

# Impact of BRICS' investment in vaccine development on the global vaccine market

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**Abstract** Brazil, the Russian Federation, India, China and South Africa – the countries known as BRICS – have made considerable progress in vaccine production, regulation and development over the past 20 years. In 1993, all five countries were producing vaccines but the processes used were outdated and non-standardized, there was little relevant research and there was negligible international recognition of the products. By 2014, all five countries had strong initiatives for the development of vaccine technology and had greatly improved their national regulatory capacity. South Africa was then the only BRICS country that was not completely producing vaccines. South Africa is now in the process of re-establishing its own vaccine production and passing beyond the stage of simply importing, formulating and filling vaccine bulks. Changes in the public sector's price per dose of selected vaccines, the global market share represented by products from specific manufacturers, and the attractiveness, for multinational companies, of partnership and investment opportunities in BRICS companies have all been analysed. The results indicate that the BRICS countries have had a major impact on vaccine price and availability, with much of that impact attributable to the output of Indian vaccine manufacturers. China is expected to have a greater impact soon, given the anticipated development of Chinese vaccine manufacturers in the near future. BRICS' accomplishments in the field of vaccine development are expected to reshape the global vaccine market and accelerate access to vaccines in the developing world. The challenge is to turn these expectations into strategic actions and practical outcomes.

Abstracts in **عربي**, **中文**, **Français**, **Русский** and **Español** at the end of each article.

## Introduction

Through their vaccine manufacturers, Brazil, the Russian Federation, India, China and South Africa have a substantial and increasing role in the global vaccine market. Together, these countries known as BRICS are increasing the production capacity for vaccines with a high global demand and vaccines that are required specifically in the developing world. BRICS are also generally replacing multinational corporations as sources of traditional vaccines – i.e. the five vaccines originally included in the World Health Organization's (WHO) Expanded Programme on Immunization<sup>1</sup> – and enhancing competition and lowering prices in the United Nations' and national vaccine markets.

In this paper, we analyse the growth of vaccine production, vaccine regulation and development in BRICS over the past 20 years. We evaluate the impact of that growth on the global vaccine market, by comparing vaccine production in each of the five countries in 1993 and 2013, analysing the relevant technology sources and collaborations, following the evolution of national regulatory authorities, and determining temporal trends in the numbers of vaccines prequalified by the WHO that were produced. We also identify some of the current limitations of BRICS' vaccine-related strategies and explore ways in which the international community might help reduce those limitations.

## BRICS' role in the global vaccine market

The vaccines needed for the Expanded Programme on Immunization<sup>1</sup> and the subsequent national immunization

programmes were initially sourced from both national and international manufacturers. Recombinant hepatitis B and *Haemophilus influenzae* type b vaccines became available in the 1980s but their production was felt too complex for many vaccine manufacturers. Three major developments subsequently influenced the global vaccine market. One was the introduction, in 2001, of highly profitable products such as the conjugate pneumococcal vaccine, which produced profits measured in billions of United States dollars (US\$).<sup>2</sup> The second major development was the growth of funding initiatives to introduce new vaccines nearly simultaneously throughout the developing world.<sup>3</sup> The third major development was the emphasis placed on quality control and assurance standards for all vaccines used worldwide. This emphasis was mainly the result of the establishment of WHO's programme of vaccine prequalification in 1987<sup>4</sup> and that programme's collaboration with large vaccine procurement agencies such as the Supply Division of the United Nations Children's Fund (UNICEF) and the Revolving Fund of the Pan American Health Organization (PAHO). Vaccine production has become a research-based global business with high industrial standards for quality and the potential for substantial profits. In the early days of the Expanded Programme on Immunization, the prices of the traditional vaccines used in the developing world were low because multinational corporations could produce the vaccines using existing capacity that the corporations did not need to supply their more usual, higher-priced markets. As new more-profitable vaccines became available, however, most of the multinational corporations

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(Submitted: 13 December 2013 – Revised version received: 31 March 2014 – Accepted: 31 March 2014)

Table 1. **Vaccine production, Brazil, China, India, the Russian Federation and South Africa (BRICS), 1993**

Country	Types of vaccine
Brazil	BCG, BMP, DTP, M, OPV, <sup>a</sup> rabies, <sup>b</sup> TT, YF
Russian Federation	DTP, <sup>c</sup> OPV, Hep B, influenza, M, YF
India	BCG, CT, DTP, JE, M, OPV, <sup>a</sup> rabies, <sup>b</sup> Td/DT, TT, YF
China	BCG, BMP, DTP, JE, OPV, M, rabies, rotavirus, TT
South Africa	BCG, DTP, OPV, rabies, TT

BCG: bacille Calmette–Guérin; BMP: bivalent meningitis polysaccharide; CT: cholera and typhoid; DTP: diphtheria, tetanus and pertussis; Hep: hepatitis; JE: Japanese encephalitis; M: measles; OPV: oral polio vaccine; Td/DT: diphtheria and tetanus toxoids; TT: tetanus toxoid; YF: yellow fever.

<sup>a</sup> Although the manufacturer technically produced the final vials of product, the starting material was imported bulk vaccine that had already been prequalified.

<sup>b</sup> Grown in vivo.

<sup>c</sup> With low-dose pertussis.

Data sources: World Health Organization<sup>8,9</sup> and Children's Vaccine Initiative.<sup>10</sup>

stopped producing the older vaccines. Fortunately, the growth of vaccine manufacturing in some of the BRICS countries has helped to keep the prices of traditional vaccines relatively low.

### Vaccine manufacturers and markets in emerging economies

Some manufacturers in low- and middle-income countries have been included in WHO's vaccine prequalification programme since the programme was established. Examples include the Pasteur Institute of Senegal and some manufacturers in the formerly communist states of central and eastern Europe – represented by the Canada-based buying group, Conpharma. By 2007, nearly 50% of the manufacturers of prequalified vaccines were based in emerging economies.<sup>5</sup> Around that time, such economies also became key importers of new vaccines.<sup>6</sup>

### Special characteristics of BRICS

In the early 1990s, the Children's Vaccine Initiative performed assessments in countries that could possibly play an enhanced role in vaccine supply. All five BRICS countries were included in these assessments. Recently, the BRICS group has attracted increasing attention as a market and development force – and not just for vaccines.<sup>7</sup>

The main functional areas of vaccine development and supply comprise clinical studies and vaccine research, development, regulation and production. Four of the BRICS countries are undertaking all of these activities and the exception – South Africa – is engaged in all but production.

## Vaccine production

We examined vaccine production in each of the BRICS countries between 1993 and 2013. There are no data available on the general quality of the vaccines produced in 1993 (Table 1), although a measles vaccine produced by the Serum Institute of India was prequalified by WHO. In 1995, yellow fever vaccines produced in Brazil and the Russian Federation came from laboratories that were approved by WHO for the production of such vaccines.<sup>8</sup>

Table 2 tracks the development and production of WHO-prequalified vaccines by the BRICS countries between 1986 and 2013. The number of prequalified products from manufacturers in BRICS – and other emerging economies – has increased over the last two decades but appears to have levelled off in recent years.

Over our study period, vaccines from manufacturers in BRICS represented a major proportion of the purchases made via the UNICEF Supply Division (Table 3) and the PAHO Revolving Fund (Table 4) from manufacturers in low- and middle-income countries – in terms of both volume and value. In 2012, just four Indian manufacturers supplied over 95% of the vaccines bought from manufacturers in BRICS by the Revolving Fund – again in terms of both volume and value.

The share of vaccines purchased via PAHO and UNICEF from vaccine manufacturers in low- and middle-income countries decreased after 2005, probably as the result of the introduction of new vaccines. For PAHO, for example, this

share fell from 56.42% of vaccine doses in 2005 to 31.27% in 2010. Although the general trend in the size of this share has been downwards, peaks have occurred when vaccine manufacturers in low- and middle-income countries have supplied vaccines needed for particular mass vaccination campaigns. There is also some evidence to suggest that the share of vaccines purchased via PAHO and UNICEF from vaccine manufacturers in low- and middle-income countries began to increase after 2010.

By 2013, manufacturers in BRICS were producing many types of vaccines (Table 5). Although most of the vaccines might be considered traditional, some were more innovative products, such as a meningococcal type A conjugate vaccine and a genetically engineered Japanese encephalitis vaccine from India and a live attenuated Japanese encephalitis vaccine from China. A novel cholera vaccine manufactured by Shantha Biotechnics in India was created using technology that was developed in Sweden before being transferred – by the International Vaccine Institute – to Viet Nam and then to India. Although not WHO-prequalified, the world's first hepatitis E vaccine – a recombinant *Escherichia coli*-based virus-like particle vaccine – was recently launched in China.

## Vaccine innovation

For each of the BRICS countries, we investigated vaccine products in the pipeline and the partnerships for vaccine innovation that have been set up (Table 6). The capability of each country to master intellectual property provisions that relate to vaccine development has been discussed in earlier publications.<sup>19–21</sup>

### Pipeline products

There are some important and innovative vaccines in the pipeline in the BRICS countries, such as the conjugate vaccines being developed in India, an influenza vaccine made from virus-like particles being developed in the Russian Federation, a dengue vaccine – based on technology from the United States National Institutes of Health – being developed in Brazil, and pneumococcal conjugate vaccines being developed in both China and India. Chinese

Table 2. Global production of prequalified vaccines, Brazil, the Russian Federation, India, China and South Africa (BRICS), 1986–2013

Year	Global production		Production in BRICS			% of global manufacturers in BRICS
	No. of vaccine types	No. of manufacturers	Country of manufacture	No. of manufacturers	Manufacturer (vaccines produced)	
1986	6	13		0	–	0
1996	13	18	India	1	Serum Institute of India (DT, DTP, M, Td, TT)	6
2006	24	22	Brazil	1	Bio-Manguinhos (YF)	36
			India	7	Biological E. (TT), Cadila Health Care (rabies), Chiron Behring Vaccines (rabies), Haffkine Bio Pharmaceutical Corporation (OPV <sup>a</sup> ), Panacea Biotec (OPV <sup>a</sup> ), Serum Institute of India (BCG, DT, DTP, DTP–hep B, hep B, M, MR, MMR, rubella, Td, TT), Shantha Biotechnics (hep B)	
2012	33	27	Brazil	1	Bio-Manguinhos (BMP <sup>a</sup> , YF)	20
			India	8	Bharat (hep B, <sup>b</sup> OPV <sup>a,b</sup> ), Biological E. (Pent., TT), Cadila Health Care (rabies), Chiron Behring Vaccines (rabies), Haffkine Bio Pharmaceutical Corporation (OPV 1–3, <sup>a</sup> OPV 1, <sup>a</sup> OPV 1+3 <sup>a</sup> ), Panacea (DTP–hep B, <sup>b</sup> hep B, <sup>b</sup> OPV, <sup>a,b</sup> OPV 1+3 <sup>a,b</sup> , Pent. <sup>b</sup> ), Shantha Biotechnics (C, hep B, <sup>b</sup> Pent. <sup>b</sup> TT), Serum Institute of India (BCG, DT, DTP, DTP–hep B, hep B, Hib, M, meningococcal A conjugate, MR, MMR, pandemic influenza, Pent., rubella, Td, TT)	
2013	33	34	Russian Federation	1	Chumakov Institute of Poliomyelitis and Viral Encephalities (YF)	27
			Brazil	1	Bio-Manguinhos (BMP <sup>a</sup> , YF)	
			China	1	Chengdu (JE live)	
			India	6	Biological E. (JE, Pent., TT), Cadila Health Care (rabies), Chiron Behring Vaccines (rabies), Haffkine Bio Pharmaceutical Corporation (OPV, OPV 1, <sup>a</sup> OPV 1+3, <sup>a</sup> TT), Serum Institute of India (BCG, DT, DTP, Diphtheria–tetanus–pertussis–hep B, hep B, Hib, M, meningococcal A conjugate, MR, MMR, OPV, <sup>a</sup> OPV 1+3, <sup>a</sup> pandemic influenza, Pent., rubella, Td, TT), Shantha Biotechnics (C, hep B, TT)	
Russian Federation	1	Chumakov Institute of Poliomyelitis and Viral Encephalities (YF)				

BCG: bacille Calmette–Guérin; BMP: bivalent meningitis polysaccharide; BRICS: Brazil, the Russian Federation, India, China and South Africa; C: cholera; DT: diphtheria and tetanus; DTP: diphtheria, tetanus and pertussis; Hep: hepatitis; Hib: *Haemophilus influenzae* type b; JE: Japanese encephalitis; M: measles; MMR: measles, mumps and rubella; MR: measles and rubella; OPV: oral polio vaccine; Pent.: diphtheria, tetanus, pertussis, hepatitis B and *Haemophilus influenzae* type b; Td: diphtheria toxoid; TT: tetanus toxoid; YF: yellow fever.

<sup>a</sup> Although the manufacturer technically produced the final vials of product, the starting material was imported bulk vaccine that had already been prequalified.

<sup>b</sup> Supplied over several years by the manufacturer but delisted in or before the year indicated.

Data sources: World Health Organization<sup>4</sup> and the manufacturers' websites.

Table 3. Vaccine purchases by the United Nations Children's Fund's Supply Division, 2000–2012

Variable by procurement year	Total	Vaccines supplied by all LMICs (% of total)	Vaccines supplied by BRICS (% of total)
<b>No. of doses</b>			
2000	1 936 414 720	754 755 370 (39)	739 275 970 (38)
2005	3 027 615 037	1 407 909 985 (47)	1 399 489 485 (46)
2010	2 526 827 681	1 159 613 756 (46)	1 038 173 256 (41)
2011	2 498 892 118	980 349 558 (39)	842 236 158 (34)
2012	1 896 227 085	779 663 585 (41)	645 498 085 (34)
<b>Value (US\$)</b>			
2000	138 745 864	55 295 154 (40)	53 773 899 (39)
2005	436 130 265	145 506 235 (33)	144 260 581 (33)
2010	749 789 337	243 120 472 (32)	226 620 354 (30)
2011	1 028 317 633	318 621 820 (31)	302 123 233 (29)
2012	1 052 784 555	338 215 383 (32)	327 180 380 (31)

BRICS: Brazil, the Russian Federation, India, China and South Africa; LMICs: low- and middle-income countries; US\$: United States dollars.

Data source: United Nations Children's Fund's Supply Division (personal communication, October 2013).

Table 4. Vaccine purchases by the Pan American Health Organization's Revolving Fund, 2005–2012

Variable and procurement year	Total	Vaccines purchased from DCMN (% of total)	Vaccines purchased from BRICS (% of total)
<b>No. of doses</b>			
2005	201 680 706	113 786 850 (56)	109 573 350 (54)
2010	205 806 237	64 347 881 (31)	58 399 687 (28)
2011	176 227 630	77 905 969 (44)	76 468 409 (43)
2012	209 752 749	104 161 874 (50)	82 380 579 (39)
<b>Value (US\$)</b>			
2005	144 827 040	45 543 701 (9)	43 422 101 (30)
2010	439 107 855	38 284 116 (12)	24 787 947 (6)
2011	337 939 685	41 319 357 (18)	31 620 162 (9)
2012	447 718 073	82 397 108 (56)	64 241 235 (14)

BRICS: Brazil, the Russian Federation, India, China and South Africa; DCMN: Developing Countries Vaccine Manufacturers Network; US\$: United States dollars. Data source: Pan American Health Organization's Revolving Fund (personal communication, October 2013).

Table 5. Vaccines produced in Brazil, the Russian Federation, India, China and South Africa (BRICS), 2013

Country and references	No. of manufacturers	Vaccine types
Brazil <sup>11,12</sup>	3	BCG, BMP, DT, DTP, DTP–Hib, Hep B, Hib, influenza, IPV, <sup>a</sup> OPV 1–3, <sup>a</sup> MMR, <sup>a</sup> MMR–varicella, <sup>a</sup> pneumococcal conjugate, <sup>a</sup> rabies, rotavirus, <sup>a</sup> Td, YF
Russian Federation <sup>13,14</sup>	4	BCG, brucellosis, diphtheria, DT, DTP, DTP–Hep B, encephalitis vaccine (EnceVir), <i>Gonococcus</i> , hepatitis (child and adult), influenza (live and inactivated), M, meningococcal A, MM, mumps, OPV, rabies, rubella, tetanus, rabies, tularaemia, varicella, YF
India <sup>8,11</sup>	10	BCG, C (inactivated oral), DT, DTP, DTP–Hep B, DTP–Hib, Hep B, Hib, influenza H1N1, JE (inactivated), meningococcal A conjugate, M, MR, MMR, OPV 1+3, <sup>a</sup> OPV 1, <sup>a</sup> OPV 1–3, <sup>a</sup> pandemic influenza (live), Pent., rabies, rubella, seasonal influenza, Td, TT, typhoid conjugate, typhoid VI polysaccharide
China <sup>11</sup>	46	Anthrax, BCG, BMP, brucellosis, DT, DTP, DTP–Hib, haemorrhagic fever with renal syndrome, Hep A, Hep A (live), Hep A–Hep B, Hep B, Hep E, Hib, influenza (split), influenza H1N1, influenza H5N1, JE (live and inactivated), <i>Leptospira</i> , M, meningococcal ACYW-135, MM, MMR, MR, OPV 1–3, rabies, rubella, TT, typhoid VI, varicella, tick-borne encephalitis, tracheitis, TT, YF
South Africa <sup>11,15</sup>	1	Hep B <sup>a</sup>

BCG: bacille Calmette–Guérin; BMP: bivalent meningitis polysaccharide; C: cholera; DT: diphtheria and tetanus; DTP: diphtheria, tetanus and pertussis; Hep: hepatitis; Hib: *Haemophilus influenzae* type b; IPV: inactivated polio vaccine; JE: Japanese encephalitis; M: measles; MM: measles and mumps; MMR: measles, mumps and rubella; MR: measles and rubella; OPV: oral polio vaccine; Pent.: diphtheria, tetanus, pertussis, hepatitis B and *Haemophilus influenzae* type b; Td: diphtheria toxoid; TT: tetanus toxoid; YF: yellow fever.

<sup>a</sup> Although the manufacturer technically produced the final vials of product, the starting material was imported bulk vaccine that had already been prequalified.

manufacturers have developed their own technologies for rotavirus, live Japanese encephalitis, human papillomavirus and hepatitis vaccines.

### Partnerships

Over the study period, many partnerships between vaccine manufacturers and multinational corporations in BRICS have been established. In India,

agreements with five multinational corporations account for an estimated 22% of pipeline vaccine products.<sup>19</sup> Five partnerships to support technology transfer in Brazil in 2006<sup>19</sup> included agreements for the transfer of knowhow but no licences for patents rights. Conversely, an agreement for the transfer of dengue vaccine technology, from the United States National Institutes of Health to

the Instituto Butantan in Brazil, included a licence for patent rights but no explicit authorization for the transfer of knowhow. In October 2013, Brazil's government-funded Oswaldo Cruz Foundation announced that it was going to develop an affordable measles and rubella vaccine with the support of the Bill & Melinda Gates Foundation. The Brazilian Ministry of Health is allocating funds to support this plan, including US\$ 727 million for the construction of a plant at the Bio-Manguinhos site to produce the vaccine.

Two vaccine manufacturers – Bio-Manguinhos in Brazil and Biological E. in India – illustrate the use of partnerships to assess innovative technologies. Bio-Manguinhos is a state-supported institution that has been charged with providing general access to any vaccine that the national health authorities consider to be a priority, as soon as possible. To help achieve this goal, Bio-Manguinhos is using agreements with GlaxoSmithKline, complemented by its own development activities and many collaborative activities with several universities.<sup>19</sup> Bio-Manguinhos has already had several technology transfer agreements with GlaxoSmithKline, relating to the development of *H. influenzae* type b conjugate, rotavirus and pneumococcal conjugate vaccines, as well as straight bulk-filling agreements for oral polio, measles, mumps and rubella and measles, mumps, rubella and varicella vaccines. The partnership agreement for the *H. influenzae* type b conjugate project specified a reference price, which was the PAHO Revolving Fund's price minus a discount for the cost of the bulk. In return, Bio-Manguinhos received

Table 6. Vaccines in the pipeline and vaccine-related partnerships, Brazil, the Russian Federation, India, China and South Africa (BRICS), 2013

Country	Pipeline products	Primary BRICS manufacturer involved in partnership	Other partner(s)	Vaccines produced through partnership (year of partnership initiation)
Brazil	Dengue recombinant (inactivated and live), DTP (low-dose), DTP–Hep B–Hib–meningococcal C–IPV, Hep A (inactivated), influenza (new adjuvant), <i>Leptospira</i> , malaria, meningococcal B polysaccharide, meningococcal C conjugate, pandemic influenza, pneumococcal protein, rotavirus, YF (attenuated and inactivated)	Bio-Manguinhos	Rockefeller Foundation Biken Institute Japan Poliomyelitis Research Institute GlaxoSmithKline	Yellow fever (1937) Measles (1980) OPV (1982) OPV (1985), Hib (1998), MMR (2003), rotavirus (2008), pneumococcal conjugate vaccine and dengue (2009) DTP–Hib (2002) BMP (2007)
Russian Federation <sup>a</sup>	DTP, DTP–Hep B, Hib, influenza, influenza H1N1, MMR, pertussis (acellular), seasonal influenza, <i>Staphylococcus–Proteus</i> –blue pus	Instituto Butantan Ezequiel Dias Foundation ViiV Healthcare Petrovax Abiotek and NT Pharma Bharat Biotech International	Novartis GlaxoSmithKline and Pfizer Pfizer Pahang Technology Resources PfizerWyeth Acambis Novavax	Influenza (1999), influenza H1N1 (2009) Meningococcal C conjugate (2009) HPV, pneumococcal conjugate vaccine, rotavirus Pneumococcal conjugate vaccine Influenza Hib NDA NDA
India	DTP–Hep B, Hep B, Hep E, HPV, influenza H1N1, JE, malaria, Pent., pneumococcal conjugate (10-valent), rabies, rotavirus, seasonal influenza	Biological E.  Cadila Pharmaceuticals (ZydusCadila) Chiron Behring Vaccines Panacea Biotec  Serum Institute of India  Shantha Biotechnics	Program for Appropriate Technology in Health GlaxoSmithKline Netherlands Vaccine Institute Intercell Novavax  Novartis Chiron Corporation Cambridge Biostability Netherlands Vaccine Institute PT Bio Farma Novartis Merck SynCo Bio Partners Aerial (France) Center for Biologics Evaluation and Research Netherlands Vaccine Institute Program for Appropriate Technology in Health Meningitis Vaccine Project Sanofi	Rotavirus (2013) DTP–Hep B–Hib–IPV (2013) Hib (1999), IPV (2005), JE (2012) NDA  NDA Combination vaccines Thermostable vaccines IPV (2005) Measles DTP–Hib Influenza, pneumococcal conjugate vaccine Meningococcal A MenAfriVac Meningococcal A, TT conjugate IPV (2005), Hib (2010) Pneumococcal conjugate vaccine Meningococcal A conjugate Cholera, typhoid

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Country	Pipeline products	Primary BRICS manufacturer involved in partnership	Other partner(s)	Vaccines produced through partnership (year of partnership initiation)
China	Cholera (tetra-valent), DTP, enterovirus 71, haemorrhagic fever with renal syndrome, Hep A–Hep B, Hep A (inactivated), Hep B (therapeutic), Hib conjugate, HPV 16/18, HPV 6/11 (condyloma acuminata), influenza (split), meningococcal conjugate (4-valent), meningococcal polysaccharide (4-valent), OPV, pneumococcal conjugate (13-valent), pneumococcal polysaccharide (28-valent), rabies (human cell), rotavirus (trivalent), TT, varicella	Beijing Minhai Biotechnology China National Biotec Group plus Sinopharm Shenzhen Kangtai Biological Products Shenzhen Neptunus Interlong Bio-Technique Shenzhen Sanofi Pasteur Biological Products Shanghai Institute of Biological Products Sinovac Walvax Biotechnology Zhejiang Tianyuan Bio-Pharmaceutical Public–private partnership <sup>b</sup>	Merck Sanofi-Pasteur Chinese National Institute of Health Program for Appropriate Technology in Health Merck Sanofi-Pasteur GlaxoSmithKline Sanofi-Pasteur Netherlands Vaccine Institute Other members of the Influenza Vaccine Supply International Task Force GlaxoSmithKline Novartis Merck	Hep B Rabies Rotavirus <i>Pneumococcal conjugate vaccine (2009)</i> , rotavirus, JE HPV JE, influenza (1996) Influenza (2008, 2009) Influenza NDA (2010) NDA (2007) MMR, other paediatric vaccines NDA (2011) Influenza
South Africa	Hep B, TT			

BMP: bivalent meningitis polysaccharide; BRICS: Brazil, the Russian Federation, India, China and South Africa; DTP: diphtheria, tetanus and pertussis; Hep: hepatitis; Hib: *Haemophilus influenzae* type b; HPV: human papillomavirus; IPV: inactivated polio vaccine; JE: Japanese encephalitis; MMR: measles, mumps and rubella; NDA: no data available; OPV: oral polio vaccine; Pent.: diphtheria, tetanus, pertussis, hepatitis B and *Haemophilus influenzae* type b; TT: tetanus toxoid; YF: yellow fever.

<sup>a</sup> The Petersburg Institute of Experimental Medicine has given the World Health Organization a non-exclusive licence for using classical reassortant vaccine strains in the production of live attenuated influenza vaccine. This technology has been successfully transferred to the Serum Institute of India and Changchun BCHO Biotechnology in China.

<sup>b</sup> Supplies vaccines from Sanofi–Pasteur, GlaxoSmithKline, Heber Biotec, Pfizer, Novartis, Biofarma and Statens Serum Institut. Data sources: Developing Countries Vaccine Manufacturers Network,<sup>11</sup> Chumakov Institute of Poliomyelitis and Viral Encephalitis and Viral Encephalitis References,<sup>13</sup> ViiV Healthcare,<sup>16</sup> Petrovax<sup>17</sup> and Jamaludin (2013).<sup>18</sup>

technical assistance. The agreement also specified maintenance of secrecy and knowhow for 10 years and limited export to the Mercosur countries. In addition, the agreement stipulated that Bio-Manguinhos would be charged a 4–5% running royalty for 5 years from the start of selling its own product.<sup>19</sup>

Biological E. is a private sector company that strives to develop and introduce standard and innovative vaccines in a manner consistent with their financial viability, using partnerships to access new technologies. One such partnership was set up with a public sector organization – the former Netherlands Vaccine Institute<sup>22</sup> – to develop a pentavalent combination vaccine.<sup>19</sup> For this vaccine, Biological E. used innovative methods to circumvent the patent-obstructed steps in the standard production process. Biological E. now has a WHO-prequalified pentavalent product that has been brought to market at the lowest price to date and is expected to capture a large share of the global pentavalent market for 2013–2015.<sup>23</sup> Biological E. has also licensed technologies – from Intercell – for the development of a Japanese encephalitis virus vaccine, for which it has the rights to market in low- and middle-income countries. In August 2013 this vaccine was prequalified by WHO for use in adults, and Biological E. expects it to be licensed soon for use in children.<sup>24</sup>

## Vaccine regulation

A vaccine manufacturer’s success on the global market depends on the market’s perception of the quality – or likely quality – of that manufacturer’s products.<sup>25</sup> Much of that perception relies on an effective system of vaccine regulation. For each of the BRICS countries, we therefore investigated the functionality of the relevant national regulatory authority – as assessed by WHO, the judgements of consumers or other regulatory authorities as to the suitability for procurement of vaccines from the country, and the regulation of clinical trials of vaccines.

## National regulatory authorities

The national regulatory authority of each BRICS country has been successfully assessed by WHO and four of the authorities – all but that of South Africa – have been judged as functional in their role as overseers of WHO-prequalified

Table 7. Registered clinical trials on vaccines, Brazil, the Russian Federation, India, China and South Africa (BRICS), 2013

Country and reference	Number of registered trials in country			Trials on new vaccine produced in country (% of any trials)
	On any vaccine	On new vaccine	On new vaccine produced in country	
Brazil <sup>34</sup>	49	46	8	16.3
Russian Federation <sup>37</sup>	11	11	2	18.2
India <sup>36</sup>	141	105	80	56.7
China <sup>35</sup>	120	100	85	70.8
South Africa <sup>38</sup>	50	38	0	0.0

Table 8. Prices of pentavalent vaccines paid by the Global Alliance for Vaccine and Immunization, 2001–2014

Year	Number of suppliers			Mean price <sup>a</sup> (US\$/dose)	Comments
	MNCs	BRICS	Other		
2001	1 (GSK)	0	0	3.50	
2004	1 (GSK)	0	0	3.56	Lyophilized vaccine, with limited supply
2006	2 (Crucell and GSK)	0	0	3.50	New supply from Crucell, with more desirable, liquid presentation
2009	2 (Crucell and GSK)	2 (Panacea and Shantha)	0	3.20	Shantha supplied 2008–July 2010
2010	2 (Crucell and GSK)	2 (Panacea and Shantha)	0	3.00	Panacea supplied 2008–May 2011
2011	2 (Crucell and GSK)	2 (Panacea and Serum Institute of India)	0	2.58	
2012	2 (Crucell and GSK)	2 (Biological E. and Serum Institute of India)	0	2.17	10-dose presentation supplied by Serum Institute of India. GSK product with limited supply
2014	2 (Crucell and GSK)	2 (Biological E. and Serum Institute of India)	1 (LG Life Sciences)	1.78 or 1.95 <sup>b</sup>	10-dose vials from Biological E (at US\$ 1.19/dose) and Serum Institute of India at (US\$ 1.75–2.10/dose). Lyophilized product in 2-dose vials from LG Life Sciences (at US\$ 1.98/dose)

BRICS: Brazil, the Russian Federation, India, China and South Africa; GSK: GlaxoSmithKline; MNCs: multinational corporations; US\$: United States dollars.

<sup>a</sup> Weighted, when there was more than one supplier, by the number of doses bought from each supplier.

<sup>b</sup> Depending on presentation, with higher mean price for lyophilized product.

Data sources: Milstien and Kaddar (2010),<sup>39</sup> United Nations Children's Fund<sup>23</sup> and World Health Organization.<sup>3,40</sup>

vaccines.<sup>26</sup> After WHO first judged its national regulatory authority to be functional in this role, in March 2011, China sought WHO prequalification for many Chinese products. Some of the necessary assessments by WHO are now under way. India's national regulatory authority most recently received a positive assessment by WHO in December 2012<sup>27</sup> – after an exceptional review that was

triggered by the withdrawal or delisting of several Indian products from WHO's list of prequalified vaccines.

In a country that has never exported its locally produced vaccines – such as South Africa – WHO will only assess the national regulatory authority if such an assessment is requested. In such cases, it is left to the regulatory authority to publish or not to publish the results.

The national regulatory authorities of four of the BRICS countries – Brazil, China, India and South Africa – were included as founding members of WHO's Developing Country Vaccine Regulators Network, along with those of Cuba, Indonesia, the Republic of Korea and Thailand. By May 2012, the national regulatory authority of the Islamic Republic of Iran joined the Network.<sup>28,29</sup>

### Other regulatory groups

Brazil, China, the Russian Federation and South Africa are members of the European Pharmacopoeia.<sup>30</sup> South Africa's Medicines Control Council also participates in the Pharmaceutical Inspection Co-operation Scheme.<sup>31</sup> Brazil is a member of PAHO's Pan American Network for Drug Regulatory Harmonization network.<sup>32</sup> South Africa is a member of the African Vaccine Regulatory Forum, which participates in the joint clinical review of applications for clinical trials in African countries.<sup>33</sup>

### Oversight of clinical trials

Each of the BRICS countries has a system for the registration of clinical trials carried out within its borders. The latest available data on the number of vaccine trials conducted (Table 7) indicate that most of the recent vaccine trials in BRICS involved new vaccines. This indicates both the dynamism of the national regulatory authorities in BRICS and the high level of innovation involved in vaccine production in most of the countries – particularly in China and India.

### Impact on vaccine prices

Table 8 and Box 1 document the impact of the BRICS manufacturers – notably Indian manufacturers – on the global vaccine market.

### Current limitations

Currently, of the vaccine manufacturers in BRICS, the Indian ones are the most globally active. The Brazilian manufacturers are also quite active but those in the Russian Federation are currently more focused on upgrading facilities – to improve production capacity and compliance with international standards – than on vaccine exports. The potential impact of Chinese manufacturers, who are now entering the global market, is immense but has yet to be realized.

**Box 1. The impact of suppliers in Brazil, the Russian Federation, India, China and South Africa (BRICS) on vaccine prices****Prices of pentavalent vaccines**

Table 8 documents the changes seen in the price of pentavalent vaccine since 2001. The Global Alliance for Vaccines and Immunization (GAVI Alliance) believes that growth in predictable demand has created a sustainable market for this vaccine – a market that is required to attract manufacturers and create the competition needed to lower prices. Such competition has, however, taken several years to develop. Between 2001 and 2005, the only supplier was GlaxoSmithKline and the supply was quite limited. Because Crucell supplied a more desirable liquid product in 2006–2007, there was no decrease in the mean price per dose paid by the GAVI Alliance. In 2008, two new suppliers entered the market – Panacea and Shantha, both from India – and the price began to drop. The Serum Institute of India joined the market in 2010 and in 2011, introduced 10-dose vials of the liquid vaccine that were then competitively priced. In 2012, however, the pentavalent vaccine of another Indian manufacturer – Biological E. – was prequalified and soon offered at a 30% lower price per dose.<sup>40</sup> This price decrease was leveraged by suppliers from a single BRICS country – India – that had high-volume capacity and the ability to profit from sales at a relatively low price point.<sup>1</sup>

**Prices of other vaccines**

The pentavalent vaccine story is not unique. As documented in a Médecins Sans Frontières publication, *The Right Shot*,<sup>41</sup> tetravalent meningococcal – A, C, W-135 and Y – conjugate vaccines were developed in 2005 and 2010. In 2011, one of these vaccines was being sold to the public sector in the United States of America at a price of 82.12 United States dollars (US\$) per dose. In contrast, the meningitis A conjugate developed by the Serum Institute of India and the Meningitis Vaccine Project was prequalified in 2010 and priced at about US\$ 0.50 per dose. This and other developments by BRICS suppliers helped drive or keep down the prices of meningitis vaccines – as revealed by the prices paid for meningitis polysaccharide vaccines by the United Nations Children's Fund between 2001 and 2013. The long-term supplier, Sanofi-Pasteur, initially supplied meningitis AC polysaccharide vaccine to the Fund at US\$ 0.25 per dose. By 2013, Sanofi-Pasteur's price for the same presentation had risen to US\$ 1.22 per dose. Between 2004 and 2012, the Brazilian supplier Bio-Manguinhos was selling the same vaccine type for about US\$ 0.85 per dose. There are other examples of BRICS suppliers being able to undercut prices charged by multinational corporations. For example, Valneva produces Ixiaro, an inactivated Japanese encephalitis vaccine made in cell culture. The per-dose price of this vaccine in the United States is currently about US\$ 195.<sup>42</sup> The corresponding Biological E. product, which is made using the same technology but manufactured in India, costs less than US\$ 16 per dose.<sup>43</sup> A live attenuated vaccine based on the same strain of virus has been developed in China and has been offered to low- and middle-income countries at a price similar to measles vaccine<sup>44</sup> – i.e. only about US\$ 0.50 per dose.<sup>45</sup>

BRICS: Brazil, the Russian Federation, India, China and South Africa.

In South Africa, vaccine manufacturing has been slow to develop and may have greater potential regionally than globally.

The focus of vaccine manufacturers in BRICS has been on the domestic market, the United Nations' market or both. These manufacturers are yet to make a substantial impact on several broader and potentially more profitable vaccine markets – such as those involving new vaccines and the vaccine demands and needs of wealthier countries and the private sector within their own countries and of many middle- and high-income countries. Full exploitation of such markets is likely to push the manufacturers in BRICS into harder competition with each other for supply agreements. For each such manufacturer, the risk of loss of a substantial market share to a new supplier and the frequent lack of a large portfolio of vaccines and other

products – that would allow the flexibility of easy diversification – may be major challenges to the sustainability of turnover and profit.

Given the relatively low returns from their vaccines – in absolute values – and the limited markets in which they are currently active, the vaccine manufacturers in BRICS must invest a greater percentage of turnover to research and development than the multinational corporations that also produce vaccines.

With increasing links through technology transfer, outsourcing and restricted supply arrangements, the more innovative vaccine manufacturers in BRICS are becoming ever more attractive targets for mergers and acquisitions by multinational manufacturers. They are therefore at increasing risk of a loss of autonomy and national and regional focus.

**Conclusion**

Most of the BRICS countries are having substantial impacts on the global vaccine market, albeit to varying degrees. The production of important traditional vaccines within BRICS is contributing to the achievement of Millennium Development Goal 4. Such production is a key component in increasing access to affordable vaccines of good quality, as it allows large-scale supplies to domestic and United Nations' markets. Through collaborations with universities, donors, international partners and multinational corporations, vaccine manufacturers in BRICS have not only provided increased production capacity for important underutilized vaccines but also developed novel vaccines for specific use in low- and middle-income countries. These manufacturers rely heavily on public sector arrangements and supply agreements with United Nations' agencies. Such reliance could stop manufacturers in BRICS from reaching their full economic potential and full sustainable impact.

The same manufacturers face several other weaknesses and challenges. These include low levels of financial and technical investment in vaccine research, the need to innovate, a dependence on limited markets, and low levels of diversity in product portfolios. Among manufacturers in BRICS, the emphasis is generally more on competition – for the same limited markets and product segments – than on cooperation. The five countries represented by the BRICS acronym are far from being a coherent group. There is a real risk of the absorption and acquisition of vaccine production facilities by multinational firms and the subsequent loss of autonomy.

In general, vaccines from the BRICS countries are currently competitively priced because the manufacturing costs in BRICS are relatively low. The prices of such vaccines may have to rise, however, to allow greater investment in vaccine research and development and the use of new processes and updated facilities to produce more complex vaccines. The prices may also have to rise as the mean income per capita in the emerging economies and, therefore, the living standards expected by the workforce increase.

It is expected that China will soon emerge as a major player in the global vaccine market and that there will be increasing differentiation between the

national vaccine manufacturers that have sufficient capacity to compete with the multinational corporations and the ones who lack the capacity. Vaccine manufacturers in BRICS could either enter into fierce competition with the multinational corporations, for an adequate share of the global vaccine market, or focus on a niche market, such as the vaccines that have more local importance.

The international public sector could help strengthen vaccine produc-

tion in BRICS, perhaps by exploiting the Global Vaccine Action Plan's Decade of Vaccines Strategy. Under certain conditions, the United Nations' procurement agencies could perhaps provide targeted support to vaccine manufacturers in BRICS, so as meet global needs for specific vaccines. Support from donors like the Bill & Melinda Gates Foundation could be focused on more upstream areas, such as research and development, technology platforms and intellectual prop-

erty rights. More cooperation between academia, biotechnology firms and public health institutions should also be encouraged. ■

#### Acknowledgements

The authors would like to acknowledge and thank all the peer reviewers for their valuable feedback and suggestions. Thanks also to Michael Hinsch for his assistance in the data mapping.

**Competing interests:** None declared.

## ملخص

### أثر استثمارات تجمع "بريك" (BRICS) في استحداث اللقاحات على سوق اللقاحات العالمي

التغيرات في سعر القطاع العام للجرعة بالنسبة للقاحات المحددة وحصصة السوق العالمي ممثلة بالمنتجات من جهات تصنيع معينة وجاذبية فرص الشراكة والاستثمار، للشركات متعددة الجنسيات، في شركات تجمع "بريك". وتشير النتائج إلى تحقيق بلدان تجمع "بريك" لأثر كبير على سعر اللقاحات وتوافرها، ويعزى معظم هذا الأثر إلى حصائل مصنعي اللقاحات في الهند. ويتوقع أن يكون للصين قريباً أثر كبير، نظراً للتطوير المتوقع لمصنعي اللقاحات في الصين في المستقبل القريب. ويتوقع أن تؤدي إنجازات تجمع "بريك" في مجال استحداث اللقاحات إلى إعادة تشكيل سوق اللقاحات العالمي وتسريع الوصول إلى اللقاحات في العالم النامي. ويتمثل التحدي في تحويل هذه التوقعات إلى إجراءات استراتيجية وحصائل عملية.

أحرزت البرازيل والاتحاد الروسي والهند والصين وجنوب أفريقيا - البلدان المعروفة بتجمع "بريك" (BRICS) - تقدماً كبيراً في إنتاج اللقاحات وتنظيمها واستحداثها على مدار العشرين سنة المنصرمة. وفي عام 1993، كانت جميع البلدان الخمس تنتج اللقاحات ولكن العمليات المستخدمة قد عفا عليها الزمن وغير موحدة المعايير، ولم تكن هناك سوى بضعة أبحاث ذات صلة، وكان الاعتراف الدولي بالمنتجات ضئيلاً جداً. وبحلول عام 2014، أطلقت جميع البلدان الخمس مبادرات قوية لاستحداث تكنولوجيا لقاحات وقامت بتحسين قدراتها التنظيمية على الصعيد الوطني. وكانت جنوب أفريقيا في هذا الوقت البلد الوحيد في تجمع "بريك" الذي لم يكن ينتج اللقاحات بشكل كامل. وتقوم جنوب أفريقيا الآن بإعادة تأسيس إنتاج اللقاحات الخاصة بها وتجاوز مرحلة استيراد اللقاحات السائبة وتركيبها وتعبئتها. وتم تحليل

## 摘要

### 金砖国家疫苗研发投资对全球疫苗市场的影响

在过去 20 多年中，被称为金砖五国 (BRICS) 的巴西、俄罗斯联邦、印度、中国和南非在疫苗生产、管制和开发方面取得相当大的发展。1993 年，五国都在生产疫苗，但使用的是过时和非标准化的流程，几乎没有相关的研究，产品的国际认可也微乎其微。到 2014 年，所有五个国家都有开发疫苗技术的强有力行动方案出台，并极大地提高其国家监管能力。这样就只有南非一个不完整生产疫苗的金砖国家。南非正在重建自身的疫苗生产，已经不再止步于仅仅是散装疫苗进口、配苗和分装的阶段。本文分析了公共部门每剂选

定疫苗的价格、以具体厂商产品为代表的全球市场份额、金砖国家公司合作和投资机会对跨国公司的吸引力等所有方面的变化。结果表明，金砖国家已经对疫苗价格和可用来源产生重大影响，其中大部分影响归因于印度疫苗生产商的产量。鉴于中国疫苗制造商在不久将来的预期发展，预计中国将很快产生更大的影响。金砖国家在疫苗开发领域的成绩可望重塑全球疫苗市场，加快发展中国家对疫苗的获得速度。而面临的挑战是把期望转变成战略行动和实际的结果。

## Résumé

### Impact de l'investissement du groupe BRICS dans le développement de vaccins sur le marché mondial des vaccins

Le Brésil, la Fédération de Russie, l'Inde, la Chine et l'Afrique du Sud – les pays connus sous le nom de BRICS – ont fait des progrès considérables dans la production, la régulation et le développement des vaccins au cours des 20 dernières années. En 1993, les cinq pays fabriquaient des vaccins, mais les procédés utilisés étaient dépassés et non normalisés. Par ailleurs, peu de recherches pertinentes étaient menées et les produits ne recevaient qu'une reconnaissance internationale négligeable.

En 2014, les cinq pays avaient pris des initiatives importantes en matière de développement technologique de vaccins et avaient largement amélioré leur capacité de régulation nationale. L'Afrique du Sud était alors le seul pays du groupe BRICS à ne pas produire complètement des vaccins. L'Afrique du Sud a maintenant amorcé le processus pour relancer sa production de vaccins et pour dépasser l'étape de la simple importation, formulation et conditionnement des vaccins en vrac. On

a analysé les variations de prix du secteur public par dose des vaccins sélectionnés, la part du marché mondial représentée par les produits provenant de fabricants spécifiques et l'attractivité des opportunités de partenariat et d'investissement pour les multinationales dans les entreprises du groupe BRICS. Les résultats montrent que les pays du groupe BRICS ont eu un impact majeur sur le prix et la disponibilité des vaccins, et cet impact est attribuable, en grande partie, à la production

des fabricants indiens de vaccins. La Chine devrait bientôt avoir un plus grand impact compte tenu du développement attendu des fabricants chinois de vaccins dans un avenir proche. Les réalisations du groupe BRICS dans le domaine du développement de vaccins devraient remodeler le marché mondial des vaccins et accélérer l'accès aux vaccins dans les pays en développement. Le défi est maintenant de transformer ces attentes en actions stratégiques et en résultats concrets.

## Резюме

### Влияние инвестиций стран БРИКС в разработку вакцин на мировой рынок вакцин

Бразилия, Российская Федерация, Индия, Китай и Южная Африка — страны, известные как БРИКС, — добились значительных успехов в производстве, регулировании качества и разработке вакцин за последние 20 лет. В 1993 году все пять стран занимались производством вакцин, однако используемые процессы были устаревшими и нестандартизированными, с малым объемом соответствующих исследований и незначительным международным признанием продукции. К 2014 году все пять стран значительно продвинулись в разработке технологий для производства вакцин и значительно улучшили свои национальные системы регулирования данной отрасли. К этому времени Южная Африка являлась единственной страной БРИКС, которая еще не имела полноценного производства вакцин. В настоящее время Южная Африка находится в процессе восстановления собственного производства вакцин и перехода от простого импорта, составления рецептов и расфасовки вакцин.

Были проанализированы изменения в ценах государственных закупок на дозу отдельных вакцин, доля мирового рынка, представленная продукцией отдельных производителей, и привлекательность партнерства и инвестиций в компании стран БРИКС для транснациональных компаний. Результаты показывают, что страны БРИКС оказали существенное влияние на цены и доступность вакцин на рынке, причем в основном это относится к продукции индийских производителей вакцин. Ожидается, что Китай также будет наращивать свое влияние, учитывая ожидаемое развитие китайских производителей вакцин в ближайшем будущем. Ожидается, что достижения стран БРИКС в области разработки вакцин приведут к изменению мирового рынка вакцин и ускорению доступа к вакцинам в развивающихся странах. Задача состоит в том, чтобы воплотить эти ожидания в стратегические действия и практические результаты.

## Resumen

### El impacto de la inversión de los BRICS en el desarrollo de vacunas sobre el mercado mundial de vacunas

Brasil, la Federación de Rusia, India, China y Sudáfrica, los países conocidos como BRICS, han hecho progresos considerables en la producción, regulación y desarrollo de vacunas en los últimos 20 años. En 1993, los cinco países ya producían vacunas, pero los procesos empleados para ello estaban anticuados y sin normalizar, había poca investigación relevante y un reconocimiento internacional mínimo de sus productos. En 2014, los cinco países contaban con iniciativas sólidas para el desarrollo de la tecnología relacionada con las vacunas y habían mejorado en gran medida su capacidad normativa nacional. Sudáfrica fue el único de los BRICS que no fabricaba vacunas en su totalidad. En la actualidad, dicho país se encuentra en proceso de restablecer su propia producción de vacunas e ir más allá de la simple importación, formulación y llenado de lotes de vacunas. Se han analizado los cambios

en los precios por dosis de vacunas seleccionadas del sector público, la cuota de mercado mundial de productos de fabricantes específicos y el atractivo para las empresas multinacionales de la asociación y las oportunidades de inversión en empresas de los BRICS. Los resultados indican que los países BRICS han tenido un gran impacto en el precio y la disponibilidad de las vacunas, y que una gran parte de ese impacto se puede atribuir a la producción de vacunas de los fabricantes de India. Se confía en que China tenga pronto un impacto mayor, dada la evolución prevista de los fabricantes de vacunas chinos en el futuro cercano. Se espera que los logros de los BRICS en el campo del desarrollo de vacunas remodelen el mercado mundial de las vacunas y aceleren el acceso a las mismas en el mundo en desarrollo. El desafío consiste en convertir estas expectativas en actuaciones estratégicas y resultados prácticos.

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