Review

Developing Countries Vaccine Manufacturers Network: Doing good by making high-quality vaccines affordable for all

Sonia Pagliusi\textsuperscript{a,+}, Luciana C.C. Leite\textsuperscript{b,1}, Mahima Datla\textsuperscript{c,2}, Morena Makhoana\textsuperscript{d,3}, Yongzhong Gao\textsuperscript{e,4}, Mahendra Suhradono\textsuperscript{f,5}, Suresh Jadhav\textsuperscript{g,6}, Gutla V.J.A. Harshawardhan\textsuperscript{h,7}, Akira Homma\textsuperscript{i,8}

\textsuperscript{a} DCVMN International, Chemin du Canal S, 1260 Nyon, Switzerland
\textsuperscript{b} Instituto Butantan, Av. Vital Brazil 1500, Sao Paulo 05503-900, Brazil
\textsuperscript{c} Biological E Ltd, 18/163, Azamabad, Hyderabad 500 020, A.P., India
\textsuperscript{d} The Biovac Institute, 15, Alexandra Road, Pinelands, Cape Town, South Africa
\textsuperscript{e} Xiamen Innovax Biotech Co., Ltd. No. 130 Xinyuan Road, Haicang District, Xiamen, Fujian 361022, China
\textsuperscript{f} PT. Biofarmasi, Jl. Pasteur no. 28, Bandung 40181, Indonesia
\textsuperscript{g} Serum Institute of India, 212/2, Off. Poonawalla Road, Hadapsar, Pune 411 028, India
\textsuperscript{h} Bharat Biotech International Ltd, Genome Valley, Turkapally, Shameerpet (M), Hyderabad 500 078, India
\textsuperscript{i} Bio-Manguinhos | Fiocruz, Av. Brasil, 4365 – Manguinhos, Rio de Janeiro 21040-360, Brazil

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\textbf{A B S T R A C T}

The Developing Countries Vaccine Manufacturers Network (DCVMN) is a unique model of a public and private international alliance. It assembles governmental and private organizations to work toward a common goal of manufacturing and supplying high-quality vaccines at affordable prices to protect people around the world from known and emerging infectious diseases. Together, this group of manufacturers has decades of experience in manufacturing vaccines, with technologies, know-how, and capacity to produce more than 40 vaccines types. These manufacturers have already contributed more than 30 vaccines in various presentations that have been prequalified by the World Health Organization for use by global immunization programmes. Furthermore, more than 45 vaccines are in the pipeline. Recent areas of focus include vaccines to protect against rotavirus, human papillomavirus (HPV), Japanese encephalitis, meningitis, hepatitis E, poliovirus, influenza, and pertussis, as well as combined pentavalent vaccines for children. The network has a growing number of manufacturers that produce a growing number of products to supply the growing demand for vaccines in developing countries.

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\textsuperscript{+} This report summarizes the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of any institution or corporation.

\textsuperscript{1} Corresponding author. Tel.: +55 11 3726 3790; fax: +55 11 3726 1505.
\textsuperscript{2} Tel.: +91 040 30213999; fax: +91 040 27675003.
\textsuperscript{3} Tel.: +91 22 20377636; fax: +91 22 20377637.
\textsuperscript{4} Tel.: +62 21 4238 0569; fax: +62 21 4238 0568.
\textsuperscript{5} Tel.: +62 21 3687 7000; fax: +62 21 3687 7176.

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1. Introduction

The Developing Countries Vaccine Manufacturers Network (DCVMN) is a unique model of an international alliance. It assembles public and private organizations to work toward a common goal of manufacturing and supplying high-quality vaccines at affordable prices to protect people around the world from known and emerging infectious diseases. Notably, the network is a voluntary public health-driven alliance of manufacturers with facilities established in developing countries and owned in majority by stakeholders in those countries [1,2]. It does not include multinational companies with manufacturing facilities in developing countries, or their subsidiaries.

Networking is the simplest model of partnership, where organizations come together regularly to share best practices and discuss areas of commonality. The aim is to enhance the organizations’ abilities to take up opportunities, such as co-development of products or technology transfer, or to deliver specific services or products.

The network is steadily growing. As of September 2012, it has 37 members in 14 countries in Latin America, the Middle East and Africa, and the Asia-Pacific region (Fig. 1). Together, these manufacturers employ more than 42,000 skilled workers, with about 70% in the Asia-Pacific region, 15% in the Middle East and Africa, and 15% in Latin America. This employment contributes to the welfare and health of families and communities and the success of national economies. The vaccine industry not only offers the prospect of long-term professional careers and skills development for individuals but also contributes actively to sustainable development and empowerment of emerging economies.

The network strengthens the capacity of manufacturers to supply high-quality vaccines by facilitating information sharing and workshops, encouraging technology transfer initiatives and innovative research, and educating the public about the availability of safe and effective vaccines from developing-country manufacturers. Since the network was established in 2000 [1], member companies have helped to significantly increase access to high-quality vaccines, at affordable prices, for people who need them most, in the poorest countries of the world.

Collectively, network members have the technologies, know-how, and capacity to produce more than 40 vaccines types. They have contributed more than 30 vaccines in various presentations that have been prequalified by the World Health Organization (WHO) for immunization programmes around the world (Fig. 2). Furthermore, more than 45 products are in the pipeline. DCVMN members, for example, will soon likely launch the next rotavirus vaccine and the next human papillomavirus (HPV) vaccine to become available globally. Also, the first prequalified Japanese encephalitis vaccine may become available from DCVMN members for global procurement in 2013. DCVMN members have played a critical role in increasing global access to vaccines, which now prevent an estimated 2.5 million deaths each year, according to WHO. A key success story has been a global increase in measles vaccination rates, which contributed to a 74% percent drop in measles deaths from 2000 to 2010 [3].
Fig. 2. Matrix of vaccines manufactured by 30 DCVMN members (as of October 2012). WHO-prequalified vaccines are indicated in black. Six DCVMN members had not yet launched their vaccines, and products from Tiantan Biologicals, which are not listed on CNBG, to which it is incorporated. Manufacturers names are as follows: ANLIS: Administracion Nacional de Laboratorios e Institutos de Salud, Argentina; Bharat: Bharat Biotech International Ltd., India; PT Biofarm, Indonesia; Biological E, India; BioManguinhos/Fiocruz, Brazil; BioNet-Asia Co., Ltd.; Birmex, Laboratorios de Biologicos y Reactivos de Mexico, Mexico; Butantan, Brazil; Cadila Pharmaceuticals Ltd., India; Centro de Ingenieria Genetica y Biotechnologia, or in English Center for Genetic Engineering and Biotechnology, Cuba; CNBG is a group of manufacturers within China (Changchun, Chengdu, Lanzhou, Shanghai, Tiantan, and Wuhan Institutes of Biological Products; Tiantan has its own membership status); CDBIO, Liaoning Chengda Biotechnology, China; Finlay Institute, Cuba; GPO, Government Pharmaceutical Organization, Thailand; Green Cross, Republic of Korea; Hofffine Biopharmaceutical Corporation Ltd., India; Hualan Bio, China; Indian Immunologicals Ltd., India; Xiamen Innova Biotech Co. Ltd., China; IVAC: Institute of Vaccines and Medical Biologicals, Vietnam; LGLS: LGLLife Sciences, Republic of Korea; Panacea Biotec, India; Pasteur Institute of Iran, Iran; QSMI: Queen Saovabha Memorial Institute, Thai Red Cross Society, Thailand; Razi Institute for Serums and Vaccines, Iran; Serum Institute of India, India; Sinovac Biotech Ltd., China; Minhai: Beijing Minhai Biological Technology Co., Ltd., China; Vacciotech: Vaccine and Biological Production, Vietnam; Vacsera: Holding Company for Biological Products & Vaccines, Egypt; Walvax Biotechnology Co., Ltd., China. Biovac Institute, S.Africa; Sinerigium Biotech, Argentina; EBiologicos Co. Ltd., Republic of Korea; and SK Chemicals Co. Ltd., Republic of Korea are not currently (as of July 2012) releasing any vaccines and do not appear in the matrix. In addition, two members joint the network recently—Hualan Biological, from China, and Incepta Ltd., from Bangladesh—are not represented in the matrix due to time constraints.

2. Network achievements

2.1. Increasing access to pentavalent vaccines

Innovative pentavalent vaccines, introduced with support of the GAVI Alliance (www.gavialliance.org), enable use of one product to immunize children against five diseases—diphtheria, tetanus, pertussis, hepatitis B, and Haemophilus influenzae type b. This reduces the number of injections a child needs to receive and the number of visits it takes to get them, therefore increasing the likelihood that a child will receive all vaccines necessary for a healthy childhood. Using a pentavalent vaccine also results in a fivefold reduction in the number of vaccine vials that need to be transported and stored and thus reduces the costs of packaging, transportation, and storage. Notably, Panacea Biotec developed and launched the first fully liquid pentavalent vaccine in 2005 [4] and has since supplied more than 35 million doses to protect several million children.

An increasing number of governments have been willing to provide pentavalent vaccine to children over the past decade (Fig. 3), leading to the highest—ever vaccine coverage among populations in developing countries. At the same time, the number of pentavalent vaccine suppliers to UNICEF has increased from one supplier in 2001–2005, to two in 2006 and 2007, to four in 2008 and 2009, and to five in 2010 [5]. The increase in the number of manufacturers correlates with a five- to six-fold increase in the number of pentavalent doses supplied to UNICEF: from 20 million doses annually in the first half of the decade (2001–2006) to 100 million doses annually in 2009 and 2010 (Fig. 3A). In addition, demand from the Pan American Health Organization amounts up to 9 million doses annually, and demand from Brazil accounts for another 9 million doses (not shown).

Because of the large base of DCVMN members, childhood vaccines have become more affordable. For example, affordability of pentavalent vaccines offered by DCVMN members to UNICEF
for use in GAVI-eligible countries doubled between 2001 and 2011. When more manufacturers can make vaccines, vaccines can become more affordable due to economies of scale, resulting in more countries introducing vaccination (Fig. 3B) and more children being protected against infectious diseases.

The new decade will lead to further development of combination vaccines. DCVMN members are actively developing hexavalent combination vaccines, which incorporate poliovirus vaccines into the pentavalent vaccines. The addition of other antigens, such as meningococcal, can form heptavalent combination vaccines and help to protect children from seven childhood killers at once, further increasing the efficiency of immunization programmes. As more manufacturers cooperate to develop better and more suitable and affordable combination vaccines, we can move toward achieving universal vaccination and eliminating and eradicating many infectious diseases globally.

2.2. Innovating to fight regional infectious diseases

Vaccine manufacturers in developing countries are striving to accelerate the production of innovative vaccines. Thanks to increased efforts and investments in research and development (R&D), many new vaccines that specifically target the disease burden in developing countries are bringing new hope. The DCVMN members’ pipeline is especially focused on regional diseases. Among 100 projects, 15 target new antigens [6]. Still, advancement through the clinical study phases remains particularly challenging (Fig. 4) because of a number of issues, from regulatory challenges to sponsorship capability. Vaccine trials are often very large and resource intensive for recruitment, data collection, and follow-up of participants.

A recent highlight in innovation is the development of a conjugate vaccine against group A meningococcal meningitis, a frequently fatal infection that causes recurring epidemics in a number of countries in sub-Saharan Africa. Africa’s so-called “meningitis belt” has an estimated population of 300 million. The new vaccine, called MenAfriVac™, was developed through the Meningitis Vaccine Project, a partnership between WHO and PATH, and produced by Serum Institute of India (SII) with conjugation technology provided by the US Food and Drug Administration under licensing agreements. In June 2011, only six months after the vaccine’s introduction, Burkina Faso, Mali and Niger reported the lowest number of confirmed meningitis A cases ever recorded during an epidemic season [7]. Widespread

![Fig. 3. (A) Number of pentavalent vaccine doses procured by UNICEF since 2000, from all manufacturers, including one DCVMN member supplying after 2008 and two additional DCVMN members supplying after 2010. (B) Number of countries that introduced pentavalent vaccines (DTPHepB Hib) since 2000, with GAVI support, supplied by various vaccine manufacturers, with DCVMN members increasing supply after 2008, when DCVMNs joined the UNICEF pool procurement.](image-url)

![Fig. 4. Number of research projects in the various phases of development across DCVMN members in 2011. Among 100 research projects, 62 are preclinical studies, 15 are phase I, 12 are phase II, and 11 are phase III clinical studies. Source: DCVMN brochure 2011, www.dcvmn.org.](image-url)
introduction of MenAfriVac™ in other sub-Saharan African countries could prevent more than 1 million cases of illness over the next decade.

Another example of outstanding innovation within the DCVMN group of companies is the development and recent approval of the world’s first hepatitis E vaccine, Hecolin®, which was jointly developed by Xiamen Innovax Biotech and the China National Institute of Diagnostics and Vaccine Development in Infectious Diseases (Xiamen University). Hepatitis E is a waterborne disease, transmitted from person to person via the fecal–oral route, with epidemics reported in Asia, the Middle East, Africa, and Central America. According to the WHO, one third of the global population may have been infected by the virus. Every year there are 20 million hepatitis E infections, over three million acute cases of hepatitis E, and 70,000 hepatitis E-related deaths (http://www.who.int/mediacentre/factsheets/fs280/en/) [8]. A phase III trial in China involving 112,604 healthy adults aged 16–65 years demonstrated that the new vaccine was well tolerated and 100% effective in preventing hepatitis E disease [9]. Experts hope that Hecolin™ can play a vital role in controlling the spread of hepatitis E around the world. With advice from international organizations to introduce the vaccine where needed, initial introduction may focus on high-risk populations, such as women of child-bearing age, chronic liver disease patients, and food industry workers. Xiamen Innovax, a member of the network, is also developing the first HPV vaccine based on virus-like particles derived from an Escherichia coli expression system and has completed phase II trials.

Another regional disease of importance for developing countries is Japanese encephalitis, a viral disease that causes acute inflammation of the brain tissue. The disease is caused by a mosquito-borne group of flaviviruses, most prevalent in Southeast Asia and the far East, where 1 in 200 infections develop into encephalitis [10]. In many Asian countries, Japanese encephalitis is a leading cause of viral encephalitis affecting residents of rural areas in endemic regions. There are 30,000–50,000 cases reported annually, with a case-fatality ratio of 30% and serious neurological sequelae. Chemical vector control is not a solution because the mosquito breeding sites (irrigated rice fields) are extensive in Asia. Consequently, vaccines against Japanese encephalitis are much needed. The currently available inactivated Japanese encephalitis vaccines are not prequalified by WHO and are occasionally reactogenic in 10%–20% people receiving them [11]. Effective attenuated vaccine made in China, as well as new-generation inactivated vaccines, could become available globally through prequalification and United Nations procurement systems.

A further important development has been the improvement of the whole cell pertussis vaccine (wp) to produce the whole cell pertussis vaccine low in lipopolysaccharide (LPS) (wpFlow). It has long been known that the whole cell pertussis vaccine is associated with occasional reactogenicity, which led to the development of the acellular pertussis vaccines (ap). However, the high cost of purifying the components of acellular vaccines renders them unaffordable for most developing countries. Instituto Butantan therefore investigated the reduction, by organic extraction, of the main component responsible for the reactogenicity of the whole cell pertussis vaccine, which is the endotoxin, LPS. This rendered the vaccine less toxic while retaining its immunogenic and protective properties [12]. As a by-product of this production process, the LPS can be used to produce an adjuvant, monophosphoryl lipid A (MPLA), which is similar, but not identical, to salmonella-derived monophosphoryl lipid (MPL), currently used as adjuvant in several vaccine formulations. This bordetella-derived MPLA has been investigated as an adjuvant for several influenza vaccine formulations, including H3N2, H5N1 and H1N1 [13,14].

2.3. Contributing to a polio-free India and beyond

WHO’s global polio eradication initiative has made great progress based on use of oral poliovirus vaccine (OPV) with a live, attenuated form of Sabin poliovirus strains. India, once known as the world’s epicenter of polio, has successfully achieved one year polio-free since its last case, recorded on 13 January 2011 [15]. In this gigantic task, Panacea Biotec, a member of DCVMN, contributed by producing and supplying more than 9.2 billion doses of OPV over two decades (1990–2011). In fact, Panacea Biotec was the first to develop monovalent types 1 and 3 and bivalent (1+3) oral polio vaccines (b-OPV), which have become the most critical weapons in the arsenal of WHO and the Indian Ministry of Health and Family Welfare to prevent the crippling disease. Bharat Biotech International, and Haffkine, also DCVMN members, have supplied each about 1.5 billion doses of trivalent OPV and b-OPV since 2006, also thanks to fill-and-finish collaborations within network manufacturers cooperating to move toward a polio-free world.

Because polioviruses have no non-primate reservoir in nature and survival of the virus in the environment for an extended time appears to be remote, interruption of person-to-person transmission by vaccination is critical for global polio eradication [16]. However, in rare instances, OPV-derived attenuated viruses themselves can cause paralytic poliomyelitis cases. Thus, interruption of wild poliovirus transmission, as well as polio eradication, will require removal of OPV from routine immunization programmes, and only inactivated poliovirus vaccine (IPV) should be required for immunization programmes in the future.

The production of IPV, currently based on the Salk or wild type strains (wIPV), is concentrated within four manufacturers today. GlaxoSmithKline (GSK) and Sanofi–Aventis are currently the largest wP IPV bulk producers, creating about 120 million doses annually. The Netherlands Vaccine Institute (NVI) and Statens Serum Institute (SSI, Denmark) also produce wIPV vaccine bulk in smaller quantities. Other manufacturers, such as Biological E, Biomanguinhos, and Panacea, have bulk purchases agreements in place to fill and finish IPV.

Recognizing the potential for increased global demand, companies are planning to expand manufacturing to increase annual wIPV capacity from 120 million doses to approximately 260 million doses. IPV manufactured using Sabin strain virus seeds (sIPV) will address some of the potential environmental biorisks of wIPV production. As the primary alternative, an IPV-technology transfer platform for developing-country manufacturers and research institutes has been established in the Netherlands, and potential transfer of this technology is taking place through WHO coordination [17].

The manufacturing of IPV is scale-sensitive (i.e., costs decline as volumes rise), as with many other vaccines produced in fixed bioreactors, and expanded production would result in meaningful economies of scale to make an affordable IPV for deployment in low-resource settings. Therefore, with increased IPV manufacturing volume, vaccine costs have the potential to decline by 30–50% [18]. In addition, having sIPV manufactured in developing countries where the vaccines are most needed would reduce transportation costs and enable the use of already-existing OPV facilities, leveraging any development and regulatory investments required for those OPV manufacturers to switch to wIPV production. Thus, the technology transfer can bring three benefits: (1) extending the utilization and capacity of existing facilities and infrastructure, (2) reducing manufacturing cost per dose as the large-scale facilities remain fully utilized, and (3) improving the competitive dynamics within the marketplace by further diversifying IPV manufacturing supply.

Remaining challenges to be tackled in the development of sIPV include equivalent immunogenicity, administration routes, and use
Table 1
Vaccines prequalified by WHO for procurement by UN agencies as of July 2012. Thirty-two types of prequalified vaccines are available to date from DCVMN members and other vaccine manufacturers (VMs). Vaccines highlighted in gray are not yet prequalified by DCVMN members (the latest list of WHO prequalified vaccines can be found at http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/index.html).

<table>
<thead>
<tr>
<th>Type of vaccine</th>
<th>DCVMN members</th>
<th>Other VM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. BCG</td>
<td>Serum Inst. India</td>
<td>Statens S. Institute, BB, Japan Lab</td>
</tr>
<tr>
<td>2. Cholera</td>
<td></td>
<td>Shanta/Sanofi, Crucell SBL</td>
</tr>
<tr>
<td>3. Diphtheria-Tetanus</td>
<td>Biofarm, Serum India BB</td>
<td>Sanofi</td>
</tr>
<tr>
<td>4. Diphtheria-Tetanus (for adults)</td>
<td>Biofarm, Serum I India</td>
<td>BB, Sanofi</td>
</tr>
<tr>
<td>5. Diphtheria-Tetanus-Pertussis (whole cell)</td>
<td>Biofarm, Serum India</td>
<td>Sanofi</td>
</tr>
<tr>
<td>6. Diphtheria-Tetanus-Pertussis (whole cell)-Haemophilus influenzae type b</td>
<td>Biofarm, Serum India</td>
<td>Sanofi, Novartis</td>
</tr>
<tr>
<td>7. Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B</td>
<td>Biofarm, Serum India</td>
<td>GSK</td>
</tr>
<tr>
<td>8. Diphtheria-Tetanus-Pertussis (whole cell)-Hepatitis B-Haemophilus influenzae b</td>
<td>Biofarm, Serum India</td>
<td>GSK Cruccell</td>
</tr>
<tr>
<td>9. Haemophilus influenzae type b</td>
<td>CGEB, Serum India</td>
<td>Novartis, GSK, Merck, Sanofi</td>
</tr>
<tr>
<td>10. Hepatitis B</td>
<td>BiOarm, CGEB, LG, Serum II</td>
<td>GSK, Shanta/Sanofi</td>
</tr>
<tr>
<td>11. Human Papilloma Virus (HPV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Influenza (Seasonal)</td>
<td>GreenCross</td>
<td>MedImmune</td>
</tr>
<tr>
<td>13. Influenza A (H1N1) – Pandemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Measles</td>
<td>Serum Ilnia, BioFarma</td>
<td>Sanofi, GPO-MBP</td>
</tr>
<tr>
<td>15. Measles and Rubella</td>
<td>Serum I India</td>
<td>Sanofi, GSK, Merck</td>
</tr>
<tr>
<td>16. Measles, Mumps and Rubella</td>
<td>Serum I India</td>
<td></td>
</tr>
<tr>
<td>17. Meningococcal A Conjugate</td>
<td>Serum I India</td>
<td></td>
</tr>
<tr>
<td>18. Meningococcal A+C polysaccharide</td>
<td>Biomanguinhos</td>
<td>Sanofi</td>
</tr>
<tr>
<td>19. Meningococcal ACW 135</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20. Pneumococcal (conjugate)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21. Polio Vaccine-Oral (OPV) Bivalent</td>
<td>Biofarm, Haffkine</td>
<td>GSK, Novartis, Sanofi</td>
</tr>
<tr>
<td>22. Polio Vaccine-Oral (OPV) Bivalent Types 1 and 3</td>
<td>Haffkine</td>
<td>GSK, Novartis, Sanofi</td>
</tr>
<tr>
<td>23. Polio Vaccine-Oral (OPV) Monovalent</td>
<td>Haffkine</td>
<td>GSK, Novartis, Sanofi</td>
</tr>
<tr>
<td>24. Polio Vaccine-Oral (OPV) Monovalent Type 2</td>
<td>Haffkine</td>
<td>GSK</td>
</tr>
<tr>
<td>25. Polio Vaccine-Oral (OPV) Monovalent Type 3</td>
<td>Haffkine</td>
<td>GSK, Novartis, Sanofi</td>
</tr>
<tr>
<td>26. Polio Vaccine-Oral (OPV) Trivalent</td>
<td>Biofarm, Haffkine</td>
<td>GSK, Novartis, Sanofi</td>
</tr>
<tr>
<td>27. Rabies</td>
<td>Cadila</td>
<td>Chiron (India), Novartis, Sanofi</td>
</tr>
<tr>
<td>28. Rotavirus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>29. Rubella</td>
<td>Serum Inst India</td>
<td></td>
</tr>
<tr>
<td>30. Tetanus Toxoid</td>
<td>Biofarm, Biological E, Serum</td>
<td>Shanta/Sanofi/BB</td>
</tr>
<tr>
<td>31. Typhoid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32. Yellow Fever</td>
<td>Biomanguinhos</td>
<td>Sanofi, IPVE, Dakkar Institute</td>
</tr>
</tbody>
</table>

of adjuvants [19]. A new polo virus vaccine must become available globally within this decade.

2.4. Responding to health security issues at national and regional levels: Influenza vaccines technology transfer initiatives

The 2009 H1N1 pandemic, detected in early 2009 in Mexico, and ongoing sporadic outbreaks of H5N1 have highlighted issues related to supply, access, affordability, and effective deployment of pandemic influenza vaccines for countries that have limited or no access to such vaccines [20]. A strategy to increase access to influenza vaccines for seasonal epidemics and pandemic influenza in all countries was developed by academic and public health experts, vaccine manufacturers, and governmental agencies from developed and developing countries. This initiative has been coordinated by WHO and has three major objectives: (1) to increase use of seasonal vaccine and expand capacity for population-based vaccination, (2) to increase vaccine production capacity in a number of developing countries and secure regional vaccine supply, and (3) to foster research and development, so that, for example, cell-based vaccines could be manufactured and circumvent the bottleneck of supply inherent to egg-based vaccine technology. In this respect, experts expect that within this decade the manufacturing process for influenza vaccines will evolve to more efficient technologies, such as cell-based vaccines, and eventually universal vaccines [21,22].

As part of the global effort to ensure equitable access to a potentially needed pandemic influenza vaccine, developing-country manufacturers have been awarded grants by WHO to establish regional manufacturing capacity for influenza vaccine [23]. DCVMN members have positively responded to the WHO initiative, assisting public health authorities in ensuring that there is manufacturing capacity in developing countries for influenza vaccine in the event of a future pandemic. Manufacturers in developing countries have started increasing production capacity and have also established pandemic pilot manufacturing plants in addition to seasonal plants [24].

There is still a need for governments to respond to the challenge by ensuring that immunization programmes show high coverage for this type of vaccine and consequently that there is consistent demand and sustainable financial support for vaccination, so that manufacturers can maintain state-of-the-art facilities and high-level technical skills. Notably, governments of 36 countries in Latin America have adopted the policy of seasonal influenza vaccination for high-risk groups among populations. Many government agencies in Latin America are procuring vaccines through the Revolving Fund of the Pan American Health Organization. This has yet to happen in the Middle East, Africa, and the Asia-Pacific region.

3. DCVMN commitment to quality: a solid basis for safety and efficacy of vaccines

Importantly, the ability to have a great vaccine portfolio, large manufacturing capacity, innovation, and technology transfer initiatives depends ultimately on the quality of vaccines supplied by manufacturers. Unlike other medical interventions, vaccines are given to healthy people, and people are far less willing to tolerate vaccines’ adverse effects. Vaccines of high quality will have the safety profile and efficacy levels needed to reduce the incidence of infectious diseases. Thus, vaccine quality is of utmost importance and represents the basis for effective and sustainable vaccination programmes.

Increasing globalization in the production and distribution of vaccines calls for equivalence and interchangeability of vaccines procured across borders and more efficient and consistent oversight capacity of vaccines by supra-national authorities. The
common denominator to ensure global quality of vaccines and minimize risks to populations could be the WHO prequalification system, consisting of a centralized procedure to assess the quality of vaccines manufactured in different countries. There are four major elements to this system: (1) a scientific review of a dossier based on the analytical quality specifications of the vaccines, (2) a scientific review of the clinical data collected and documented during clinical testing of the candidate vaccine in human subjects, (3) testing of samples related to the intermediate and final product, and (4) onsite audit of the manufacturing facilities.

In this context, the DCVMN liaises members with WHO prequalification services and independent quality compliance and certification professionals. It also facilitates training courses and provides technical assistance to manufacturers to increase the number of prequalified vaccines available for global use. Enlarging the manufacturers’ base for procurement can make vaccines more affordable while reducing supply risks and transportation/storage costs. The network now has eight manufacturers that are supplying about 30 WHO-prequalified vaccines in various presentations, among the 32 types of vaccines prequalified by WHO (cf. http://www.who.int/immunization_standards/vaccine_quality/PQ_vaccine_list_en/en/index.html). Table 1 shows prequalified vaccines and their origin by manufacturer. Prequalified vaccines for choler, influenza, HPV, meningococcal A/C/W, rotavirus, pneumococcal disease, and typhoid are not yet available from developing-country manufacturers (see gray areas in Table 1).

When manufacturing vaccines, at least three quality aspects are important: quality control, quality assurance, and quality management. Quality control (QC) is a set of activities, based mostly on analytical testing, intended to ensure that requirements such as purity, sterility levels, and potency are actually being met. Quality assurance (QA) is a set of activities intended to establish confidence that quality requirements will be met; these activities cover issues such as duly calibrated equipment, qualified and skilled professionals, supplies, and water systems [25]. QC and QA are equally important parts of quality management systems, which ensure that products meet the customers’ requirements. The system can be strengthened by regular internal or external inspections and audits that can identify, remediate, or prevent quality risks within the manufacturing process. Manufacturers need strong partners to independently assess risks to quality, and they need to rapidly react to any quality issues. DCVMN members are strongly encouraged to implement such inspections/audits regularly.

4. Conclusion and outlook into the new decade of vaccines: opportunities and challenges

Over the past decade, developing-country vaccine manufacturers have built a successful track record of producing innovative, high-quality, and affordable vaccines, changing the landscape of vaccination globally. These manufacturers have played a crucial role in increasing access to vaccines toward universal use. Through strategic alliances and technology transfer initiatives, they have been able to supply combination vaccines to children, make large areas of the world polio-free, fight regional disease epidemics (most notably meningitis in Africa), and bring innovative recombinant hepatitis vaccines to those who need them.

The network has a growing number of companies that produce a growing number of vaccines to supply the growing demand for vaccines in developing countries. This growth reflects the strong will of DCVMN members to contribute to improving the health and well being of people in all regions. It also reflects a higher awareness of infectious diseases, an increased willingness of people to be vaccinated, and a commitment by governments and global health agencies to support vaccination as a public good.

Importantly, large-scale supply of pentavalent combination vaccines was achieved through collaboration among manufacturers trusted within the network, supported by technology transfer agreements based on international cooperation, and with financial support from the international community—notably GAVI—that committed to procurement. The challenge is now to sustainably maintain the pace of growth. This growth offers new opportunities to leverage vaccine manufacturing capacity in developing countries, develop new international R&D initiatives and product development partnerships, create new joint ventures for improving access to available vaccines, and increase distribution networks and benchmarks for quality and best practices. Additionally, new technologies becoming available from developing-country manufacturers offer opportunities for technology transfer agreements to industrialized manufacturers, so overcoming regulatory barriers.

Approximately 70% of global vaccines are now produced by large multinationals based in North America and Europe, with the remaining 30% being produced by the vaccine industry in emerging and developing countries. The vaccine industry in these countries is growing rapidly, in volume, innovation, technology sharing, and effective partnerships. When it comes to the supply of children’s vaccines, the figures are actually reversed, with 70% of vaccines being produced by developing-country manufacturers. In addition, the global market is growing by 16% annually, with higher growth rates in emerging countries. It has been estimated that revenues for preventive vaccines rose from US$2.7 billion in 2009 to $24.3 billion in 2010 [26]. Only about $1 billion of this amount is related to procurement by UNICEF for delivery in developing countries [27], corresponding to approximately 4% of the global value of vaccines supply, equivalent to 2.5 billion vaccine doses. In 2012, UNICEF expects to achieve the highest volume of procurement ever. In addition, the Pan American Health Organization’s Revolving Fund procures about 180 million doses annually, valued at $405 million, on behalf of 39 Latin American countries and territories. About 75% of the vaccines procured by UN agencies (UNICEF/PAHO) are produced by manufacturers in emerging countries [28]. A larger base of vaccine manufacturers to supply immunization programmes permits better management of vaccine availability, and procurement agencies may have options for more secure supplies and lower-cost distribution on a regional basis.

Many manufacturers in emerging countries are now investing in upgrading their manufacturing facilities, improving their quality systems, and increasing production capacity. In the coming five years, developing-country manufacturers should be able to license, prequalify, and launch the next rotavirus vaccine and the next HPV vaccine. These advances will help to substantially reduce child disease and mortality as well as cervical cancer risk and mortality, contributing to reaching millennium development goals 4 and 5.

As developing-country manufacturers continue to cooperate, increasing numbers of technology transfer agreements are being sought and negotiated to speed up access to new vaccines. Still, incentives for more efficient initiatives are needed to foster and support so-called South-South technology transfers in the new decade, such as for cholera and typhoid vaccines, new affordable rotavirus, HPV, and combination vaccines.

In the Decade of Vaccines, DCVMN members should be able to supply most of the childhood vaccines, such as affordable pentavalent and other combination vaccines, to close the 15% gap between industrialized and developing countries in DTP vaccination coverage. Novel vaccines remain largely underused in the developing world, and DCVMN members are highly committed to license, launch, and prequalify rotavirus, pneumococcal, Japanese encephalitis (JE), cholera, meningococcal, and typhoid vaccines. Further, vaccines against neglected diseases—such as dengue fever, Hand-foot and mouth disease, leishmaniosis and Chagas disease—are in the pipeline to better protect low-income
populations from diseases and premature mortality, fulfilling our mission. DCVMN members also wish to step up now to challenges in R&D in the search for vaccines against the big killers of HIV, malaria and tuberculosis, as most people affected by these infections are in developing countries, and the DCVMN is the right “blend” of public and private companies to deliver such vaccines within this decade. Innovative international partnership models are sought to create synergies for implementation of global quality standards across all members of the network. The long-term goal of the Network is to supply high-quality vaccines to all people where needed in a sustainable manner, rendering vaccines a universal good.

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Conflict of interest

The authors are employees of the respective indicated organizations, and have no conflict of interest to declare.

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