphtheria, tetanus, and acellular pertussis-combined vaccine, Vi polysaccharide-based typhoid vaccine, leptospira vaccine, and Group A Meningococcal polysaccharide vaccine. SBPI is engaged in technology development and improvement through its

multiple research establishments of technology platforms, through which it develops technologies for vaccines and several other biological products.

Wuhan Institute of Biological Products, Wuhan, China, is engaged in the manufacture of biological products in the range of vaccines, blood products, new therapeutic substances, diagnostic reagents, and medical devices.^[37,38] The vaccines include Vero cell-based enterovirus 71 inactivated vaccine, live-attenuated JE vaccine, diphtheria-tetanus-pertussis (whole cell) adsorbed vaccine, diphtheria-tetanus combined adsorbed vaccine, Group A meningococcal polysaccharide vaccine, typhoid Vi polysaccharide vaccine, and leptospira vaccine. Wuhan Institute was founded in 1950. It had many accolades in the past. It specialized in medical microbiology, immunology, cell engineering, and genetic engineering besides others. It employed nearly 1,200 people of various skills, and the factory area is stated to be spread on over 400,000 m².^[39] The company got into a scandal^[40] in 2018 as reported earlier, by selling substandard diphtheria, tetanus, and whooping cough vaccines for infants, and this was investigated at the highest level in the country to take corrective measures and restore the lost reputation. The Chinese Politburo stated, “[This case] has caused the serious adverse impact, both exposing gaps in our monitoring system, and reflecting systemic flaws in the production and distribution of vaccines. We must learn our lesson, be vigilant, clean up the chaos with severe punishment, and accelerate the improvement of a long-term mechanism for vaccine and drug regulation.” After complete punitive actions taken against the defaulters and after tightening the systemic flaws, the company has resumed production.^[41]

DISCUSSION AND CONCLUSIONS

The Chinese vaccine industry represents a vital part of the health-care infrastructure of the country. Vaccination is the most essential cost-effective means of ensuring the good health of people. Vaccination is provided to the infants, the pregnant mothers, and the older people to protect from various age-related viral diseases as also for the adult population. Presently annually, China has to take care of about 18 million newborn and slightly more number of pregnant women, which is a stupendous task. Category-1 vaccines are provided free of cost to the target recipients and aim at protecting them against 17 individual infectious microbial diseases, whereas Category-2 vaccines are to be procured by paying the costs. Category-2 vaccines are for protection from another 11 infectious microbial diseases. Several of the Category-2 vaccines are equally essential, such as those against rabies, papillomavirus, varicella, and

pneumococcal infection. Extensive use of vaccines against these diseases ensures further improvement in the health care of people. The use of these vaccines would no doubt require additional resources.

In China, major health-care establishments belong to the government. The major government establishments of China on vaccines-related health-care issues are CNBG companies, which are the leading manufacturers of vaccines in China. CNBG has six institutes of biological products besides other assets; the six institutes are also engaged in the manufacture, distribution, and sale of vaccines through their manufacturing companies and establishments, which are situated in various parts of China. There are also a couple of other nationally held biotech companies that are engaged in the manufacture of vaccines. The CNBG companies supply more than 50% of all the vaccines consumed in the mainland of China. CNBG is a research-driven biotech establishment engaged in R&D, manufacturing, marketing, and distribution of vaccines and blood products.

The China National Pharmaceutical Group Corporation (Sinopharm) of China owns CNBG; CNBG is a subsidiary of Sinopharm. Sinopharm is under the SASAC of the State Council of China and is engaged in 10 core business activities, which include activities in biopharmaceutical products that include vaccines. The Sinopharm infrastructure shoulders the social responsibility of Chinese national medical and pharmaceutical reserve on a sustainable long-term basis. At times of emergency emanating from epidemics and disaster, Sinopharm promptly swings into action and start supplying medicines, diagnostic kits, and every other materials required to tackle the situation and to bring back sound public health conditions in the country. The Sinopharm infrastructure is thus an infallible asset of the country.

China produces a large number of vaccines, presently estimated at 55 different types, which are used to protect against 28 individual types of infectious microbial diseases. The country has presently a total of 41 vaccine manufacturing companies. The manufacturing capacity appears to be over 1000 million doses per annum, and the present annual production is over 700 million doses. The imports of vaccines have remained low.

There is perhaps a need for expansion of the number of vaccines used in the Chinese EPI program, and if additional funds are available, then considerations for use of one or more from the list of vaccines against such diseases as typhoid fever, varicella, papillomavirus, *H. influenzae* responsible for meningitis, and multivalent pneumococcal

polysaccharide vaccines could be considered for inclusion. Such actions would no doubt improve the spectra of protection of the children and young people of the country against these diseases.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Ghosh: Human vaccines industry in China, 2019: Part-I

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