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SHORT COMMUNICATION

The Developing Countries Vaccine Manufacturers' Network (DCVMN) is a critical constituency to ensure access to vaccines in developing countries

Suresh Jadhav[a], Mahima Datla[b], Hans Kreeftenberg[c], Jan Hendriks[c,*]

[a] *Serum Institute of India Limited (SIIL), Pune, India*
[b] *Biological E Limited, Hyderabad, India*
[c] *Netherlands Vaccine Institute, Bilthoven, The Netherlands*

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Summary Six years after its establishment, the Developing Countries Vaccine Manufacturers' Network (DCVMN) has become the main representing body for emerging vaccine manufacturers from the developing world.

The Network's main strategic priority (increase access to DPT-based combination vaccines containing vaccines against Hepatitis B (HepB) and *Haemophilus influenzae* type b (Hib)) has now come close to fulfillment due in part to the transfer of conjugation technology from The Netherlands Vaccine Institute (NVI) to various manufacturers of the Network.

It is argued that at the international level more push mechanisms for product development involving DCVM are needed, including those promoting access to technology and transfer of technology, know how and technical skills from Organization for Economic Co-operation and Development (OECD) countries to developing countries.

At the national level, governments of countries in which DCVMN manufacturers operate should provide more generous funding for all aspects of vaccines and immunization including incentives to manufacturers to develop and import new technologies.

These two approaches will contribute to the long-term viability of domestic or regional vaccine manufacturing, which in itself is critical to ensure global equity of access to vaccines.

Introduction

The OECD recently held a high level forum on policy coherence in Medicines for Neglected and Emerging Infectious Diseases in the regal Hotel Oranje in Noordwijk-aan-Zee, The Netherlands. The forum brought together representatives of developed and developing countries, industry,

* Corresponding author at: Netherlands Vaccine Institute, P.O. Box 457, 3720AL Bilthoven, The Netherlands. Tel.: +31 302744298; fax: +31 302744439.
E-mail address: j.hendriks@nvi-vaccin.nl (J. Hendriks).

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Table 1 Members of the Developing Countries Vaccine Manufacturers' Network (DCVMN)

	Name	Category
1	Bio-Manguinhos (Fiocruz-Fiotec), Brazil	(1)
2	Bio Farma, Indonesia	(1)
3	Finlay Institute, Cuba	(1)
4	LG Life Sciences Ltd., Seoul, Korea	(1)
5	Panacea Biotech Limited, India	(1)
6	Serum Institute of India, India	(1)
7	Biological E. Limited, India	(2)
8	Bharat Biotech International Ltd., India	(2)
9	Indian Immunologicals Limited, India	(2)
10	Zydus Cadila Healthcare Limited, India	(2)
11	Instituto Fundaco Butantan, Brazil	(2)
12	Laboratories De Biologicos Y Reactivos De Mexico S.A. De C.V. (BIRMEX), Mexico	(2)
13	The Biovac Institute, South Africa	(2)
14	Queen Saovabha Memorial Institute, Thailand	(2)
15	Razi Vaccine & Serum Research Institute, Iran	(2)
16	China National Biotec Corporation, China	(2)
17	Dalian JGAD Bioproducts Co. Ltd., Dalian, China	(2)
18	Xiamen YST Biotech Co. Ltd., China	(2)
19	IVAC (National Institute of Vaccines & Biological Substances), Vietnam	(2)
20	Vabiotech, The Company for Vaccine & Biological Production No. 1, Vietnam	(2)

(1) members holding WHO-pre-qualification of one or more of their products, located in countries with fully- functional National Regulatory Authorities (NRA) as defined by WHO; (2) members working towards attaining the status of WHO pre-qualification.

academia, non-governmental organizations and international organizations and agreed on a coherent ''Noordwijk Medicines Agenda'' [1].

This agenda calls for improving global health by accelerating development and delivery of medicines, vaccines and diagnostics for infectious diseases affecting developing countries.

Coincidently the DCVM-Network (see Table 1), the international representing body of emerging vaccine manufacturers, originated some 6 years ago in the same Hotel Oranje in Noordwijk at the 2001 Partner's meeting of the Global Alliance for Vaccines and Immunization (GAVI).

This communication highlights the development of the Network and lessons learned since, with a particular perspective towards increased recognition of domestic or regional vaccine development and manufacturing as a critical step for increasing access to neglected and underused vaccines in developing countries.

DCVMN origin

DCVMN is a voluntary public health driven alliance of vaccine manufacturers owned by and located in developing countries that offer a consistent and sustainable supply of quality vaccines that are affordable and accessible to developing countries [2]. These countries account for the majority of newborns in the world and DCVMN members supply (next to most of their own local public markets) currently the vast majority of all the vaccines procured by UNICEF and PAHO for the developing world. For example, the DCVMN contribution in vaccine doses to PAHO's 2007 tenders ranged from 5 to 100%, the average being 70% (Table 2). In fact, two out of every three children born in the world get immunized with at least one vaccine that comes from a manufacturer from the DCVMN.

When the DCVMN was created following a series of WHO meetings of public sector vaccinology institutions, the majority of initial members were focused to their local markets only. Interestingly, this is now not longer the case; in fact the transition from ''suppliers to the local market'' to ''suppliers to the global market'' signifies most clearly a major development that has taken place among DCVMN since it originated. Its main purpose is now ''to provide a consistent and sustainable supply of quality vaccines at an affordable price to developing countries and also to the entire globe'' [3].

Strategic goal: availability of Hib-containing combo vaccines

In 2007, a dedicated website has come on air (www.dcvmn.com) that outlines mission, vision and objectives of the Network and also provides useful company profiles of its members and supportive organizations [3]. To be eligible for DCVMN membership a company must be either a public sector manufacturer in a developing country or must be majority held (51% or greater) by a person or combination of people citizens of the developing country in which the company produces vaccines.

The Network's main strategic priority formulated at the start was to increase access to HepB and Hib containing DPT combination vaccines. This was in line with the objectives of GAVI, which was just launched after an initial subsidy of the Gates Foundation [8]. It was hoped at that time that GAVI would support the Network by ''push'' mechanisms such as facilitating access to technology [2]. Most DCVM at that time

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Table 2 Vaccines procured by the Pan American Health Organisation (PAHO) from members of the DCVMN in 2007

	Vaccine	Total quantity	Quantity awarded	DCVM-member	%
1	BCG 10 dose vial	11,440,000	6,520,800	Manufacturer A	57
2	DPT 10 dose vial	11,182,204	10,623,094	Manufacturer A	95
3	DT (Adult) 10 dose vial	32,400,000	32,400,000	Manufacturer A	100
4	DT (Ped) 10 dose vial	612,000	183,600	Manufacturer A	30
5	Hep B 1 dose recom (Ped)	7,000,000	5,000,000	Manufacturer B	71
6	Hep B 1 dose recom	364,286	364,286	Manufacturer B	100
7	Hep B 10 dose recom	6,240,486	6,240,486	Manufacturer B	100
8	MR 10 dose	4,000,000	2,800,000	Manufacturer A	70
9	MMR 1 dose	9,750,000	6,250,000	Manufacturer A	64
10	MMR 10 dose	5,914,286	3,414,286	Manufacturer A	58
11	Polio	42,000,000	2,000,000	Manufacturer C	5
12	TT 10 dose	430,000	265,000	Manufacturer A	62
13	Yellow fever 5/10 dose	11,000,000	11,000,000	Manufacturer D	100

Average from DCVM A–D = 70

were DPT manufacturers serving a substantial part of the developing country vaccine demand for pediatric vaccines and, although this had not been investigated in a study, it was assumed that GAVI goals would be most cost-effectively be obtained when the new vaccines to be introduced (HepB and Hib) would be combined with DPT made by DCVM. Thereby GAVI would also make effective use of their existing DPT manufacturing infrastructure and distribution channels. For DCVM such international support was important as access to technology is one of the main conditions determining the long-term viability of local vaccine manufacturing [4]. The expected donor support to the Network at that time did not materialize, partly due to international concerns for unfair subsidizing certain individual manufacturers. Despite this initial[1] lack of donor support the Network's main strategic priority has now nearly been reached at a global scale. Key factors to this success included the transfer of conjugation technology from The Netherlands Vaccine Institute (NVI), the ability of the ''receiving'' DCVMN members to invest upfront in this conjugation technology and their ability to absorb the transferred technology [5].

Development and technology transfer of Hib conjugation technology by NVI

NVI developed since 1999 an up-scalable and patent-free process for the production of a conjugate vaccine against Hib, based on the Robbins conjugation technology [6,7] and transferred the process at pilot scale to three different DCVMN members: Bio Farma (Bandung, Indonesia), Serum Institute of India Ltd./SIIL (Pune, India) and Biological E. Limited (Hyderabad, India) [5]. This wider NVI Hib technology transfer programme, as well as the up-scaling, clinical trial and licensing, was financed mainly by three involved DCVMN members themselves. Lessons learned in this programme have been described elsewhere [5].

[1] Recently in 2006 USAID has provided some funding to the Network for training purposes.

Due to a near monopoly situation, the GAVI market price for Hib containing combination vaccines has not decreased for nearly 5 years. GAVI now expects that the entry into the market by DCVM will lead to this needed decline for Hib containing vaccines, just as the price of DPT-HepB combo vaccines dropped 40% since 2001 mainly as a result of entry into the market of new manufacturers from developing countries [8].

Recently, one DCVM, the Serum Institute of India Ltd. (SIIL) obtained with the NVI Hib process technology a license from the Indian Government for the indigenous production of monovalent Hib and also for pentavalent (DTP–Hep B–Hib) vaccine. In the near future, SIIL expects to get the necessary clearance for supply to United Nation Organizations. With a capacity to produce over 100 million doses of the vaccine, it is expected that with the imminent availability of additional Hib vaccine products there will be a reduction of the global vaccine price in the next few years. When licensure is obtained by the other DCVM that have absorbed the NVI technology (Biological E and Bio Farma) such reduction will be further sustained.

These kinds of joint development and technology transfer projects with DCVM will increase the availability of Hib vaccines for affordable prices on the global vaccine market. Next to this successful example of technology transfer from an OECD public sector institution as NVI, other approaches to obtain Hib conjugation technology were recently summarized in a case study on access to vaccine technologies [9]. These involve OECD Industry and include importing Hib bulk by Bio-Manguinhos in Brazil with eventual technology transfer and importing Hib bulks for formulation and marketing in India by Bharat Biotech and Panacea Biotech [9].

Vaccines for development: access is key

Involving DCVM in the development and creation of vaccines will increase the likelihood that any given vaccine or vaccine combination needed in those countries will become available because DCVM are by nature closely interacting with

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their national or (in the case of India) regional immunization programmes. They also liaise closely with their local national regulatory authorities. Therefore DCVM are more likely to develop and manufacture affordable products targeted to the needs of the population.

Currently new and promising policy innovations [10] for new generation vaccines[2] and possible future vaccines[3] are developed in the global vaccine landscape. These build on the existing GAVI Alliance that was created initially mainly for under-used vaccines.[4] With GAVI funds, UNICEF has in the past 5 years predominantly purchased from OECD manufacturers under-used vaccines for low-income countries, in particular, monovalent HepB and Hib vaccines, and combination vaccines containing Hib and HepB.

The new policy innovations that have received much media attention lately include the International Finance Facility for Immunization (IFFIM), Product Development Partnerships (PDP's like the International AIDS Vaccine Initiative (IAVI), the Malaria Vaccine Initiative (MVI) and MVP) and Advance Market Commitments (AMCs) [10]. These innovations will be applied mainly for new generation and future vaccines and (with the exception of PDP's, which can activate push mechanisms) seem focused to pull mechanisms.

We argue here that more push mechanisms should be put in place at the international level to attain DCVM's involvement. In particular this can be achieved by increasing access to technology (also critical for viability of the manufacturer) by joint research and development programmes and by transfer of technology and know how (including how to deal with IPR issues [9,11]). DCVM are now on the one hand expected to lower the global vaccine prices for underused vaccines such as pentavalent combinations, but at the same time they have like any other manufacturer to invest in product development and to meet the costly international cGMP quality standards and regulatory requirements for clinical studies necessary to pre-qualify through WHO for supply of vaccines to UN agencies.

At the national level, governments of countries in which DCVMN manufacturers operate should provide more generous funding for all aspects of vaccines and immunization including incentives to manufacturers to develop and import new technologies. A good example of this approach is Brazil, where 80% of the vaccines distributed come from two DCVM. Successive governments have over the last decades substantially invested in a public industrial complex including two DCVM [Instituto Butantan in Sao Paulo and the Bio-Manguinhos in Rio de Janeiro]. Both have attained a GMP status. Similarly, the establishment of a strict national control authority, entirely independent from the manufacturers, was created ensuring international quality levels. This was done in the framework of a national self-sufficiency programme for vaccines and sera based upon competitiveness [12].

[2] New generation vaccines: Pneumo, Rota, HPV, Japanese Encephalitis [10].

[3] Possible future vaccines: HIV/AIDS, TB, Malaria [10].

[4] New and under-used vaccines: HepB and Hib conjugate-containing combination vaccines, including the traditional EPI DTP vaccines, Typhoid, Cholera [10].

Perspectives: influenza vaccine production capacity in developing countries

The threat of a potential new flu pandemic has sparked a renewed interest at the global level in domestic or regional vaccine production in developing countries. Currently, influenza vaccine production capacity is vastly insufficient to meet the global demand in case of a pandemic. Influenza vaccine manufacturing is now mainly located in Europe. Developing countries, notably in Asia rightly fear that in case of a pandemic they will not have access in time to affordable pandemic influenza vaccines, if they have to rely entirely on the European-based influenza vaccine industry, which will primarily serve OECD markets. The latest World Health Assembly reached after 6 days of closed-door meetings a tedious agreement on a new resolution on best practices for sharing virus samples to address new pandemics such as avian flu. This resolution addresses in part the concerns of a group of developing countries led by Indonesia focusing on access to vaccines for developing countries [13]. The WHA resolution acknowledges the need for facilitation of acquisition by developing countries of capacity for manufacturing in-country influenza vaccines.

The Global Pandemic Influenza Action Plan to increase vaccine supply of WHO aims to close the current influenza vaccine production gap of several billion doses [14]. In line with this plan, WHO has taken recent steps to engage DCVM: six members in Brazil, India, Indonesia, Mexico, Thailand and Vietnam were awarded grants in 2007 for technology transfer to establish manufacturing capacity for influenza vaccine [15].

The Noordwijk Medicines Agenda (NMA) calls for the need to explore models to promote innovation and stimulate the development of new vaccines for neglected and emerging infectious diseases. Amongst several others mechanisms, the promotion of transfer of technology, knowledge and technical skills from OECD countries is encouraged. The NMA also calls for new partnership models between developing and developed countries to accelerate R&D for neglected diseases.

The DCVMN has evolved over the last years into a significant international constituency critically involved in matters of global vaccine security concern. The experiences between DCVMN-members and the NVI described here on the Hib conjugate vaccine are an example of such a model that could be applicable also to other neglected vaccines. To foster the contribution by developing countries to global R&D efforts, incentives are to be designed to strengthen and utilize their capacity and institutions. This includes a good understanding of intellectual property and strengthening their capacity to manage IP issues [9]. In this respect it is encouraging to note that the Intergovernmental Working Group on Public Health, Innovation and Intellectual Property, due to convene in November 2007, drafted a new global strategy containing specific elements on transfer of technology and management of IP [16].

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