VMPA STUDY

VACCINE MANUFACTURING AND PROCUREMENT IN AFRICA

An analytical assessment of vaccine manufacturing capacity and procurement mechanisms for establishing sustainable vaccine manufacturing capacity in Africa

UNIDO UNITED NATIONS INDUSTRIAL DEVELOPMENT ORGANIZATION
AVMI AFRICAN VACCINE MANUFACTURING INITIATIVE
World Health Organization

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This study was conducted by a working team of consultants comprising Amitabh Mehta, Jean-Marie Préaud, Richard Van Duyse, Sarah Schmitt and was coordinated by Miloud Kaddar, health economist, under the overall guidance of Juergen Reinhardt, Senior Industrial Development Officer and Project Manager, assisted by Alastair West, PMPA Business Plan Coordinator and Martin Nicholson, International Pharmaceutical Expert.

The VMPA study was coordinated through the VMPA Management Team, comprising Patrick Tippoo (AVMI), Martin Friede (WHO HQ), Alastair West (UNIDO HQ), Jan Hendriks (WHO HQ), Martin Nicholson (UNIDO HQ), Claudia Nannei (WHO HQ), Moredreck Chibi (WHO HQ), Chidi Nweneka (AVMI) and Ebrahim Mohamed (AVMI). This was accomplished through the expert guidance of the VMPA Strategic Advisory Group, (Martin Friede (Chair), William Ampofo (Co-chair), Alastair West, Tina Lorenson (BMGF), Marc LaForce (Consultant, SIIL), Janet Byaruhanga, (African Union), Heather Deehan, (UNICEF SD), Margareth Ndomondo- Sigonda, (NEPAD, AU) and Oyewale Tomori, (TFI WHO AFRO)) and with support from the U.S. Department of Health and Human Services, Samuel Adeniyi-Jones, Anne Yu, Alicia Kimbrel and Christopher Chadwick. Administrative support was provided by the AVMI Secretariat (Melissa Schouw, Daria Kow, Charlie Nemugumoni and Akhona Gura).

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Executive Summary

Over the past decade, global and African stakeholders have been promoting the concept of establishing sustainable vaccine manufacturing capacity on the African continent. Experts and stakeholders alike have provided both a number of justifications as well as opposing considerations to this concept.

To move forward, the African Vaccine Manufacturing Initiative (AVMI), supported by United Nations Industrial Development Organization (UNIDO) and World Health Organization (WHO), sponsored the Vaccine Manufacturing and Procurement in Africa (VMPA) study. The assessment, conducted by expert consultants, analysed the global and regional contexts, conducted a landscape analysis and suggested options for further consideration and investigation for the establishment of sustainable vaccine manufacturing capacity in harmony with the Pharmaceutical Manufacturing Plan for Africa (PMPA). The four components of the study included:

- assessment of the vaccine market dynamics
- the vaccine procurement and financing mechanisms
- the feasibility of establishing sustainable vaccine manufacturing
- cost drivers and funding mechanisms to establish sustainable vaccine manufacturing in Africa.

The VMPA study covered all 54 African countries including all WHO AFRO countries as well those WHO EMRO countries located in the African Continent. The VMPA study was guided by advice from an expert Strategic Advisory Group (SAG). The methodology combined field observations, quantitative and qualitative approaches, desk review, questionnaires and interviews with manufacturers, resource persons and experts as well as regular consultation with the VMPA Study management team and the SAG.

This study provides a comprehensive overview of the current situation, main directions, issues, challenges and opportunities relating to vaccine manufacture on the continent.

The study found that developing vaccine production in Africa is a debatable and contentious question. As things stand, established external manufacturers and suppliers are responding to most of Africa's funded demand. However, there is a place for existing and potential African manufacturers to develop their capacities for manufacturing in the next 10-20 years, when considering, for example, economic and population growth projections for the continent over the next 30 years. It must be noted that the conditions required for entering a new stage in a dynamic process such as this, in all aspects of manufacturing, are still to be studied in depth.

Whilst it can be argued – given industry and market dynamics - that there is limited space for multiple major players in the vaccine production field in Africa, a number of regional hubs could be established. This would require the right level of political and technical support, including a clear, well-funded and coherent regional policymaking and planning approach, allowing development of the necessary ecosystem to establish a viable, competitive and sustainable vaccine manufacturing capability.

It is intended that the outputs and outcomes of the VMPA study will be used to consult and advocate with key stakeholders to advance the development of African vaccine manufacturing considerations, within the Pharmaceutical Manufacturing Plan for Africa (PMPA) framework and strategic plan.

Summary of Key Findings

A comprehensive list of findings and conclusions is provided in Section 6 of this report. In brief:

- Total Africa Vaccine market, including public and private Extended Program of Immunization (EPI) and non-EPI vaccines, is estimated at 1.2 billion USD in 2013 and represents 5.5% of global vaccine market.
- Development of a more comprehensive and sustainable vaccine manufacturing industry in Africa requires active intervention in order to establish a conducive business environment.
- Vaccine supply in Africa is almost entirely external and influenced by funding sources and global community policies and incentives. Marginal manufacturing exists in Senegal, Egypt, South Africa and Tunisia.
- There are eight companies with existing or potential vaccine manufacturing capacities in Africa. Only one of these companies exports a WHO prequalified vaccine (Yellow Fever).
- Three companies with locally produced and marketed products are able to supply vaccines that include all upstream and downstream processes. A further company is in the late stage of vaccine development and manufacturing, but it is limited to downstream processes. Four companies are considered at the preliminary planning phase of vaccine development and production, three of which have had past experience in producing some basic vaccines.
- The United Nations Children's Emergency Fund Supply Division (UNICEF SD) Procurement Services is the predominant procurement mechanism for 45 of 54 countries. The percentage of UNICEF vaccine sales in Africa compared to the total UNICEF vaccine sales is around 60%.
- Current procurement and related practices could be an obstacle to utilization of any African manufactured vaccines and therefore require in-depth consideration for sustainability of local vaccine production.
- The National Regulatory Authority (NRA) functionality required for vaccine manufacturing is very limited in Africa. African Vaccine Regulatory Forum (AVAREF), a regional platform, is playing a positive role but cannot replace local NRAs.
- From 2002 to 2015, 171 vaccine clinical trials have been conducted in Africa, putting pressure on the capacity of regulators and ethics committees to meet all the necessary standards.
- African demand is booming in terms of number of doses of vaccine and vaccine types, growing population, increased immunization coverage and expenditures and funding support for new vaccine introductions.
- The potential for African vaccine manufacturers to develop capacities in the next 10 to 20 years exists but there may be limited place for more than two or three sub-regional hubs.
- There is little empirical evidence from African manufacturing to examine, and, though there are plans for new facilities, confidentiality concerns limit access to data.
- Barriers to entry, requirements and risks are high, and industrial and commercial competition for routine vaccines is very challenging, demanding and costly.
- Scientific, technical, managerial and financial resources are important parameters for sustainability.

- Building a manufacturing facility can cost between approximately USD 60 million to USD 130 million, with CAPEX attracting over 60% of all costs, however this can be rationalized through economies of scale and scope.

- New technologies can help reduce/defer upfront expenditure.

- Key requirements for sustainability include a highly-specialized workforce, quality management systems and other international standards which are important cost drivers to achieve and maintain Good Manufacturing Practices (GMP) requirements.

- The lack of an enabling ecosystem in most African countries combined with the lack of existing support will increase indirect costs and present challenges to the feasibility of production in Africa.

- Financing sources in Africa are mainly government budgets supplemented by grants, fee income and in some cases loans or private financing. Several innovative financing methods and techniques are being discussed, and incentives and subsidies by governments and partners can reduce manufacturing investment and operational costs.

List of Acronyms

AEFI	Adverse Event Following Immunisation
AFD	Agence Française pour le Développement
AfDB	African Development Bank
AFRO	WHO African Regional Office
AIDS	Acquired Immune Deficiency Syndrome
AMP	Agence de Médecine Préventive
API	Active Pharmaceutical Ingredient
AS	Auto disabling syringes
AU	African Union
AUC	African Union Community
AVAREF	African Vaccine Regulatory Forum
AVMI	African Vaccine Manufacturing Initiative
BARDA	Biomedical Advanced Research and Development Authority
BCG	Bacille de Calmette et Guérin Vaccine
BMGF	Bill & Melinda Gates Foundation
BRICS	Brazil, Russia, India, China and South Africa
BRV	Bovine Reassortant Vaccine
BSE	Bovine Spongiform Encephalitis
BVI	Botswana Vaccine Institute
CAPEX	Capital Expenditure
CAGR	Compound Annual Growth Rate
CBER	Biologics Evaluation and Research
CDC Nigeria	Centre for Disease Control Nigeria
CDIBP	Chengdu Institute of Biologic Products, China
CoGs	Cost of Goods
COMESA	Common Market for Eastern and Southern Africa
CSL	Commonwealth Serum Laboratories, Australia
CSR	Corporate Social Responsibility
CT	Clinical trials
DCVM	Developing Countries Vaccine Manufacturers
DCVMN	Developing Countries Vaccine Manufacturers Network
DG	Director General
DNA	Deoxyribonucleic acid
DTP	Diphtheria Tetanus Pertussis Vaccine
DTP-Hib	Diphtheria Tetanus Pertussis Haemophilius type Vaccine
DTPHepB	Diphtheria Tetanus Pertussis Hepatitis B Vaccine
EDCTP	European & Developing Countries Clinical Trials Partnership
EMA	European Medicines Agency
EMP	WHO Department of Essential Medicines and other Health Technologies
EMRO	WHO Regional Office for the Eastern Mediterranean
EPHI	Ethiopian Public Health Institute
EPI	Extended Program of Immunization
ERC	Research Ethics Review Committee
FDA	Food and Drug Administration (USA)
Flu	Influenza
FMD	Foot-and-Mouth Disease

FTE	Full time Equivalent
Gavi	Gavi, The Vaccine Alliance
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
GNI	Gross National Income
GSK	Glaxo Smith Kline
Hep B	Hepatitis B Vaccine
HHS	United States of Health and Human Services
Hib	Haemophilus influenzae type b Vaccine
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HR	Human Resource
HSE	Health & Safety Executive
ICH	International Conference on Harmonization
ICTPR	International Clinical Trials Registry Platform
IDP	Institutional Development Plans
IFFIm	International Finance Facility for Immunization
IFPMA	International Federation of Pharmaceutical Manufacturers Association
IIV	Influenza, Seasonal Inactivated
IPA	Institut Pasteur Algérie
IPD	Institut Pasteur de Dakar
IPM	Institut Pasteur Maroc
IPT	Institut Pasteur Tunisie
IPV	Inactivated Polio Vaccine
IsDB	Islamic Development Bank
KAVI	Kansallinen Audio Visuaalinen Instituuti
KEMRI	Kenya Medical Research Institute
JE	Japanese Encephalitis
JV	Joint-venture
LA	Lab Access
LAIV	Live attenuated influenza vaccine
LIC	Low-Income Country
LIMC	Lexicon Iconographicum Mythologiae Classicae
LR	Lot Release
LTA	Long Term Agreement
M	Measles Vaccine
MA	Market Authorization
MCC	South African NRA – National Regulatory authorities
Men A	Group A Meningococcal
MIC	Middle-Income Country
MMR	Measles, Mumps, and Rubella
MNC	Multi-national Companies
MOH	Ministry of Health
MOU	Memorandum of Understanding
MR	Measles Rubella
MVP	Meningitis Vaccine Project
NACA	National Association for Clean Air
NEPAD	New Partnership for Africa's Development
NGO	Non-Governmental Organization
NIP	National Immunization Programme

NITAG	National Immunization Technical Advisory Group
NRA	National Regulatory Authority
ODA	Overseas Development Aid
OOP	Out of Pocket
OPEX	Operational Expenses
OPV	Oral Polio Vaccine
PACTR	Pan African Clinical Trials Register
PAHO RF	Pan American Health Organization Revolving Fund
PATH	Program for Appropriate Technology in Health
PCV	Pneumococcal Conjugate Vaccine
PM	Project management
PMPA	Pharmaceutical Manufacturing Plan for Africa
PPP	Public Private Partnerships
PQ	Pre-qualification
PSPQ	Programmatic Suitability of Vaccine Candidates for WHO PQ
PMS	Post Marketing Surveillance
QA	Quality Assurance
QC	Quality Control
QMS	Quality Management System
R&D	Research & Development
RIIP	Réseau International des Instituts Pasteur
ROI	Return on Investment
RV	Rotavirus Vaccine
SIA	Security industry Association
SA	South Africa
SACU	Southern African Customs Union
SADC	Southern African Development Community
SIF	Sustainable Immunization Financing
SIIL	Serum Institute of India Limited
TA	Technical assistance
TB	Tuberculosis Vaccine
Td	Tetanus diphtheria
TFI WHO AFRO	Task force on Immunization World Health Organization Regional Office of Africa
TGA	Australian Therapeutic Goods Administration
TP	Technology platform
TT	Technology transfer
TTD	Taxes, Tariffs or Duties
UEMOA	Union Economique et Monétaire Ouest-Africaine
UK	United Kingdom
UN	United Nations
UNICEF RO	UNICEF Regional Office
UNICEF CO	UNICEF Country Office
UNICEF SD	UNICEF Supply Division, Copenhagen Denmark
UNIDO	United Nations Industrial Development Organization
UNITAID	United Nations
US	United States
USAID	United States Agency for International Development
USD	United States Dollars
USP	Unique Selling Proposition
VGF	Viability GAP funding

VMPA	Vaccine Manufacturing and Production in Africa
WHO	World Health Organization
WHO PQ	World Health Organization Pre-Qualification
WHOCC	World Health Organization Collaborating Centers
YF	Yellow Fever Vaccine

1. Background, Study Objective and Methods

The burden of infectious diseases continues to be disproportionately high in some African countries, particularly in sub-Saharan Africa, with significant impacts on health and socio-economic development. Furthermore, the burden of vaccine preventable diseases remains high despite the increasing availability of life saving vaccines, which are recognized as one of the most cost-effective and preventive health care interventions and disease countermeasures.

Predominantly donor or publicly funded in Africa, access to vaccines is considered in many countries to be both a public good and human right. Uninterrupted supply of high quality vaccines is essential in minimizing the negative health, social and economic impacts of vaccine preventable diseases.

While there are a limited number of high quality vaccine manufacturers globally, there are almost no significant manufacturers of vaccines on the African continent. African vaccine demand is booming but African vaccine research, development and manufacturing remain in their infancy. This external dependency (on suppliers outside Africa) is a source of vulnerability and risk which is increasing as countries are introducing new vaccines, and disease outbreaks are occurring. Most of the African countries are increasingly relying on international donors, suppliers and manufacturers. By way of example, the 2009 H1N1 Influenza pandemic highlighted the African continent's lack of capacity to develop, manufacture or access flu pandemic and other strategic vaccines, as required in public health emergency situations. More recently, the 2014 Ebola outbreak in Western Africa has resulted in strong recommendations from the African Union and others regarding support for the acceleration of local vaccine development and manufacturing.

Furthermore, in addition to improving responses to emergency situations, African vaccine manufacturing could improve security and sustainability of vaccine supply, and respond to unmet health needs of a growing population and rapid socioeconomic development in Africa.

The prominence of developing vaccine manufacturing capacity in Africa is underlined by the Global Vaccine Action Plan resolution at the 2015 World Health Assembly (WHA). This calls for Member States to seek opportunities for national and regional vaccine production and to investigate procurement options for improved access and supply.[1]

1.1 AVMI – African Vaccine Manufacturing Initiative

In September 2010 during the International Vaccine Technology Workshop in India, a group of interested Africans launched the African Vaccine Manufacturing Initiative (AVMI). Looking beyond the provision of vaccines in emergency situations, the AVMI intends to coordinate efforts of African vaccine manufacturers and other interested parties, who have a vision to see Africa produce its own vaccines and biologicals for both routine and emergency situations. Working with governments, regional bodies, non-governmental organizations (NGOs), the private sector, academic institutions, and relevant key opinion leaders, AVMI aims to partner in creating an environment on the African continent which is conducive to the emergence, development and sustainability of vaccine and biological manufacturers that meet global quality standards.

The mission of the AVMI is to "Promote the establishment of sustainable human vaccine manufacturing capacity in Africa". The AVMI aims to play a catalytic and coordinating role in achieving this mission together with interested companies, institutions, international organizations and individuals.

[1] http://apps.who.int/medicinedocs/en/d/Js20186en/

Since 2010, AVMI has adopted a constitution and established a framework and work-plan to guide its activities. AVMI proposes to:

- Mobilize the African continent, through high level advocacy, to manufacture preventive and therapeutic vaccines and/or other biological products against diseases of public health importance;
- Encourage partnerships between African manufacturers of vaccines and biologicals and other interested stakeholders who have a vision of Africa producing its own vaccines;
- Attract and secure skills and financial resources for establishing vaccine manufacturing capacity in Africa;
- Promote adequate scientific and technical capacity building of Africa's vaccine manufacturers in all aspects of production and distribution of vaccines and/or other biological products.

1.2 Arguments in favour and against vaccine manufacturing in Africa

Contradictory points of view exist regarding the feasibility of developing a successful and sustainable vaccine manufacturing enterprise in Africa. Arguments in favour and against are summarized in Table 1.

Table 1 Arguments in favour and against vaccine manufacturing in Africa

In favour of vaccine manufacturing in Africa	Against vaccine manufacturing in Africa
1. Security of quality vaccine supply	1. Failure in the past, and recent experiences in vaccine manufacturing
2. Addressing the Africa specific disease burden	2. Complexity and high cost of vaccine development and manufacturing
3. Dealing efficiently with pandemic diseases and outbreaks	3. Vaccine production already dominated by big pharmaceutical firms
4. Responding to the unmet health needs	4. Fragmented and dependent vaccine market in Africa
5. Increasing demand from growing population and market	5. Lack of human and technical capacity
6. Socioeconomic, industry and life science development	6. Absence of long-term vision and political will to invest in public health goods and technologies.
7. Partnership opportunities	

1.3 Vaccine Manufacturing and Procurement in Africa (VMPA) Study

With the support of the United Nations Industrial Development Organization (UNIDO) and the World Health Organization (WHO), the AVMI held an expert consultation in October 2014 to discuss options for the development of a strategic approach to this issue.

As a result of this consultation, an Africa-wide study was commissioned. The Vaccine Manufacturing and Procurement in Africa (VMPA) study was conducted during 2015, with the general objective focusing on an analytical assessment of vaccine manufacturing capacity and procurement mechanisms in Africa, principally with four priority areas for assessment:

1. Current and future vaccine market dynamics in Africa

2. Vaccine procurement mechanisms in Africa and associated financing mechanisms
3. Technical feasibility of establishing sustainable vaccine manufacturing capacity
4. Financing and funding mechanisms to establish vaccine manufacturing in Africa

The VMPA study covers all African countries, including all WHO AFRO countries as well as those WHO EMRO countries located in the African Continent. All Gavi eligible and non-Gavi eligible countries from the continent were included in this study, totaling 54 countries.

The VMPA study has been guided by advice from an expert Strategic Advisory Group. The outputs and outcomes of the study are being used to consult with and advocate for key stakeholders to advance the development of African vaccine manufacturing considerations within the Pharmaceutical Manufacturing Plan for Africa (PMPA) framework and strategic plan.[2]

The working group composed of 5 consultants with different profiles (scientific and technical backgrounds) has been using a mix of methods. These methods include field observations, quantitative and qualitative approaches, desk review, questionnaires and interviews with manufacturers, resource persons and experts, as well as regular consultations with the study management team and the Strategic Advisory Group.

This study provides an overview of the current situation, main directions, issues, challenges and opportunities and a list of gaps and unanswered questions for further discussion and work.

[2] http://apps.who.int/medicinedocs/en/d/Js20186en/

2. Vaccine Market Dynamics

2.1 Introduction

To set the stage for any informed discussion on human vaccine manufacturing and procurement in Africa, it is fundamental to gain a good understanding and comprehensive knowledge of the dynamics of the global vaccine market, its foundations and its recent developments.

Advances in life sciences and biomedical technologies are revolutionizing the old paradigms and offering new opportunities in the area of vaccine development and production. New public health objectives, global health initiatives and product development partnerships are changing the thinking and models for vaccine access and vaccine security[3].

Similarly, the concentration of research, development and most of the production in industrialized countries, increasing regulatory requirements, risks and costs of vaccine business and the emergence of capable producers, particularly in India and China, reduce the chances of the successful entry of any new independent actor that would not immediately be able to compete.

This section highlights some features and particularities of vaccines and their markets, examining global and regional trends in supply and demand, before identifying key vaccine growth determinants and analyzing main stakeholders and strategies operating in Africa.

This analysis will help to identify the nature and extent of the obstacles facing any vaccine production enterprise in Africa, as well as discern possible pathways or opportunities for Africa to establish a sustainable and viable local vaccine manufacturing industry.

2.2 Vaccine features and vaccine market dynamics

Market dynamics is a fundamental concept in supply, demand and pricing economic models. Any change in either the supply or demand for a specific group of products forces a corresponding change in the other; these variances cause pricing signals.[4] In a free (open) market where no entity has the ability to influence or set prices, the price of goods is determined by the market, that is, buyers and sellers, collectively. However, the vaccine market is not a free and open market (Table 2), and it differs from that of medicines (Table 3).

[3] Vaccine Security is the concept of securing uninterrupted sustainable supply of highest quality vaccines and is one of the pillars of UNICEF SD strategies. http://www.unicef.org/supply/index_vaccine_security.html

[4] A price signal is information conveyed to consumers and producers, via the price charged for a product or service, which provides a signal to increase supply and/or decrease demand for the priced item.

Table 2 Vaccine market is not a free and open market

Demand is not free; it is *induced, prompted* by health professionals, government institutions, donors and WHO (and other international stakeholders)
Collective and public funding is dominant in almost all countries, particularly for immunizations targeting vulnerable populations (children, mothers, elderly people etc.).
Concentrated production/supply: 4 or 5 Multinational manufacturers (MNC) produce more than 80% of the global vaccines market by value. There are very few producers and suppliers. High entry barriers to industry including lengthy and risky development and production processes.
On the demand side, we have a limited number of purchasers: Governments, health insurance institutions, and 2 big procurement agents: UNICEF SD, PAHO RF.
Pricing is also not free or based only on economic fundamentals, but rather "set" artificially high or artificially low.

Table 3 Vaccines are different from medicines

Vaccines are biological products made from living organisms; their development cycle is quite different from that of a chemical product.
There are no "generic" vaccines; any change in the product has to go through the entire quality, safety & efficacy evaluation process, resulting in additional time delays and cost implications.
Risk of failures in product development and production is high.
There is a very high "risk aversion" due to the fact that vaccines are administered to healthy people, particularly children, pregnant women and vulnerable populations.
Vaccines are highly regulated products (at both a national and international level) requiring lengthy internal and external quality assurance processes, with strong regulatory bodies and strict procedures.
Vaccines are predominantly used for prevention of disease, as opposed to medicines which are largely curative or for disease treatment.
Positive externalities are significant since protecting an individual has the potential to protect a whole community and reduce the risk of transmission.
Most successful vaccines are of public health importance and therefore included into the National Immunization Programmes (NIP).
Public funding (through government, health insurance budgets or donor funding in low-income countries) features as a mechanism to guarantee wide and equitable access to priority vaccines.
Out of pocket payments (OOP) for vaccines and immunization is very low, even in low-income countries.
Vaccines and immunization are also politically and media sensitive. Any disease outbreak, vaccine adverse effect, shortage, rumor or misuse of vaccines is immediately commented on by governments, interest groups and in the media.
There is a very limited secondary market for parallel importation of or counterfeit vaccines as opposed to medicines.
The vaccine market is relatively small compared to the pharmaceutical market (less than 5% of the global pharmaceutical sales).
There is a relatively limited range of product choices in terms of presentations, formulations, and delivery methods of vaccines.

2.3 Vaccine industry and global market dynamics

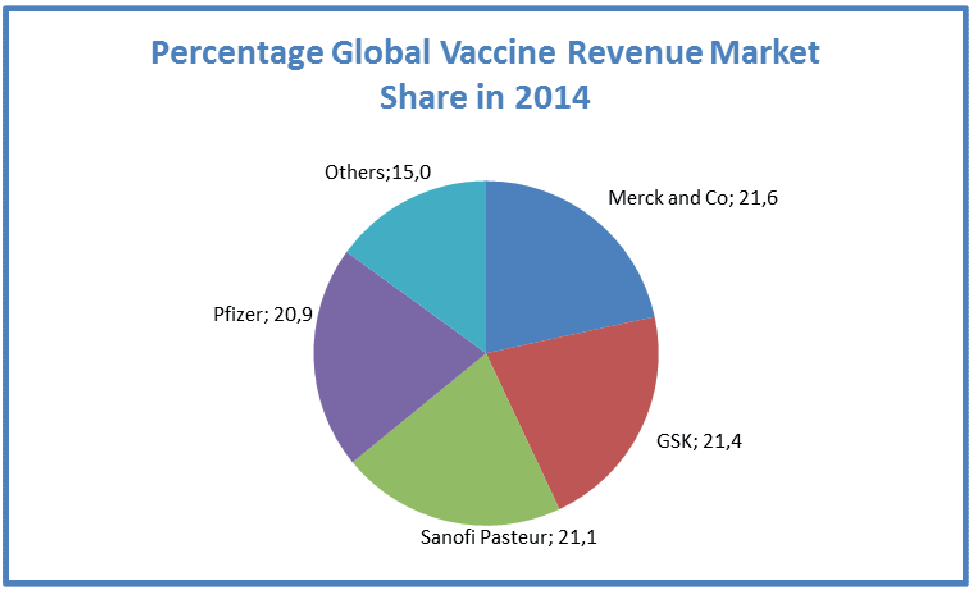
2.3.1. Vaccine industry

The vaccine industry is becoming one of the key drivers and profitable segments of the pharmaceutical sector. The vaccine industry has reinvented itself in the past decade by bringing innovations to the traditional manufacturing processes. These changes are transforming the vaccine industry environment, increasing the entry barriers, making the regulation more stringent and the market very multi-faceted.

Consequently, there has been a reduction in the number of manufacturers in the world. In 1997, there were at least 55 countries producing vaccines[5], in 2015, less than 20 countries had any kind of vaccine production facilities in place. Almost all the public-sector vaccine manufacturers disappeared, with very few exceptions for countries with large populations or captive markets.

Furthermore, there is an ongoing concentration of the number of vaccine manufacturers due to mergers and acquisitions over the last two decades, with a great acceleration in recent years resulting in the formation of four mega-producers of vaccines (GSK, Pfizer, Sanofi Pasteur and Merck) representing more than 80% of global sales by value (see Figure 1).

Figure 1 Global vaccine revenue market share



Source: Statista, 2015

While maintaining a strong focus on vaccines for industrialized country markets, multinational companies (MNCs) also sell their products in developing countries and emerging markets and participate in Global Health Initiatives. To compete in these markets, MNCs may outsource and participate in joint development activities and technology transfers[6].

Another feature of the global vaccine market is the fact that it is made up of individual markets for individual vaccines or vaccine types, each with their own specificities, particularly on the supply side. As there are relatively few vaccine manufacturers that meet international standards of quality established by WHO and industrialized countries, many of the individual vaccine markets are semi monopolies or oligopolies either by product, formulation or presentation. The limited number of vaccine suppliers and resulting production capacities leads to a tenuous balance between demand and supply in many individual vaccine markets.

In the 1980s, emerging market manufacturers started entering the vaccine market and have assumed a significant role since then. These manufacturers now play a critical role in the supply of vaccines to developing countries, particularly basic and some combination vaccines. They supply about half of UNICEF's vaccine procurement as measured by volume of doses, representing more than 30% of the value of UNICEF's total

[5] Milstien J, Batson A, Meaney W: A systematic method for evaluating the potential viability of local vaccine producers. Vaccine, 1997, 15, 1358-63

[6] IFPMA, Technology Transfer: a Collaborative Approach to Improve Global Health The Research-Based Pharmaceutical Industry Experience, Geneva, 2011

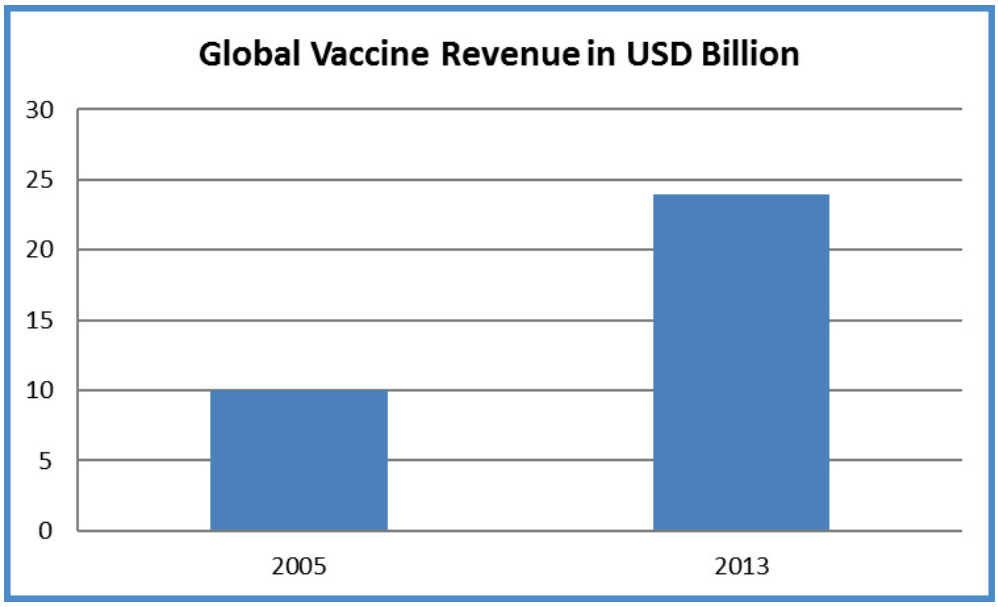
vaccine procurement in 2013. A total of 1.55 billion doses with a value of USD 507 million were from emerging market manufacturers.[7]

The entry of developing country vaccine manufacturers has resulted in lower prices due to increased competition and higher production capacities for individual vaccines. A few emerging market manufacturers are also trying to expand their production capacities to include newer vaccines. Emerging market manufacturers are represented by the Developing Countries Vaccine Manufacturers Network (DCVMN).

2.3.2 Global vaccine market trends

Despite the fact that the vaccine market is relatively small compared to the global medicine market (2% in 2010, around 4% in 2015 to 2016 by value), the vaccine market is growing more rapidly (10 to 15% annual growth rate compared with 5 to 7% for medicine sales). While the vaccines industry has a high entry barrier for second-generation manufacturers, it also has a high potential to generate blockbuster sales. The vaccine market has developed into a highly attractive and profitable market due to advancements in genomics, development and manufacturing technologies, as well as increasing demand from developed and developing countries including emerging economies. Pediatric vaccines continue to represent the major share in volume and value, but a significant growth of vaccines for adults is observed, as well as for adolescents.

Figure 2 Global vaccine revenues

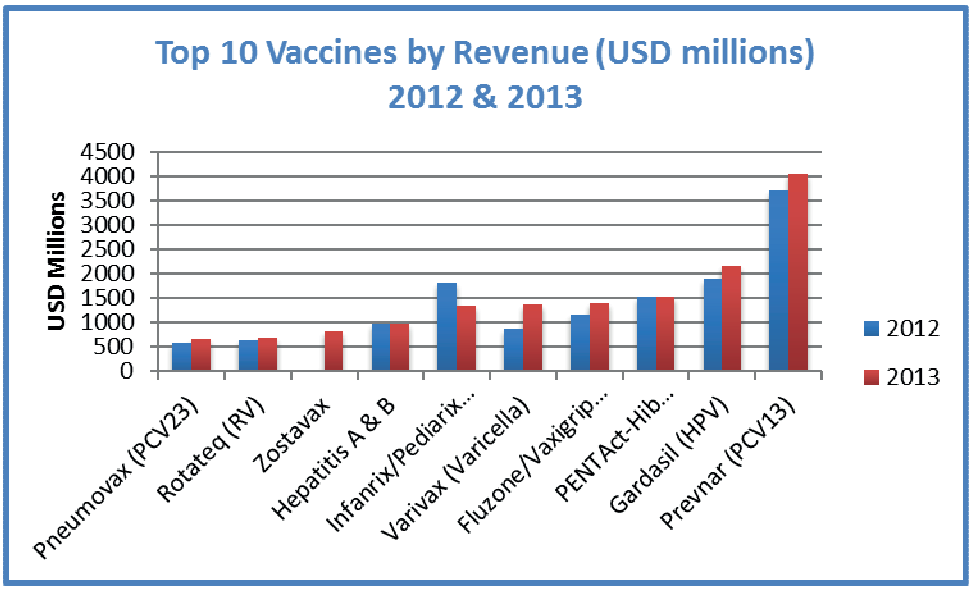


Sources: Vaccine Nation, Statista 2015

Newer and more expensive vaccines and presentations are coming into the market faster than ever with clear domination of the Multinational Companies.

[7] http://www.unicef.org/supply/files/3._Overview_of_UNICEF_vaccine_procurement.pdf

Figure 3 Top 10 vaccine revenue



Source: Evaluate Pharma and GEN. Published by Vaccine Nation (Cameron Bisset)

2.3.3. Global vaccine market prospects

The global human vaccines market is expected to grow at a CAGR of 10 to 11% during the period 2016 to 2020. The major factors driving the growth of this market are high prevalence of infectious diseases, rising government and nongovernmental funding for vaccine development, increasing investments by companies, and increasing focus on immunization programs in developed and developing countries. A major trend being witnessed in the global human vaccines market is the escalation in strategic alliances, mergers and acquisition to increase the market penetration or to enhance the product portfolio of the parent company (e.g. case of GSK).

Three other reasons to explain this rapid growth include:

1. New vaccines are being developed as a result of new technologies.
2. New markets are emerging both in developed and developing countries and particularly in emerging economies (BRICS countries) and in the UN/donor funded markets through the UNICEF, PAHO RF and Gavi Alliance financial support.
3. The increase in 'per vaccine' price from the new technology vaccines, e.g. BCG versus Pneumococcal Conjugate Vaccine (PCV).

Organizations and companies around the world are trying to devise effective vaccines for dozens of diseases. At least one hundred vaccines are currently in licensing or development phase, mostly to respond to the needs of developed countries with some interesting exceptions on global health priorities and neglected tropical diseases, including Malaria, Dengue, HIV/AIDS, TB, and Ebola.

2.4 Vaccine market in Africa: past and current trends

Figure 4 Vaccine market at a glance

Global vaccine market estimated at USD 24 billion in 2013

Africa Vaccine market estimated at USD 1.2 billion in 2013

Africa/Global vaccine market: 5.5%

UNICEF vaccine sales to Africa in 2013: USD 810 million and 2014: USD 899 million

UNICEF vaccine sales in Africa/Total UNICEF vaccine sales: ~ 60%

The African vaccine market is highly influenced by the segmentation induced by the donor policies and MNCs. The main criterion for donor support is the Gross National Income (GNI) per capita as estimated annually by the World Bank. This has been the main parameter on which financial and technical support is provided to countries in terms of access to new and underutilized vaccines, lower and subsidized prices and financial and technical support to immunization services and health systems. Out of the 54 recognized sovereign states of the African continent, 40 were Gavi eligible in 2015 (list in Annex 1), spread over sub-Saharan Africa and representing 59% of population in Africa. Besides poverty, income levels and eligibility for Gavi support, two other factors play an important role: whether the country has a large population or not and whether the country is an island or a landlocked entity.

From the demand side, the vaccine market in Africa is growing rapidly but remains segmented and highly driven by the global community and public sector support. On the supply side, almost all the vaccines and related technologies are imported and reliant on external inputs. The funding flows are increasing at a rapid pace, mainly due to donor supported vaccines introduced into the National Immunization Programmes (NIP) in the last 15 years.

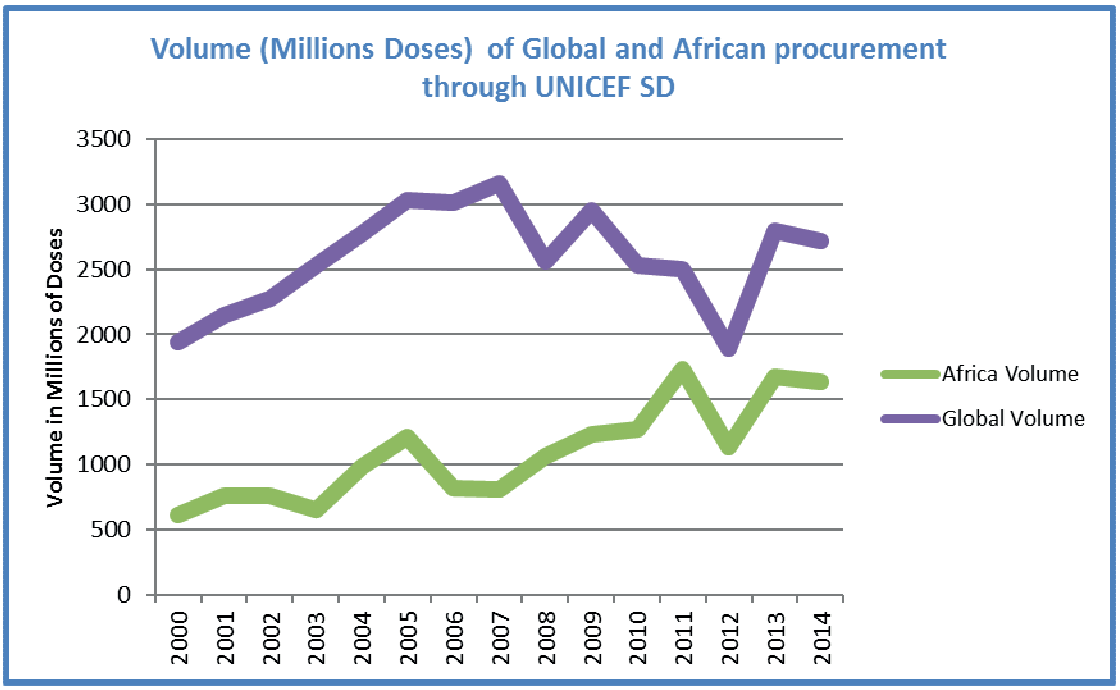
2.4.1 A booming demand for vaccines

The fundamental drivers of vaccine demand are well known: population growth, national income increase, health spending, numerous unmet needs, international and national recommendations and policies and availability of vaccines. These factors explain the strong demand for vaccines in Africa. What is more interesting in the last two decades are the efforts to revitalize the NIP, improve supply and provide financial support to low-income countries through UNICEF, United States Agency for International Development (USAID) and the Children Vaccine Initiative in the 90's and more importantly through the Global Health Initiative, called Gavi[8] since the early 2000's.

One can measure the vaccine demand growth in Africa by looking at the number of doses and value of the vaccines supplied by UNICEF SD to the African continent: it increased from 100 million USD in 2002 to 900 million in 2014 (Figure 6). In terms of volume (Figure 5), the increase is less impressive (600 million doses in 2000; 1.6 billion doses in 2014). This is due to the high prices of recently introduced vaccines (Pentavalent, PCV, RV, and HPV).

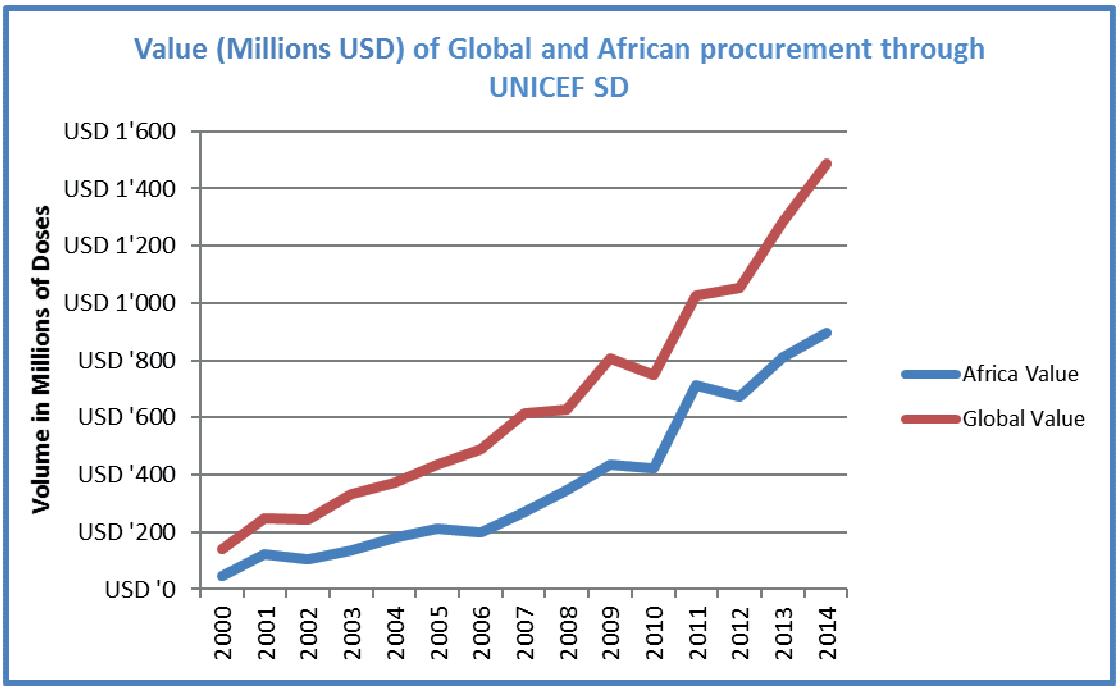
[8] http://www.gavi.org/

Figure 5 UNICEF SD Global and African continent volume



Source: UNICEF SD

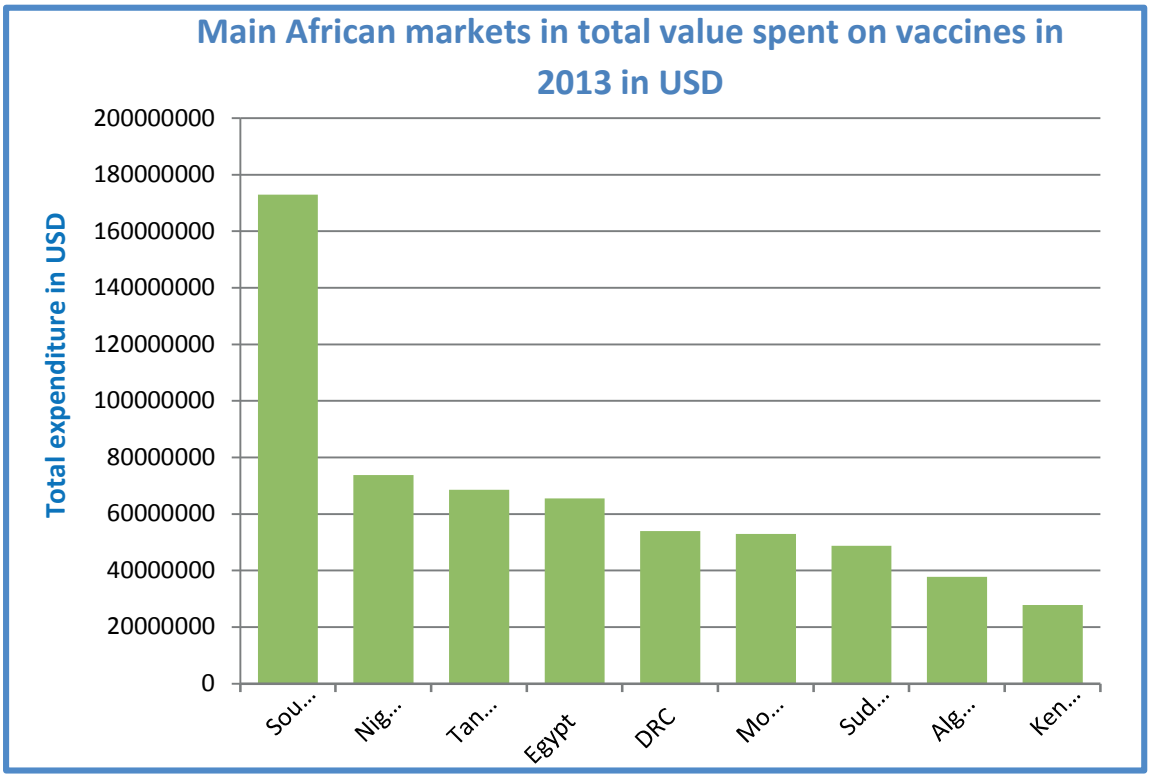
Figure 6 UNICEF SD Global and African procurement value



Source: UNICEF SD

The top ten vaccine markets in Africa by value are indicated in Figure 7. South Africa is the biggest vaccine market for three reasons: population size, number of vaccines in use in the public and private sectors and price level of vaccines. Five out of the ten top markets are in Gavi eligible countries (Nigeria, Tanzania, DRC, Sudan and Kenya)

Figure 7 Main African country markets by value



Source: WHO

The rapid expansion of the number of vaccines included in the NIP since 1995 has also contributed to the booming demand as vaccine demand in Africa remains mainly driven by the public sector. Remarkably, many low-income countries have introduced, in a quite short period, a number of underutilized and new vaccines switching from the six traditional EPI vaccines to eight or ten (or in the case of Ghana to 12 in 2015) vaccines.[9] However NIPs in some middle-income countries (for example, certain Northern African countries) are lagging behind in the introduction of certain newer vaccines such as PCV, RV, HPV and MR. This may be due to a number of factors including high prices of new vaccines (unsubsidized by external sources), limited supply availability, and possibly political sensitivities and issues.

2.4.2 A highly dependent supply

Africa is the continent that is most dependent for its vaccine supply from external sources, with more than 99% of the products and related technologies imported as finished products. Local production is, relatively speaking, almost nonexistent except at a very modest level in Egypt and Tunisia, a limited but visible level in Senegal and a more promising level in South Africa (although no production has been achieved yet). A number of African vaccine producers have disappeared in the last 25 years, particularly in North Africa, Nigeria, Ethiopia and other places. A number of factors have led to the termination of production: lack of technical and regulatory skills, limited capital and, more importantly, lack of long term strategy to cope with new technologies, GMP and QA requirements and increasing competition.

As NIPs are requiring increasing quantities of doses and a larger number of vaccines/antigens, local producers are unable to offer almost any vaccines, making African countries more and more reliant on external sources.

[9] Gavi New Vaccine Introduction www.Gavi.org

Table 4 The high dependency of Africa for its vaccine supply: some issues and challenges.

Supply of vaccines to African countries could be delayed if demand from developed country and emerging markets is high (e.g. cases of PCV, RV).
Frequent shortages and supply tensions (e.g. BCG, DTP, Men C, PCV, RV) disrupts NIPs and, more importantly, reduces immunization coverage of the target population.
Vaccines are not adapted for the African context and NIP needs (e.g. RV and cold chain requirements, PCV serotypes, delivery methods etc.).
Manufacturing of non-profitable products could be abandoned by multinational companies due to strategic choices and preference may be given to more attractive markets and profitable products (example of BCG, OPV, Measles, DTP etc.).
Demand for increasing manufacturing capacity for products of importance to Africa is not met by multinational companies (e.g. Men C, YF etc.).
Vaccine research and development is delayed because of non-viable and/or short-term market potential (e.g. Ebola, neglected diseases).
Unavailability of vaccines for individual African middle-income countries because of the preference given to donor funded/UN contracted or developed country markets.
Price increases because of sole source production or supply.
Diseases are not correctly identified as priorities for prevention and control.
There is not enough information on local disease burden or programmatic feasibility which affects demand forecasts and planning for supply.
Pharmaceutical companies are less inclined to develop medicines or vaccines that generate small returns on investment.
AEFI and post marketing surveillance are seen as less important to track than in other regions.

2.4.3. Vaccine funding: increasing but fragile

In most African countries both immunization and vaccine expenditures are dramatically increasing, particularly in the public sector. This is driven in part by the high-level commitment of governments and donors since the early 2000's.

Since Gavi was established, the donors' and partners' support for the introduction of life saving vaccines and immunization services has been constant and remarkable. More and more vaccines were supported both for routine service and SIAs with or without co-financing requirements.[10]

Out of the USD 8.2 billion total Gavi commitments to supporting vaccines and immunization services in the 2001 to 2013 period, USD 5.3 billion was allocated to Africa. According to Gavi, actual disbursement for African eligible countries was around USD 3.8 billion for the same period of time (out of USD 5.3 billion).

Data from WHO and UNICEF show that individual government expenditures on routine immunization have broadly increased over the last five years, with a 17% increase observed between 2010 and 2014. The percentage spent in countries on vaccines varied between 47% and 62%[11]. The trend reported by most African countries is promising, as there are signs of good progress being made in terms of immunization and government vaccine expenditure.

[10] http://www.gavi.org/support/nvs/
[11] http://www.who.int/immunization/programmes_systems/financing/data_indicators/en/

The increasing government support for vaccines and immunizations was certainly boosted by the co-financing policy implemented by Gavi. According to Gavi, for the 2008 to 2012 periods, the amount paid for by the African governments is estimated at USD 100 million and is projected to reach USD 700 million for the 2016 to 2020 periods.

This global picture reveals the remarkable changes and positive dynamics in immunization and vaccine financing in Africa, but it does not reflect the variety of situations existing in Africa.

Table 5 Financing: challenges and issues in Gavi eligible Africa countries

Share of government funding for vaccines as part of the total vaccine expenditure in Gavi eligible African countries is decreasing due to the relatively high prices of recently introduced vaccines with the support of Gavi.
Most of Gavi eligible countries are fully complying with their co-financing obligations but some have been considered, for certain periods of time, as defaulters or late payers.[12][13]
A pressing concern is that graduating countries, particularly in Africa, are experiencing payment delays and payment defaults while the co-financing requirements for these countries will only increase in the coming years.
Countries comply with their Gavi co-financing requirements but are not funding their basic vaccines with domestic funds.[14]

For non-Gavi eligible countries, funding sources and mechanisms for vaccines in the public sector are mainly through the government budgets (90%). They are increasing at a rapid pace as can be seen in table 6 below.

*Table 6 Estimated government budgets for EPI vaccines in Algeria, Morocco and South Africa***

Value of EPI purchases by Government (million USD)							
	2010	**2011**	**2012**	**2013**	**2014**	**2015***	**2016***
Algeria			33.6	35.2	33.5	51.7	142
Morocco	51	50,9	52,6	40	38	38	
South Africa				140	150		

* forecast. ** This budget is much higher if non-EPI vaccines are included such as Meningococcal, YF and flu vaccines
Source: WHO and VMPA study estimates

A private market for vaccines does exist in some countries but remains marginal in low-income countries and very limited in middle-income countries, with the exception of South Africa (estimated around USD 33 million per year in 2012 to 2015).
Health Insurance schemes are marginally involved in supporting preventive programmes or reimbursement of vaccines not available as products or presentations in the public sector. Out of pocket payment is relatively rare. Informal payments and parallel or illegal imports of vaccines do exist but at limited scale.

[12] Source WHO: http://www.who.int/immunization/programmes_systems/financing/data_indicators/en/
[13] (Cameroon, Ghana, Congo Rep, Angola, Djibouti, Guinea, Guinea Bissau, Kenya, Uganda, South Sudan, Tanzania)
[14] In 2014 for example more than 14 governments were not paying for their basic vaccines (Burundi, Malawi, Sudan, Zimbabwe, Djibouti, Eritrea, Comoros, CAR, Guinea Bissau, Liberia, Sierra Leone, Somalia, and South Sudan).

3. Vaccine Procurement in Africa

3.1 Introduction

African vaccine manufacturers will want to sell any vaccines manufactured to countries within the African continent. The manufacturers will therefore need to have a good understanding of the vaccine procurement mechanisms operating in Africa. Vaccine procurement attracts political interest; it is not a simple matter of shopping. It is a complex system of linked activities defined by legislation, rules and practices both national and international.

Effective vaccine procurement is crucial for the programmatic performance of the National Immunization Programme (NIP) of every country; it is therefore a priority area for both governments and international partners alike.

For each of the procurement component activities that can affect market access, whilst there are some commonalities between countries actions, there are also significant and specific differences.

Identifying the challenges and opportunities for market access in African countries will assist in establishing stable market demand to support sustainable African vaccine manufacturing.

Vaccine procurement is therefore an important aspect of this study for two key reasons:

1) Procurement is the system for attaining sustainable financing for any vaccine products manufactured. Market entry is determined in part by the nature of the procurement system in operation. Optimizing procurement opportunities and minimizing challenges can therefore create a favourable market environment for any African-manufactured vaccine.

2) Efficient procurement mechanisms (including optimal use of current procurement mechanisms and development of new alternatives) could reduce some of the currently identified negative scenarios used as justification against local production. These include, in particular, security of vaccine supply, addressing of the Africa specific disease burden, dealing efficiently with pandemic diseases, responding to the unmet needs and growing population.

In summary, procurement optimization is a necessary consideration for local production and a credible and viable approach to improve the vaccine supply situation in Africa.

3.2 Landscape analysis of procurement mechanisms operating in Africa

3.2.1 Procurement categorization

In simple terms, for publicly funded/supplied vaccines (for use in the NIPs), countries in Africa in 2015 fall into three categories for vaccine procurement as shown in table 7 below. A full list of countries under each category is provided in Annex 2, covering the past six years from 2010. Countries allocated to Category 3 have been deduced through elimination, based on the data provided by UNICEF SD.

Table 7 Procurement mechanisms operating in 54 countries of the African continent

Category	Definition	Number of Countries	% of the African Population
1	Procuring all vaccines through UNICEF SD procurement services	37	54%
2	Procuring some vaccines through UNICEF SD procurement and self-procuring remainder of vaccines	8	36%
3	Self-procuring all vaccines (not using UNICEF SD)	9	10%

However, a caveat to this statement is that some governments in category 1 above will be procuring some non-EPI vaccines for limited population use through publicly funded self-procurement. These vaccines may include vaccines for use by certain groups such as the military, health workers or educators, vaccines/sera used for treatment (e.g. rabies, anti-venoms etc.), and vaccines for travelers (e.g. Hepatitis A, YF, Men A, etc.), depending on the country context.

3.2.2 UNICEF Supply Division procurement

It is clear from the data provided that UNICEF SD procurement service is the current predominant procurement mechanism operating in Africa. Analysis of these data indicates that in the past six years:

- eight of the 54 countries have not utilized UNICEF SD procurement services for any vaccines at all;
- 31 countries have only used UNICEF SD for the procurement of EPI vaccines;
- two countries have only ever partially used UNICEF SD for some of their EPI vaccine needs;
- 13 countries fluctuate in use, changing annually based on needs to either fully or partially procurement vaccines through UNICEF SD or not utilize those services at all;
- therefore 23 countries have at least tried some form of self-procurement in the six-year period.

What can also be determined from this data is that at least 46 of the 54 countries have some ability to allow for procurement by an external (not national) agency, and that for the 15 partial use and fluctuating use countries, it is not a legal requirement to procure only through UNICEF SD.

For the 46 countries on the African continent that have used UNICEF SD procurement services in the past six years, the use of UNICEF SD procurement services can be:

- a legal requirement (embedded in legislation or government order (This scenario is only likely for the 31 countries that have only ever used UNICEF SD);
- a requirement for use of donor funds for procurement of vaccines (This scenario is true for at least the 39 Gavi eligible countries);
- the method used due to the absence of know-how or skills for public self-procurement;
- the method used to ensure quality and regular vaccine supply;
- the method used due to the favourable price of vaccines through UNICEF SD;
- or a combination of the above justifications.

Utilization of UNICEF SD procurement services may also be linked to a requirement for utilizing WHO prequalified vaccines in the NIP, as the vast majority of vaccines supplied through UNICEF have obtained WHO prequalification.

Most, if not all, countries will self-procure some vaccines or sera that are either not part of the EPI program and/or are not available through UNICEF SD procurement services.

It cannot be assumed that those nine countries self-procuring all vaccines (in the past six years) are restricted from utilizing UNICEF SD procurement services through legislative or other provisions; however, this may be the case in some countries.

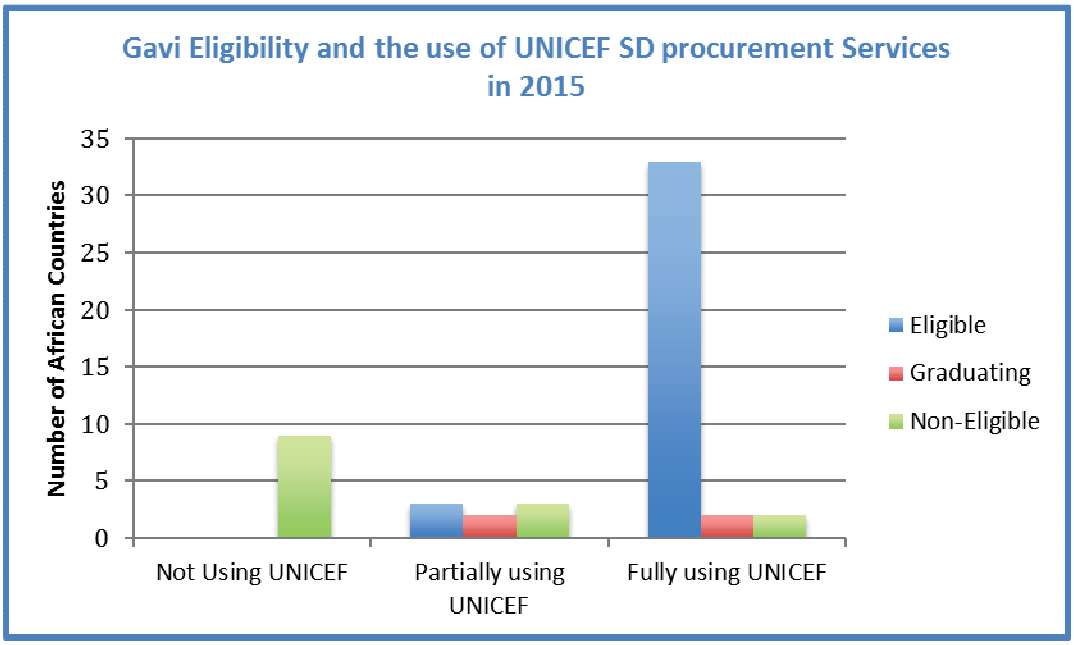
There is currently no complete data set available to indicate the allocation of countries within Africa to each of the justifications or reasons for use of UNICEF SD or self-procurement. On a case-by-case basis, this could be assessed to ascertain the viability of access to individual country markets for an African manufactured vaccine, without becoming a supplier through UNICEF SD.

3.2.3 Gavi Alliance

The Gavi Alliance was established in 2000 to improve access to new and underused vaccines for children living in the world's poorest countries. It is now the largest donor providing subsidized vaccines, and other funding support, to the African continent. Gavi policies and strategies have significant influence on the shape of the vaccine market in Africa and the changing vaccine needs of the NIPs.

Gavi eligibility is linked to UNICEF SD procurement but not exclusively. The following Figure 8 indicates that all Gavi eligible and Gavi graduating countries use UNICEF SD either partially or fully in 2015. It also shows non-Gavi eligible countries also used UNICEF SD in 2015.

Figure 8 Gavi eligibility and use of UNICEF SD procurement services



Source: VMPA study team based on Gavi and UNICEF data

The intention of this section is not to reiterate Gavi policies, which are publicly available,[15] but to note where those policies may affect the possible utilization of a locally manufactured vaccine. The five key areas, which could affect the potential utilization of any locally manufactured vaccine, are summarized in Table 8 below and in the following brief sections. These factors may change over time as determined by Gavi governing bodies, with very little ability to influence by individual countries.

Table 8 Gavi policies and strategies summary

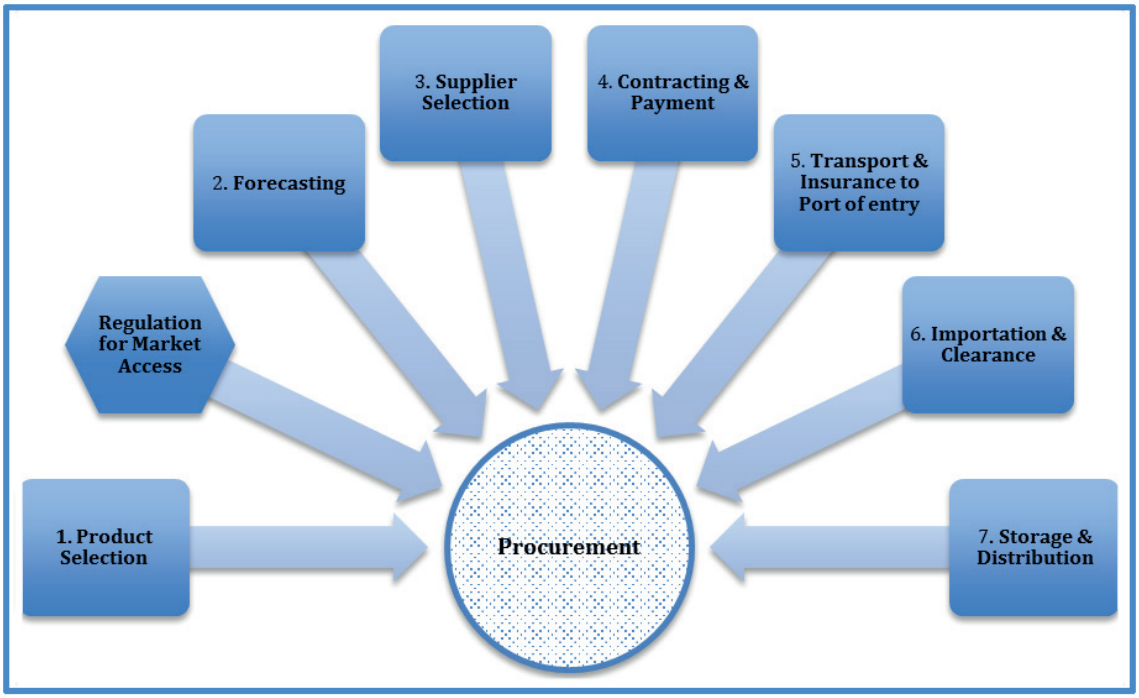
Gavi Policy or agreement	Action	Effect for consideration for African vaccine manufacturing market access
Gavi Eligibility	The number of countries with access to Gavi funding	Gavi eligible countries are eligible for lowest priced vaccines when procured through UNICEF SD.
Gavi Vaccines	The vaccines supported by Gavi which are required to be WHO-prequalified for financial support	All Gavi supported vaccines are WHO-prequalified.
Gavi procurement	Gavi procurement agent for Africa is currently UNICEF SD.	None of the Gavi eligible African countries self-procure Gavi supported vaccines. Most Gavi eligible countries procure all vaccines (donor and domestic funded) through UNICEF SD.
Gavi co-financing and Gavi graduation	The level of financing required from country sources other than Gavi per vaccine	As the value of co-financing increases, some countries may self-procure the non-Gavi volumes. The level of co-financing is based on volume of doses, so the higher the price the greater the expenditure required.
GAVI agreement with manufacturers on vaccine price commitments	Setting price benchmarks and references. Higher prices from alternative sources are difficult to justify for individual governments.	Gavi and partners have worked with individual suppliers to guarantee prices of Gavi supported vaccines for graduating and graduated countries. These agreements currently require continued use of UNICEF SD procurement services.

3.3 Specific country functions in procurement and related areas that affect market access.

Vaccine procurement is a process; there are however a number of related factors which influence the activities and outcomes. Figure 9 shows not only steps in the procurement process (1 to 7), it also includes the key input of the regulation process for market access as this determines the availability of products for procurement.

15 GVAP 2014 Report, WHO Geneva

Figure 9 Procurement processes



For each of the inputs to the procurement process, there are different considerations that need to be taken into account for any African producer engaging in domestic or exported supply of vaccines to African countries.

For countries utilizing UNICEF SD procurement, the degree to which UNICEF country office (and other in-country partners including WHO) are involved in the additional activities, or undertaking these on behalf of the countries varies widely.

Broadly UNICEF SD takes responsibility for steps 3, 4 and 5 (providing the vaccines to the port of entry) and assist in the annual compulsory forecasting process. However, in countries with less developed systems and countries in conflict or post-conflict situations, UNICEF, WHO and partners may be engaged in or completely leading/conducting all the steps in the process.

For a vaccine supplier not operating within the UNICEF SD procurement system, there would be a need to ensure the other activities could be conducted to ensure satisfactory supply.

Table 9 Areas of procurement, possible effects on market access and options

Area	Issue	Consideration
Forecasting	Although both UNICEF and WHO provide forecasting tools for countries to identify needs, the level of utilization is variable. In countries with very limited capacity UNICEF, WHO or other partners tend to conduct this process on their behalf.	Improving country capacity for forecasting will improve the optimization of both procurement processes and the opportunity for market entry by any African manufactured vaccine. Longer term forecasting provides potential suppliers a useful indication of the future market for individual products.
Product Selection	Product selection harmonization should be considered an essential factor for the optimal use of any African manufactured vaccine. Primarily because optimal economies of scale will be reached when the demand is more focused on a small selection of products and presentations. Product harmonization should be primarily based on addressing health and contextual needs rather than adjusting to supply restrictions.	Optimal product presentation and regional harmonization will assist in creating economies of scale for African vaccine manufacturing. Countries and their clinical advisory bodies can assist any African manufacturers in determining the optimal product profiles and presentations required to best suit their needs.
Regulation (Market Access)	There is very limited NRA functionality in African countries with regards to market authorization. Some of the key issues include: • WHO prequalification can be a requirement for market entry or use of a vaccine in countries; • Some countries require registration of vaccines in specific countries, and vaccines may need to meet multiple regulation requirements to gain market access; • Individual country regulations may require specific consideration to optimize for vaccines and create an enabling environment for local vaccine production. Local agency rules can be a significant additional cost or barrier of entry to any country market and need to be assessed against sustainable market access and the potential for profit from any vaccine supplied.	Harmonization of regulation requirements would be an enabling factor to enhance the opportunity of successful African vaccine manufacturing. Individual countries would need to review the requirements for registration and assess whether their system is optimized for both improved procurement and for the possibility to utilize any African manufactured vaccines.
Procurement Rules & Regulation	Self-procuring countries have various and variable country specific requirements for procurement, whether for vaccines alone or for all publicly funded products.	The degree to which individual procurement rules and regulations affect the opportunity for procurement of locally manufactured vaccines would need to be assessed on a case-by-case basis to establish possible market entry.
Financing	Source of financing affects the possible procurement options for vaccines and the potential use of local manufactured vaccines.	Donor policies on eligible supplier and procurement mechanism use needs to be considered for market access. Rules and regulations governing the use of

		domestic funds for procurement need to be taken into consideration.
Transport	International transport of vaccines is conducted predominantly by air. Most supply agreements require, at a minimum, delivery of the vaccines to port of entry. Direct air transport links with cold chain facilities may be limited between African countries. While work continues to develop vaccines that require less cold chain control (thermostable vaccines), it is likely the international transport of vaccines will remain a complex and costly system.	Any African vaccine manufacturer would need to identify a secure and direct method of cold chain air transport to any country it supplies with vaccines.
Trade and Importation	Trade agreements in Africa are established between specific groups and sub-regions of countries. Importation of goods from countries without established trade agreements may be more challenging.	Supplying vaccines within established trade groups may be a more simple starting point for any export of African manufactured vaccine. Establishing an Africa wide agreement on vaccine supply could be part of any policy on vaccine manufacturing developed for the continent.
Customs clearance	Customs clearance procedures are specific to each individual country and can be extremely challenging. A clearance agent is often required for the import of goods. In some countries, a specific agreement is reached with customs on preclearance and expediting vaccines to ensure the maintenance of cold chain. In some less developed countries, the UN is involved in this activity.	Acknowledging the specifics of the current procedures and actors in each country where vaccines are exported will be needed for developing the necessary procedures to maintain effective cold chain delivery. Some information on this aspect may be available from WHO or UNICEF.
Taxes, tariffs and duties (TTD)	UN consignments are normally exempt from any taxes, tariffs or duties (TTD) for the supply of goods. UNICEF requires through its MOU with a country that vaccines and supplies are exempt or the sole responsibility of the government. In some countries, the application of TTD can dramatically increase the cost of the vaccines to the NIP and can make purchase cost prohibitive.	TTD application assessment would be required in each importing country as it may specifically affect the price able to be offered, in particular if delivery is required beyond the port of entry. Establishing an Africa wide agreement on vaccine supply and the application of TTD could be part of any policy on vaccine manufacturing developed for the continent.
Payments	Payment terms are one of the more complex aspects of supply contracts and can significantly affect the ultimate price of the vaccine for both parties to the contract. Various methods exist to limit risk; some are specified in the procurement laws of the country.	Understanding the specifics of payment terms and the impact on the supplier will be required when considering supply agreements within the region.

3.4 Enhancing procurement mechanisms in Africa

Procurement mechanisms very rarely change without specific intervention. There is some level of natural progression, for example from donor to government funding, which can trigger changes, as identified in section one of this report.

To optimize the potential from African vaccine manufacturing the challenges posed through limited capacity in procurement should be addressed *in parallel* with any manufacturing capacity development.

Annex 3 provides further detail on areas for improvement in vaccine procurement which could both positively affect the market access for African vaccine manufacturers and the security of supply of vaccines in Africa overall.

4. Vaccine Production Feasibility

4.1 Introduction

Whatever criteria we use, the conclusion is always the same: currently vaccine manufacturing is very limited in Africa. Whatever we compare: past/present, volume of doses/value of sales, number of products and number of countries, imported vaccines/locally produced vaccines, we end up with the fact that vaccine production is limited for now. However, when we look at the demand side, the picture is totally different, as Africa is making rapid progress in improving its immunization coverage and the adoption of new vaccines. So therefore, the market demand for vaccines is ever increasing.

In this section, we assess the current and planned capacities and capabilities in Africa for vaccine manufacturing, present the vaccine production requirements and compare these to the existing manufacturer capacities. In addition, we review the status and effects of the national regulatory authorities and the vaccine clinical trials processes in Africa. Finally, we conclude this section by outlining options for the way forward and next steps in the area of vaccine manufacturing in Africa.

4.2 Assessment of current and planned capabilities and capacities in Africa for vaccine development and manufacture

We identified eight companies with either existing or potential vaccine manufacturing capacities[16] and divided them into three groups based on their actual capacity to manufacture vaccines:

Table 10 Current vaccine production capacities

GROUP 1: Companies with locally produced and marketed products: **3**	**GROUP 2:** Companies at late stage of industrial development and manufacturing (no vaccines currently produced): **1**	**GROUP 3:** Companies at very preliminary planning of vaccine development (no vaccines currently produced): **4**
Pasteur Institute in Dakar, Senegal*	**Biovac,** South Africa	**Pasteur Institute**, Algeria
Pasteur Institute Tunis, Tunisia**		**Pasteur Institute**, Morocco
Egyvac-Vacsera, Egypt**		**EPHI**, Ethiopia
		Biovaccines, Nigeria

*** Vaccines: Yellow Fever**
**** Vaccines: BCG**
***** Vaccines: Tetanus toxoid, Cholera Typhoid, Cholera/typhoid, DT, DTP, DTP-Hib, Meningitis AC (polysaccharide)**
Other products: Insulin, various antisera

Group 1: The three companies with locally produced and marketed products, Institut Pasteur Dakar (IPD, Senegal), Institut Pasteur Tunis (IPT, Tunisia) and Vacsera (Egypt) are able to supply vaccines that have been produced locally, including all upstream and downstream processes: production of active pharmaceutical ingredients (API), formulation, fill and finish, visual inspection, labeling, packaging, and dispatch under cold chain. IPD is unique in the sense it is the only company in Africa that produces a WHO prequalified vaccine, namely, yellow fever. This vaccine is the only vaccine produced and marketed by IPD. In contrast to IPD, Vacsera has a large portfolio of marketed vaccines of which seven to some extent are produced locally. None of

[16] From the eight companies initially questioned, six responded to the general questionnaire, and for the two who did not reply, it is considered that information is not sufficient to conduct a proper analysis.

them have been prequalified by WHO. Vacsera also has a portfolio of vaccines in development that could be marketable in the future. IPT capabilities are limited to the manufacture of BCG vaccine and BCG liquid concentrate for the treatment of bladder cancer.

Group 2: Biovac is a company at late stage of vaccine development and manufacturing (downstream processes). The company is currently focused on formulation and filling of vaccine into vials and syringes from imported API, along with visual inspection, labelling, packaging, and dispatch of vaccines under cold chain. Vaccine development capabilities, including fermentation, purification and conjugation technologies, are mainly related to conjugate vaccines. Biovac has developed a conjugate Hib vaccine technology which has been successfully transferred to two Asian vaccine manufacturers, one of which has incorporated the technology into a commercialized a pentavalent combination product.

Group 3: Four companies are considered at the preliminary planning phase of vaccine development and production. They have had past experience in producing some basic vaccines (Pasteur Institutes in North Africa), but all of them ceased vaccine production in the late nineties. For the last ten years, they have been exploring opportunities to restart vaccine production and have been developing some plans but without any significant implementation. Some of them have a level of scientific and technical capacity but lack strategies, market analysis, business plans and related budgets. In this group, IP Algeria has ceased human vaccine production in 2000 but continues to import and distribute EPI and non-EPI vaccines for the public sector. IP Morocco ceased all vaccine production in 2001. EPHI (Ethiopia) has capacities and/or capabilities to produce rabies vaccines with Fermi technology, which is an old and no longer sustainable technology. EPHI is acquiring capacities and capabilities to develop rabies vaccines from cell culture and Men A, C, W vaccines. Biovaccines (Nigeria) has not provided enough data or information to allow for an objective evaluation of their capacities and capabilities but appear to have no vaccine production currently.

4.3 "Pharmaceutical Value Chain" assessment

An approach to assess the capacities and capabilities of the eight existing and potential vaccine manufacturers is to use the "*pharmaceutical value chain*" tool. The **"***pharmaceutical value chain***"** is a spectrum of progressive pharmaceutical operations with increased technological complexity. At one end of the chain is the exclusive import of finished pharmaceutical products and, at the other end, a research-based pharmaceutical industry. Between these extremes are various stages of pharmaceutical manufacturing, including production of active pharmaceutical ingredients (API). This chain can also be adapted and applied to the vaccine manufacturing value chain.

Each step potentially leads to the next, with added value, complexity, investment and regulatory requirements. It is critical that an acceptable level of international quality standards is followed at every level.

- **Level 1:** Distribution of imported finished vaccine products.
- **Level 2:** Packaging and labeling of imported vaccine products following national or international Good Manufacturing Practice (GMP) standards.
- **Level 3:** Vaccine product manufacturing from imported bulk (fill & finish) following national or international GMP standards.
- **Level 4:** API manufacturing: Production of active pharmaceutical ingredients and excipients following national or international GMP Standards.
- **Level 5:** Research and development of new formulations, processes and new chemical or biological entities following national or international Good Laboratory Practice/Good Clinical Practice (GLP/GCP) and ethical standards.

Table 11 describes the five stages of the vaccine value chain for the eight African companies identified in this VMPA study, using a dashboard view to estimate the level of capacities and capabilities in Africa.

The companies have a heterogeneous level of capacities and capabilities regarding levels of vaccine manufacturing complexity. It is notable that most of the companies have developed the functions of importation, storage and distribution, which are not “manufacturing” functions *per se,* but rather commercial functions, requiring significantly less capital, operational and technical investment.

Table 11 Vaccine value chain assessment summary

African Companies / CAPABILITIES	GROUP 1: Companies with locally produced and marketed products			GROUP 2: Companies at late stage of vaccine development & manufacturing	GROUP 3: Companies at preliminary planning stage of vaccine development			
	Institut Pasteur Dakar (Senegal)	**Vacsera** (Egypt)	**Institut Pasteur** (Tunisia)	**Biovac** (South Africa)	**Institut Pasteur** (Algeria)	**Institut Pasteur** (Morocco)	**EPHI** (Ethiopia)	**Biovaccines** (Nigeria)
Level 1: **Import for Distribution**								
Level 2: **Packaging and Labeling**								
Level 3: **Product Manufacturing (fill & finish)**								
Level 4: **API Manufacturing**								
Level 5: **Research and Development**								

	Insufficient information Provided
	Current capacity
	Could meet requirements or has performed action in the past
	Has not performed action and does not meet requirements to do so

4.4 Key vaccine manufacturing requirements and challenges in the context of Africa

The level of complexity for manufacturing biological products is described in terms of: human resources (scientific level of staff, academic network), source of raw materials, manufacturing facilities, quality systems in place, technical environment (utilities, cold chain and logistics, technical resources) and project management. Each area is explained further in Annex 4.

Table 12 shows the estimated levels of complexity for a selection of different vaccine types and technology platforms in each of the areas of manufacturing described above. They range from the least complex platforms, such as those required for older vaccines, for example yellow fever, through to the complexity of new vaccines such as pneumococcal conjugate vaccines and the highly anticipated but complex vaccines for HIV, Ebola and malaria.

Whilst most of the African companies have achieved, or could have the ability to conduct labeling and packaging, very few are at a very limited stage of product and API manufacturing, and none are currently able to perform the full value chain cycle to produce a vaccine.

Table 12 The level of complexity for manufacturing a biological product

Requirements Products	Staff: scientific knowledge, technical skills	Source of reliable raw materials	Manufacturing facilities			Quality Management Systems in place	Reliable technical environment Maintenance	Project management
			API	Fill, finish	Labeling & Packaging			
HIV/AIDS	+++	+++	+++	++	+	+++	++	++
Malaria	+++	+++	+++	++	+	+++	++	++
Ebola	+++	+++	+++	++	+	+++	++	++
Tuberculosis	++	++	+++	++	+	+++	++	++
Yellow Fever	++	++	+++	++	+	+++	++	++
Meningitis conjugate	+++	+++	+++	++	+	+++	++	++
Rabies	++	++	+++	++	+	+++	++	++
Tropical diseases	+++	+++	+++	++	+	+++	++	++
Sera	++	++	++	++	+	+++	++	++
MAbs for therapy	++	++	+++	++	+	+++	++	++
DTP	++	++	+++	++	+	+++	++	++
Measles	++	++	+++	++	+	+++	++	++
Polio	++	++	+++	++	+	+++	++	++
Pneumococcus	+++	+++	+++	++	+	+++	++	++
Diagnostics	++	++	+++	++	+	++	++	++

Level of complexity	
+++	Very high
++	High
+	Normal

4.5 Landscape analysis of the current regulatory capabilities and clinical trial capacities in Africa

The National Regulatory Authorities (NRAs) are essential in the entire vaccine value chain, from vaccine research, to development, production, distribution, administration and evaluation of vaccines. Having a recognized and well-functioning NRA is critical for manufacturers to commercialize and market their products domestically or for export.

As most of the African countries procure WHO PQ vaccines through UNICEF SD procurement services, the need to have a fully functional NRA capable of all regulatory functions for vaccine assessment has not been a high priority until recently. Self-procuring and/or manufacturing countries should have an NRA able to perform all necessary regulatory functions as defined by WHO, according to their status (importing or manufacturing), as indicated below.

Table 13 Vaccine source and required regulatory functions

Regulatory functions	Vaccine Source		
	UNICEF SD Procurement	Self-Procurement (Importing)	Manufacturing
Regulatory system (RS)	√	√	√
Marketing authorization and licensing (MA)	√	√	√
Pharmacovigilance (PV) including AEFI monitoring	√	√	√
Lot release (LR)	*	√	√
Laboratory access (LA)	*	√	√
Regulatory inspections (RI)	*	#	√
Oversight or clinical trials (CT)	√	√	√

Source: WHO

* Undertaken by WHO on behalf of UN agencies or producing countries

Undertaken by the producing country

Given the limited capacity to procure or manufacture vaccines on the continent, the development of relevant NRA capacity in Africa has been limited. However, with the changing environment in Africa, including economic, health system development and graduation from donor support, country systems improvement (including NRA capacity) is now an increasing priority.

Assessments of some NRAs (for medicines and vaccines) have been conducted by WHO expert teams, and institutional development plans (IDP) to address gaps have subsequently been developed. Details on the results, areas for improvement, recommendations and list of actions are confidential to the countries. However, general and common gaps are found in regulatory systems, legal frameworks, marketing authorization, pharmacovigilance, and authorization of clinical trials. One major and common gap is the need to establish, implement and maintain Quality Management Systems (QMS) in the national regulatory system, encompassing all regulatory functions. Investment in human resources that includes adequate staffing and training plans and, specific technical and managerial skills development are most frequently identified gaps. It

should be noted that WHO provides regulatory capacity building in some priority countries to address gaps in regulatory systems, functions and processes.

NRAs from Senegal and Egypt have been assessed as functional by WHO; and a number of other NRAs are considered as fairly strong and reasonably good in pharmaceuticals, with some experience in dossier review of vaccines as well, e.g. South Africa, Ghana, Zimbabwe, Tanzania, Kenya, Algeria, Morocco, and Tunisia. To assist in the establishment and development of NRAs in Africa, WHO initiated the African Vaccine Regulatory Forum (AVAREF) in 2006 to support NRAs in making informed decisions concerning authorization of clinical trials, evaluation of product registration dossiers, and any other challenging issues related to the evaluation of vaccine quality. Significant progress has been made, but regulation remains a bottleneck. While initially focused on vaccines, AVAREF is beginning to expand its scope to cover medicines and diagnostics as well.

4.6 Clinical trial capacities and requirements

A growing number of vaccines under development are targeting infectious diseases as well as neglected tropical diseases. Many novel vaccine clinical trials are taking place in Africa in order to evaluate the quality, safety and efficacy of new vaccine candidates. The country where the most clinical trials for vaccines in the African continent are conducted is South Africa. Projects such as the Meningitis Vaccine Project and Malaria Vaccine Initiative have invested in site capacity building and ICH-GCP training and upgrading in several study sites throughout Africa. Several vaccine manufacturers, including GSK and Merck, have performed vaccine clinical trials in African countries against a number of pathogens including HIV, Malaria, Influenza, Rotavirus, Pneumococcus, Meningococcus and Papillomavirus. This is creating a lot of pressure on the capacity of regulators and ethics committees.

Research ethics committees and NRAs in Africa are responsible for protecting the health and safety of participants in clinical trials conducted in their countries, but very often they are lacking in capacity to collect the right data and conduct the required evaluation. Ensuring that clinical trials are approved in an appropriate and timely manner, and that data generated in novel vaccine trials meet international standards for acceptability, will contribute to ensuring the safety of subjects, the validity of clinical trial data and the strengthening of technical and research capacity. This is a challenging task in Africa.

In its 2014 report on the progress of the Global Vaccine Action Plan (GVAP), it was noted that “a substantial minority of vaccine randomized clinical trials (RCTs) remain unreported” and that “failure to report clinical trial results in a timely manner is considered to be a breach of current, widely accepted, international standards (e.g. the Declaration of Helsinki), and is likely to lead to a reporting bias, which has major adverse consequences”[17]

AVAREF is acting as a regional cooperation mechanism and platform, to build capacity for regulatory oversight of vaccine trials in Africa so that it is technically adequate and efficient. AVAREF promotes a regional approach to clinical trial regulation. AVAREF guidelines could also become the basis for the development of tools for evaluation of dossiers for the licensure of products. It could also promote mutual recognition among participating countries.

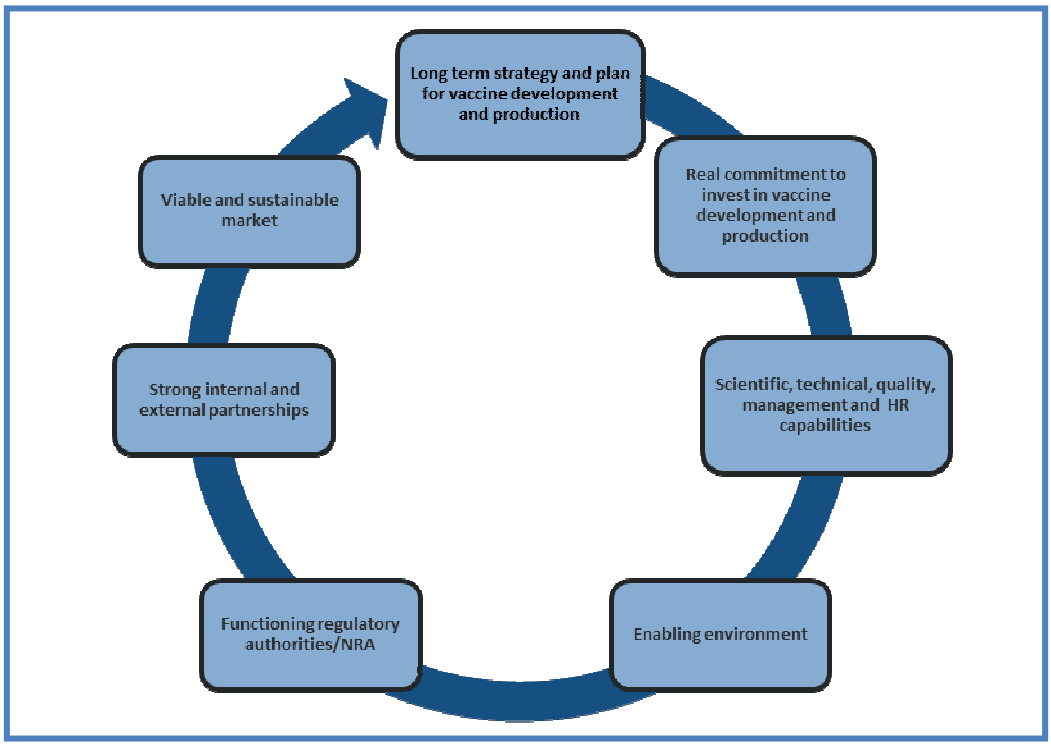
[17] GVAP 2014 report, WHO Geneva, page 114

4.7 Potential capacity of African manufacturers to develop manufacturing facilities

The following brief observations are a tentative mapping of the possible future vaccine development and manufacturing possibilities in Africa. This is still to be adjusted to the technical and environment challenges specific to each country and manufacturer. Annex 5 provides further detail.

Critical success factors for setting vaccine production can be visualized in Figure 10 below.

Figure10 Critical success factors for vaccine production



Taking these requirements into account:

- South Africa would be the best positioned country to develop manufacturing facilities in Africa due to a number of factors: population and public market size, strong NRA, existing public private partnership, number of clinical trial sites and experience, high scientific and technical capacities, regional influence, country infrastructure.
- Manufacturers in Maghreb (specifically, Tunisia, Morocco, and Algeria) have sustainable infrastructure including quality, HR, scientific capacity, technical expertise and significant experience with pharmaceutical manufacturing. There is also a sub-regional market.
- Ethiopia, Kenya, Zimbabwe, Ghana and Tanzania: national authorities are in the process of strengthening capacities for pharmaceutical and biological products.
- Senegal has good experience of vaccine production, but it is limited to yellow fever vaccine which is WHO pre-qualified. It enjoys support from France and WHO and has good facilities and staffing.
- Other African countries face significant challenges with respect to establishing a vaccine manufacturing facility in their territories and will have to consider this option very carefully and take

- the full investment of time, effort and money into account. One of the main obstacles is the lack of infrastructure in general, for example, unreliable energy supply (frequent breakdowns), difficulties regarding the procurement of raw materials and spare parts for equipment and other logistics constraints. In addition, lack of resources and expertise, non-functional NRAs and other factors, such as political constraints, may provide further significant barriers.

5. Vaccine Manufacturing: Cost Drivers and Actual Trends, Funding Sources and Mechanisms

5.1 Introduction

No viability study can be complete without an analysis of financial feasibility and sustainability in the context of manufacturing vaccines in Africa. This section of the VMPA study uses an evidence-based approach and analyses the cost drivers that underlie vaccine manufacturing, in addition to financing methods that are currently being used in Africa, and those that could be galvanized to finance manufacturing in the future.

This analysis will help to identify where the major costs originate, and how to approach the various financing sources in an optimized manner in Africa.

Chapter 5 summarizes the VMPA results on costs and financing and is broken into four constituent parts:

1. An analysis of the generic cost drivers that underlie vaccine manufacturing;
2. A quantitative analysis of current manufacturing costing data available in the African context, including relevant data from other developing country manufacturers;
3. An analysis of current financing sources being used by manufacturers in Africa;
4. An analysis of potential sources of financing using a global perspective.

5.2 Generic cost drivers of vaccine manufacturing

A feature of the vaccine manufacturing industry is high upfront costs, and significant ongoing operational and maintenance expenditures. Further, the vaccine industry is one with high capital intensity of 12% (compared to pharmaceuticals which are 9%)[18].

The manufacture of vaccines is very complex and highly regulated.[19] The manufacturing costs are significant[20] due to:

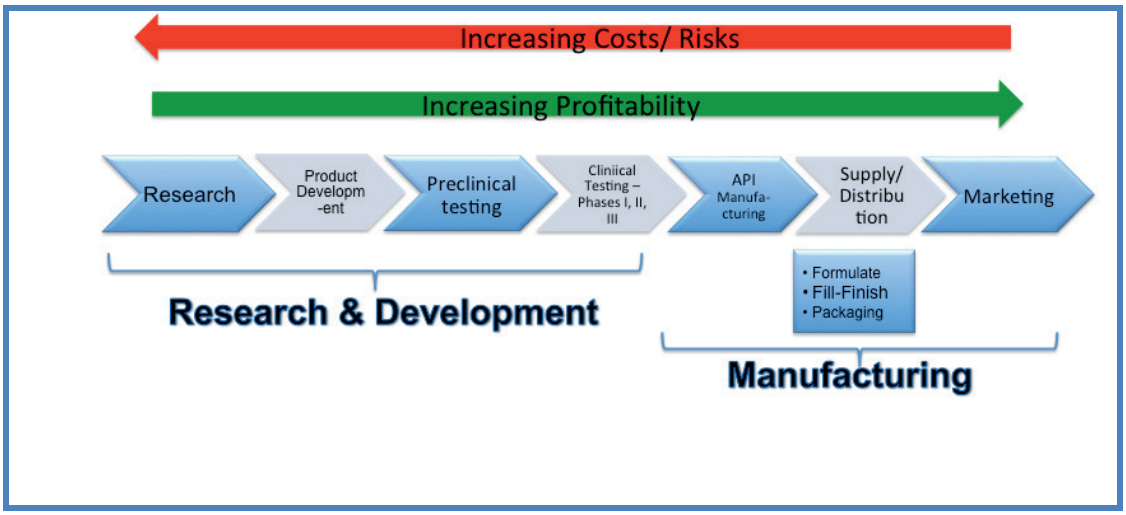
- Complexities of types of manufacturing;
- High risk of failure;
- Complex logistics, cold chain, internal warehouse processes;
- Stringent quality management system.

[18] (capital investment/ revenues generated) Andrew Sinclair, Peter Latham, Vaccine Production Economics
[19] Good manufacturing practices (GMP) are the practices required in order to conform to the guidelines recommended by agencies that control authorization and licensing for manufacture and sale of drug products, and active pharmaceutical ingredients.
[20] Datla, M. Understanding Vaccine Manufacturing, Gavi workshop, Geneva

5.2.1 The manufacturing life-cycle

Figure 11 provides an overview of the vaccine lifecycle, including R&D and manufacturing. The earlier processes are considered riskier due to the uncertainties involved, while profitability increases towards the right side of the life-cycle. Vaccine manufacturing for the purposes of this report is assumed to include API production, formulation, fill finish and packaging.

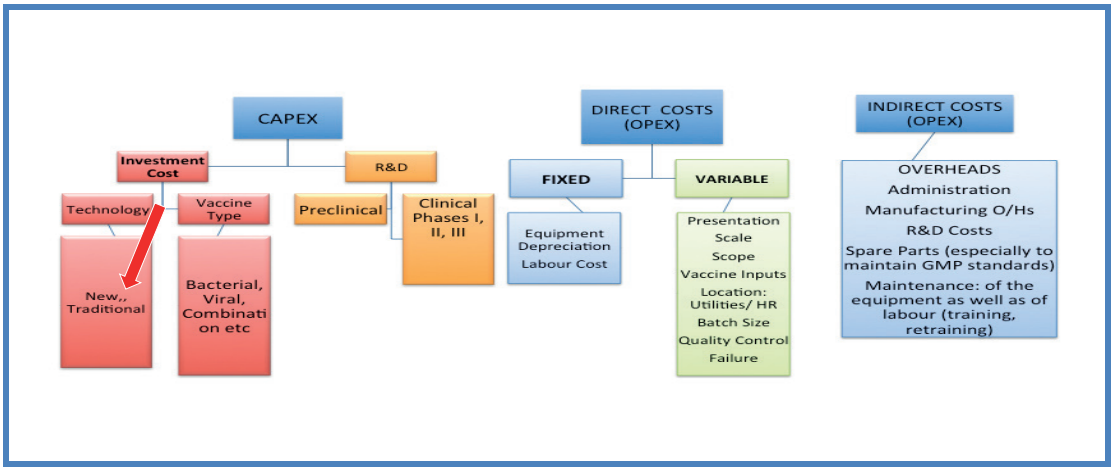
Figure 11 R&D and manufacturing processes



5.2.2 Cost drivers & Cost of Goods

There are several cost drivers underlying vaccine manufacturing, as documented by different studies and presentations[21]. These can be grouped broadly into capital expenditure (CAPEX), and direct and indirect operating (OPEX) costs.

Figure 12 Cost drivers



[21] Gavi, Mercer Management Consulting (2002); Mahima Datla, Understanding vaccine manufacturing

Table 14 Cost drivers explained

Cost Drivers	Explanation
Capital Expenditure (CAPEX)	Capital expenditure (CAPEX) refers to funds used by a company to acquire or upgrade physical assets such as property or equipment. Within vaccine manufacturing, these also include downstream R&D activities, preclinical and clinical trials, associated with bringing the product to commercial production.
Investment Costs	Investment costs are estimated at 60% of total manufacturing cost[22], and form the highest cost barrier. They constitute the highest risk for financiers, investors and manufacturers. They include buildings for API manufacturing, formulation-fill-finish, storage, equipment, quality control facilities, and support structures such as pilot facilities and animal houses. The time to build, start-up and validate the facility add significantly to the overall cost. It will be several years (5 to 10 years on average) before a facility can be established, licensed and become ready for production, all the while attracting costs without any income flow to meet the same. Newer, single-use technologies for production are reducing and deferring capital costs.[23]
R&D costs	Every vaccine has to undergo extensive pre-clinical and clinical trials to demonstrate efficacy and safety, adding to the cost of the final product
Direct OPEX	The direct operating expenditure (OPEX) in vaccine manufacturing can be divided into fixed and variable costs associated with production. Typically, the variable costs will rise as the volume increases, while the fixed costs decrease as in the CAPEX case.
Fixed Costs	Labor costs, predominantly highly specialized and qualified scientists, are treated as fixed due to the high level of expertise needed.
Variable Costs	Main drivers are volume, presentation, formulation, packaging, and quality control activities.
Indirect OPEX	The indirect costs are related to administrative and manufacturing overheads as well as to maintenance, commercial production costs and quality management
Administrative and Manufacturing Overheads	Arise from interaction with numerous stakeholders - regulators, governments, suppliers and other organizations, lawyers for intellectual property and legal issues, market intelligence experts, and communication/public relations teams. The facility itself is highly secure to reduce contamination and stop hazardous bio-waste leakages, increasing costs.
Spare Parts and Maintenance	Are needed often, especially to maintain GMP standards and operation. Regular retraining staff operating the equipment is also required. Hereafter re-testing/re-validation of particular systems, based on an assessment, are required, all of which increase costs.
Additional costs to commercial production	Once the new facility has been established, costs of commissioning of equipment, qualification and validation runs, trial runs, engineering batches, simulation runs, media runs, stability batches, inspection, labeling and cartonning runs, all need to be taken into account.
Quality Management Systems	High costs of implementation and maintenance of QMS, which is a key requirement to obtain NRA market authorization and WHO PQ.

Manufacturing costs are also determined by the *presentation* choice. Vaccine are packaged in single or multi-dose vials, pre-filled syringes, lyophilized options, with varying costs, overfill rates, and warehousing needs.

[22] Mahoney, R (1990, 2002), Mercer Management Consulting (2002)
[23] ,[13] Levine, H.L. 2010; Sinclair, A. Latham P. Production Economics

Figure 13 Manufacturing cost: variability by vaccine presentations

Estimated manufacturing cost per dose, including an injection device and excluding the cost of vaccine solution, for 10-dose vials, 1-dose vials, and a prefilled AD device by hypothetical vaccine producer in a developing country			
	(a) Manufacturing Cost (USD)		
	10-Dose Vial	1-Dose Vial	Prefilled AD Device
(b) Production (Labour and Equipment)	0.015	0.040	0.042
(c) Material packaging syringe	0.090	0.217	0.200
(d) Vaccine overfill adjustment (%)	100	113	98
Total manufacturing cost	**0.105**	**0.257**	**0.242**

(a) Based on a production rate of 120 units/minute, with manual inspection and packing, and a USD 5000/year direct labor

(b) Includes quality control tests, facility and utility costs and depreciation, based on a 10-year life span for all manufacturing equipment.

(c) All costs include vial/device, stopper, aluminum crimp seal, label, carton, or pouch and a USD 0.04 vaccine vial monitor. Vials include a USD 0.07 auto-disable syringe.

(d) Based on recommended levels of overfill for injectable vaccines.

Bulletin of the World Health Organization 2003, 81 (10)

Studies[24] show that filling costs for single dose vials are 2.5 times higher than for multi-dose vials:

- Single dose vials fill fewer doses per minute (cost is circa 3 times that for a 10-dose vial)[25]; single dose JE vaccine/vial = 55 cents in China, 5 doses/vial = 85 cents equivalent to 17 cents/dose
- Overfill in vials higher than in pre-filled syringes (PFS);
- Packaging costs: PFS high, then multi and single dose vials;
- Lyophilization requires additional capital investment and is a longer process with increased costs;
- Costing per dose for the different presentations range from high to low in the following order: Lyophilised – pre-filled syringe – single-dose vial – multi-dose vial.

5.3 Cost of vaccine manufacturing in Africa

Cost of vaccine manufacturing in the context of Africa is determined by multiple factors, some are common to any location or product ; others are dependent on the quality of existing support infrastructures and the difficulties to reach and maintain GMP and international quality requirements.

[24] Mercer Management Consulting (2002)
[25] P.Heyman, BDPharmaceuticalSystemsR&D, personal communication, 2000; Expert feedback on Chinese manufacturing

5.3.1 Empirical cost estimates

Figure 14 Cost estimates at a glance

a) Building a manufacturing facility (20 million doses) can cost between USD 60 million to USD 130 million, depending on vaccine technology and formulation according to estimates made by WHO[26].

b) CAPEX attracts over 60% of all cost, which can be rationalized through economies of scale and scope. New technologies can help reduce/defer upfront expenditure.

c) A highly-specialized workforce is a key contributor to OPEX costs. Lack of existing support infrastructure in Africa can increase indirect costs such as maintenance, as can importing of spares and material via taxes and transportation. Incentives and subsidies by governments can reduce costs.

d) Quality management systems and international standards are important cost drivers to maintain GMP and quality requirements and achieve access to market.

5.3.2 Specific factors and drivers of vaccine manufacturing cost in Africa

- *Human resources and education:* with few African educational institutions in the field of vaccinology, microbiology and vaccine or biotech manufacturing, highly qualified FTEs are scarce, leading to higher costs in attracting and retaining staff.
- *Maintenance & calibration:* with no significant vaccine manufacturing industry currently in Africa, there is a resultant lack of support infrastructure for maintenance of manufacturing facilities. While maintenance is required regularly and quickly, experts have told of long delays in service personnel from Europe coming to remedy issues, and of the increased cost of their travel. Cost of maintenance and calibration is also higher typically**,** as compared to other Developing Countries Vaccine Manufacturers (DCVMs) due to an underdeveloped vaccine manufacturing ecosystem and lack of infrastructure.
- *Pricing and Price Independence:* Vaccines, being public sector goods with the government and UN agencies as major partners, experience a strong downward pressure on the price, limiting independence and volume linked elasticity. Pricing policy of governments in Africa (e.g. Egypt) is stringent and distant from free market prices. Further, lack of a domestic private market and inaccessible foreign public and private markets restrict revenue generation possibilities, opportunity to cross-subsidize profits, and access to tiered pricing benefits.
- *Incentives:* In some cases, incentives are being offered to subsidize manufacturing from African countries.
- *Utilities:* Availability and (increased) cost of sustainable and reliable utilities (water, electricity, generators) lead to additional spending on water plants and purification units, back-up UPSs**,** generators and waste disposal systems.
- *Demand dynamics and stability:* It is riskier to establish demand stability with a very large single buyer with huge bargaining power coupled with stringent WHO PQ requirements.
- *Functional local NRA:* Factors outside the control of the manufacturer, but directly affecting its ability to generate profits, include the need for functional (as assessed by the WHO) NRAs. This restricts the

[26] Syarifah Liza Munira: Viability of local vaccine production in developing countries: An economic analysis of cost structures, market shares and vaccine prices, Department of Global Health, Australian National University

manufacturers' ability to access export markets – both public and private - essential for profitability in terms of sales volumes, tiered pricing etc.

- *Competition:* Finally, heightened competition from multinational companies and developing country manufacturers could make procurement cheaper than manufacturing.

5.4 An analysis of the current and previous sources of vaccine manufacturing financing in Africa

Financing the manufacturing of vaccines is defined as the sources of financing to meet all costs identified in the manufacturing process. Data and information were gathered from existing and potential manufacturers to not just understand the diversity, or lack thereof, of funding sources, but also to get an insight into one of the possible reasons for lack of investments in the sector which would explain the lack of growth.

Financing sources in Africa are mainly government budgets supplemented by fee income and grants. One manufacturer is structured as a PPP with some private financing, fee income, a local development bank loan with another receiving financing from an international development bank with links to the country.

5.4.1 Financing of Public Private Partnerships (PPP)

Biovac, the South African firm, is the sole vaccine manufacturer structured as a PPP currently in Africa. There is a shared ownership of the government of 47,5% and the private sector of 52,5% (Biovac Consortium). It represents a suitable case study for consideration of a 'typical' PPP-based funding structure.

Financing for the entity is, in line with the PPP status, a mixture of:

- Initial equity injection by the shareholders.
- A defined fee charged for handling vaccines, as defined in the supply agreement with the government of South Africa.
- Local development bank loans, (Industrial Development Corporation, part of the Department of Trade and Industry).
- Bilateral grants "in kind" and technical support from the WHO and other entities.
- Grants granted by the Department of Trade and Industry to stimulate local production.

It is clear that the current revenue structure is unsuitable for strong growth/expansion and that new sources of funding are required for funding planned growth**,** to align the cash flows with fewer gaps and allow repayment of the fixed costs to be closer to the period where revenue generation becomes a reality. Opportunities with international development financiers and other funders including commercial banks should be explored.

5.4.2 Public funding

The majority of the manufacturers have been funded and subsidized since their inception, and continue to receive finance from government budgets coupled with revenue streams from ongoing business.

One noteworthy exception to this is the existence of loan funding on a bilateral basis from a donor development bank l'Agence Française pour le Développement (AFD) and from the Islamic Development Bank with ties to the region.

Within the public-sector units, however, our analysis revealed optimization of the costs and good cash flow management. Funding via supply contracts and favourable credit terms with loyal suppliers was being carried out although the confidential nature of such relationships hinders detailed analysis of them.

Based on the above, it could be inferred that government funding has been the predominant source of funding for the vaccine companies, quite possibly due to the public market nature of the product and National Immunization Programmes. However, it could be also inferred that government funding is predominant due to the lack of interest from other financing sources. There are several reasons that could explain why private funding and the private sector have dampened interest in entering or expanding into the industry.

As seen in previous chapters, a large part of the low-income countries and low-and-middle-income countries in Africa are supplied with vaccines by organizations such as UNICEF SD and partly funded through Gavi. Co-financing means that government budgets face an opportunity cost strongly in favour of supporting that mechanism rather than investing in manufacturing capabilities in the region, for reasons also discussed earlier in the report. This indirect, and highly leveraged, subsidy would certainly have consequences for manufacturers in addition to the pricing anomalies noted below.

Restriction due to pricing policy of governments could have a strong effect on the funding sources as well. Where the current sales price per dose can be even below the cost per dose (if manufactured in Africa), a manufacturer's interest may not only be dampened, but also have a negative effect on attracting funding sources that can be used. Thus, the pricing policy will ensure that funding remains as close to the government as possible.

Finally, the lack of a significant and mainly inaccessible imperfect private market with the possibility of tiered pricing appears to be another indirect effect (via revenue dampening) of non-typical commercial activity, which could attract diversified and non-governmental financing and financing sources.

5.5 Cost optimization and innovative financing methods

5.5.1 For investment costs

- Investment costs are high: thus diversified funding sources that are the most flexible need to be found, likely from multilateral banks and with the following characteristics:
    - Diversified capital structure;
    - Large borrowings;
    - Low interest rates;
    - Long repayment periods, and;
    - Long grace periods.
- As investment costs are high and upfront, and repayment subject to time lag, terms and conditions to defer payments of both interest and principal should be sought.
- PPP solutions should be explored and pursued, leveraging government involvement, maximizing government subsidies and incentives.
- Strategies to outsource or revisit on a cost-benefit approach, non-essential expenditures so as to streamline CAPEX, and converting CAPEX into OPEX should be considered.

5.5.2 For the cost of goods

- Cost of Goods (CoG) optimization is the driver of success and should be pursued.
- Optimize economies of scale and scope by increasing volume and multi vaccine manufacturing facilities.
- Manufacturers, particularly in developing countries, have faced similar issues as Africa. Their learning should be collated and utilized to overcome some of the issues, thereby reducing costs.

5.5.3 For the revenue stream

- Tight margins mean that Viability Gap Funding (VGF) type supplementary funds to subsidize the return profiles for investors and manufacturers should be sought.
- Sustainability requires “volume business” due to downward price pressure. Regional hubs to increase demand, alongside approved NRAs to maximize market access and exports should be developed.

5.5.4 For financing consideration

- There is a lack of knowledge amongst financiers about vaccine manufacturing. A clear business case should highlight risks, investment potential and address perceptions of vaccines as a loss-leader for public good with donors, multilateral banks and commercial banks. The approach to vaccine production financing should be based on a broader economic perspective rather than just an infrastructure or a health product project perspective.
- Diversification of financing sources should be explored in order to make the business more sustainable and lower risks by looking at innovative financing opportunities, e.g. Joint Ventures, partnerships with DCVMs, biotech companies, research centers and global health initiatives and agencies.
- PPP style structures for consideration, with:
    - a mixture of grant and loan funding;
    - seed investments by government in cash and/or kind, combined with grants, VGF leveraged with funds from multilaterals and push-funding;
- Private sector funding from Corporate Social Responsibility (CSR).
- Hybrid structures with an element of financing and tech transfer, with an opportunity for access to one of the largest future “consumer” markets.

- Investigation of bilateral sovereign stakeholders' policies towards Africa that can be leveraged to create financing options not just for manufacturing itself, but for building the eco-system to support sustainability, for example, specialized Human Resources (HR), R&D facilities, university degrees, practical training. Several of the most successful developing country vaccine manufacturers are from two countries interested in working with Africa (India and China). This interest could be leveraged for mutual benefit.
- The effects of taxation have largely been excluded from our analysis due to the heterogeneous area we are dealing with. We have noted that tax subsidies do exist and could be a useful tool in financing options, though no work has been done on what profits taxation levels could attract. With margins typically very low, excessive taxation could make the incremental difference to a decision of whether to proceed or not financially. Further analysis in this field is therefore warranted.

As noted, the sources of funding for current manufacturers in Africa are fairly limited. This lack of diversified financing could be hypothesized as one of the reasons for a lack of increased or accelerated growth in the vaccine industry in Africa. New trends in innovative financing, which could be further examined for a "fit-for-purpose" evaluation, include:

- Funds: Social Impact, Development and Private
- Corporate Social Responsibility (CSR) and Africa unique consumer market
- Islamic finance options
- International Finance Facility for Immunization (IFFIm) and domestic health bond type structures in Africa
- Ratings and sophisticated banking systems
- Market shaping, AMC and its uses
- Alternative sources of income to supplement direct financing

6. Key Findings

Developing vaccine production in Africa is a highly contentious issue. It can be argued that since established external manufacturers and suppliers are responding to most of Africa's funded demand, current vaccine market trends and dynamics are not in favour of vaccine production in Africa. Barriers to entry, funding requirements and risks are high; industrial and commercial competition for routine vaccines is challenging, demanding and costly.

However, on the pro-side for local production, there is a place for existing and potential African manufacturers to develop their capacities of manufacturing in the next 10 to 20 years. Development of a more comprehensive and sustainable vaccine manufacturing industry in Africa requires active intervention in order to establish a conducive business environment. A number of factors need to be concomitantly addressed in order to develop sustainable vaccine development and manufacturing projects in Africa, including scientific, technical, managerial, and financial resources.

6.1 Vaccine Market

Vaccine products and vaccine markets are different from medicine products and markets and have their own peculiarities and features. This limits the number of players as a result of more stringent regulatory requirements, high entry barriers, increasing cost and high risk of failures. Emerging manufacturers are becoming major suppliers at a global level for basic and underutilized vaccines for developing countries and UN procurement agencies. African demand is booming in terms of number of doses and vaccine types because of an increase in population growth, immunization coverage and vaccine expenditure. Vaccine supply in Africa is almost totally external and highly influenced by the funding sources and global community policies and incentives. There is currently a low level of local production on the continent, focused in Senegal and Egypt and with some significant prospects in South Africa.

6.2 Vaccine Procurement

UNICEF SD Procurement Services is the predominant procurement mechanism utilized in Africa. Forty five of 54 countries use UNICEF SD to a greater or lesser extent, covering approximately 90% of the African continent by population. If the status quo remains, then a logical method for an African vaccine manufacturer to gain market access in Africa would be to become a WHO-prequalified supplier through UNICEF SD. Sources of financing (donor or domestic) and related policies affect the possible procurement options for vaccines and the potential use of local manufactured vaccines. Seventeen countries accounting for 47% of the African population conduct some level of self-procurement of vaccines.

High variation of procurement rules and regulations, habits and practices in all areas of procurement requires specific individual market assessments in order to gain access and assess the viability of supply to the individual countries.

6.3 Vaccine Manufacturing

Vaccine manufacturing is currently very limited in Africa.

Eight companies with either existing or potential vaccine manufacturing capacities have been identified.

Three companies are able to supply vaccines that have been produced locally including all upstream and downstream processes. Only one of these companies exports a WHO prequalified vaccine. One company is in the late stage of vaccine development and manufacturing but limited to downstream processes. Four

companies are considered to be at the preliminary planning phase of vaccine development and production, three of which have had past experience in producing some basic vaccines.

The companies have heterogeneous levels of capacities and capabilities for manufacturing vaccines. It is notable that most of the companies have developed the functions of importation, storage and distribution which are not "manufacturing" functions *per se* but rather commercial functions. These are potentially lucrative functions, requiring significantly less capital, operational and technical investment. Very few are at a very limited stage of product and API manufacturing.

Full NRA functionality required for vaccine manufacturing is limited to three vaccine producing countries in Africa that need to implement all necessary functions. Some other NRAs are considered to be strong in pharmaceuticals and have potential in the functions required for vaccines.

In the period 2002 to 2015, 171 vaccine clinical trials were conducted in Africa. This is putting significant pressure on the capacity of regulators and ethics committees to meet all the necessary standards.

6.4 Funding and Financing Vaccine Manufacturing

Building a manufacturing facility can cost in the region of USD 60 million to USD 130 million. With CAPEX attracting over 60% of all cost, this can be rationalized through economies of scale and scope. New technologies can help reduce/defer upfront expenditure. A highly-specialized workforce and quality management systems to meet international standards, which are necessary to achieve and maintain GMP compliance and sustainability, are important cost drivers. Unavailability of such systems and lack of existing support will increase indirect costs in Africa and decrease feasibility of production.

It should be noted that there is little empirical evidence from African manufacturing to examine, and though plans for new facilities are in existence, confidentiality concerns limit access to data and therefore the ability to analyze relevant local industry case studies.

Financing sources in Africa are mainly government budgets, supplemented by grants, fee income and in some cases loans or private financing. Several innovative financing methods and are being discussed or may be relevant, and Governmental incentives and subsidies are likely to play a big part in reducing manufacturing costs.

7. Conclusion

Whilst it can be concluded that there is limited space for multiple major players in the vaccine production field in Africa, a number of sub-regional players could be established with the right level of political and technical support, under a clear and funded regional policy and plan to develop the necessary ecosystem. Thus, there exists the potential, with a long-term strategy, to create a viable, competitive and sustainable vaccine manufacturing industry in Africa.

See Annex 6 for proposed next steps

Annexes

Annex 1 Countries included in the VMPA study, including WHO region and Gavi eligibility

Country	WHO Region	Gavi Eligibility
Angola	AFR	Graduating
Congo Brazzaville	AFR	Graduating
Ghana	AFR	Graduating
Algeria	AFR	NON
Botswana	AFR	NON
Cape Verde	AFR	NON
Egypt	EMR	NON
Equatorial Guinea	AFR	NON
Gabon	AFR	NON
Benin	AFR	YES
Burkina Faso	AFR	YES
Burundi	AFR	YES
Cameroon	AFR	YES
Central African Rep.	AFR	YES
Chad	AFR	YES
Comoros	AFR	YES
Cote d'Ivoire	AFR	YES
Djibouti	EMR	YES
DR Congo	AFR	YES
Eritrea	AFR	YES
Ethiopia	AFR	YES
Gambia	AFR	YES
Guinea-Bissau	AFR	YES
Guinea-Conakry	AFR	YES
Kenya	AFR	YES
Lesotho	AFR	YES
Liberia	AFR	YES

Country	WHO Region	Gavi Eligibility
Nigeria	AFR	Graduating
Libya	EMR	NON
Mauritius	AFR	NON
Morocco	EMR	NON
Namibia	AFR	NON
Seychelles	AFR	NON
South Africa	AFR	NON
Swaziland	AFR	NON
Tunisia	EMR	NON
Madagascar	AFR	YES
Malawi	AFR	YES
Mali	AFR	YES
Mauritania	AFR	YES
Mozambique	AFR	YES
Niger	AFR	YES
Rwanda	AFR	YES
Sao Tome & Principe	AFR	YES
Senegal	AFR	YES
Sierra Leone	AFR	YES
Somalia	EMR	YES
South Sudan	AFR	YES
Sudan	EMR	YES
Tanzania	AFR	YES
Togo	AFR	YES
Uganda	AFR	YES
Zambia	AFR	YES
Zimbabwe	AFR	YES

Annex 2 UNICEF SD data indicating use of UNICEF procurement services from 2010 to 2015 (2010 to 2014 based on actual use, 2015 based on forecast intent provided by countries)

Country/Year	2010	2011	2012	2013	2014	2015
Algeria	None	None	None	None	None	None
Angola	Partial	Partial	Partial	Partial	Partial	Partial
Benin	Fully	Fully	Fully	Fully	Fully	Fully
Botswana	None	None	None	None	None	None
Burkina Faso	Fully	Fully	Fully	Fully	Fully	Fully
Burundi	Fully	Fully	Fully	Fully	Fully	Fully
Cameroon	Fully	Fully	Fully	Fully	Fully	Fully
Cape Verde	Fully	Fully	Fully	Fully	Fully	None
CAR	Partial	Fully	Fully	Fully	Fully	Fully
Chad	Fully	Fully	Fully	Fully	Fully	Fully
Comoros	Fully	Fully	Fully	Fully	Fully	Fully
Congo Brazzaville	Fully	Fully	Fully	Fully	Fully	Fully
Cote d'Ivoire	Partial	Partial	Fully	Fully	Partial	Partial
Djibouti	Fully	Fully	Fully	Fully	Fully	Fully
DR Congo	Fully	Fully	Fully	Fully	Fully	Fully
Egypt	None	None	None	None	None	Partial
Equatorial Guinea	Fully	Fully	Partial	Fully	Fully	Fully
Eritrea	Fully	Fully	Fully	Fully	Fully	Fully
Ethiopia	Fully	Fully	Fully	Fully	Fully	Fully
Gabon	Fully	Fully	Fully	Fully	Fully	Fully
Gambia	Fully	Fully	Fully	Fully	Fully	Fully
Ghana	Fully	Fully	Fully	Fully	Fully	Fully
Guinea-Bissau	Fully	Fully	Fully	Fully	Fully	Fully
Guinea	Fully	Fully	Partial	Fully	Fully	Fully
Kenya	Fully	Partial	Partial	Partial	Partial	Partial
Lesotho	Fully	Fully	Fully	Fully	Fully	Fully
Liberia	Fully	Fully	Fully	Fully	Fully	Fully
Libya	None	None	None	None	None	None
Madagascar	Fully	Fully	Fully	Fully	Fully	Fully
Malawi	Fully	Fully	Fully	Fully	Fully	Fully
Mali	Fully	Fully	Fully	Fully	Fully	Fully
Mauritania	Fully	Fully	Fully	Fully	Fully	Fully
Mauritius	None	None	None	None	None	None
Morocco	Fully	Fully	Fully	Fully	Fully	Partial
Mozambique	Partial	Partial	Partial	Partial	Partial	Partial
Namibia	None	None	None	None	None	None
Niger	Fully	Fully	Fully	Fully	Fully	Fully
Nigeria	Partial	Partial	Fully	Partial	Partial	Partial
Rwanda	Partial	Fully	Fully	Fully	Fully	Fully
Sao Tome & Principe	Fully	Partial	Partial	Fully	Fully	Fully
Senegal	Fully	Fully	Fully	Fully	Fully	Fully
Seychelles	None	None	None	None	None	Partial
Sierra Leone	Fully	Fully	Fully	Fully	Fully	Fully
Somalia	Fully	Fully	Fully	Fully	Fully	Fully
South Africa	None	None	None	None	None	None
South Sudan	Fully	None	Fully	Fully	Fully	Fully
Sudan	Fully	Fully	Fully	Fully	Fully	Fully
Swaziland	None	None	None	None	None	None
Tanzania	Fully	Fully	Fully	Fully	Fully	Fully
Togo	Fully	Fully	Fully	Fully	Fully	Fully
Tunisia	None	None	None	None	None	None
Uganda	Fully	Fully	Fully	Fully	Fully	Fully
Zambia	Fully	Fully	Fully	Fully	Fully	Fully
Zimbabwe	Fully	Fully	Fully	Fully	Fully	Fully

Data Source UNICEF SD

Annex 3 Areas for improvement in procurement and related areas

Area	Possible Improvement	Partners Engaged	Comments	Level of Effort Required Green – Relatively Simple Orange – Moderate Effort Red – Considerable effort
Product Selection	Engagement of clinical and programmatic country actors in identifying preferred presentations and appropriate vaccines for the African context. Could feed into regional plans and identification of needs for action by manufacturers. Could also inform future prioritization of vaccine introduction.	WHO - Programmatic Suitability of Vaccine Candidates for WHO Prequalification (PSPQ) Working Group AFRO and EMRO TAG West African Health Organization (WAHO) UNICEF RO in Africa	Identification of short, medium and long term needs, can assist in the development of appropriate vaccines and presentations of current and future vaccines for the African context.	**Mechanisms already in existence, ongoing engagement and consideration required.**
Product Harmonization	To optimize potential economies of scale and to ensure appropriate formulation and presentations are manufactured by any African manufacturer, regional agreement on product harmonization would assist.	AFRO TAG, West African Health Organization (WAHO) AVAREF	Product harmonization requires political will and clinical engagement to ensure optimal outcomes.	**This is a challenging but not impossible option, vested interests, historical arrangements and subjective opinions can be addressed with appropriate will and evidence to benefit from the process and outcomes.**
Forecasting	Engagement of country actors in short, medium and long term vaccine needs and demand forecasting. Regional and country needs can be identified and demand versus available supply assessments can inform future planning on both sides.	UNICEF and WHO	Forecasting needs and identifying short medium and long term demand can lead to improved security of supply through active engagement with current and future manufacturers and suppliers. This activity is also beneficial for assessing future financial impact, planning and budgeting.	Mechanisms already in existence, ongoing engagement and consideration required. Training may be required in some contexts to engage fully.
Contracting & Supply processes	Developing capacity in self-procurement specifically addressing the needs in vaccines and related technologies: areas, which differ from	UNICEF Gavi WHO African Development Bank	Limited technical assistance is currently available in this area but has been identified as an area for focus in Gavi graduating and MIC where self-	Training would be required but needs should be assessed on a case-by-case basis. Changes in procurement can take

Area	Possible Improvement	Partners Engaged	Comments	Level of Effort Required Green – Relatively Simple Orange – Moderate Effort Red – Considerable effort
	other public procurement.	SACU Southern African Customs Union	procurement is considered a development progression.	significant time and requires political will and support.
Vaccine and Immunization Legislation	A number of procurement optimization aspects could be included in the development of vaccine and immunization legislation. Some regions have made implementation of appropriate immunization legislation a priority activity[27].	Sabin SIF project. AUC, WHO AFRO and EMRO West African Health Organization (WAHO) African Development Bank	Once specific legislation obstacles or gaps are identified using the development of immunization specific legislation to supersede any legislative obstacles in regulation, procurement and TTD can address a number of issues and obstacles	Changing legislation and ensuring that all relevant optimization factors are appropriately included can be a lengthy and challenging process. Possibility to learn from other regions.
Specific Exemptions	Where changing legislation is considered too difficult, options for specific exemptions such as the ability to outsource procurement, modify procurement or payment procedures, the removal of TTD, expedited clearance procedures etc. could be a viable alternative on a case-by-case basis.	African Development Bank West African Health Organization (WAHO) UEMOA, COMESA, SADC, SACU (Southern African Customs Union)	Examples are available for review and adaptation to specific contexts.	**While simpler than changing legislation this still requires identification of needs and best approaches to resolve obstacles.**
Regulation	Considerable potential regulation issues were identified in section one of this report.	WHO AVAREF SADC	Improving regulatory capacity is considered a priority for all countries whether manufacturing self-procuring or procuring through UNICEF SD. Regulation optimization, regulation harmonization and fast track review of WHO prequalified products have been identified as beneficial priority activities.	**While some aspects are more simple to address, others require significant long-term effort.** **There are a number of supportive initiatives and procedures to follow.**

[27] http://www.sabin.org/updates/blog/immunization-financing-legislation-latin-america

Annex 4 Key vaccine manufacturing requirements and challenges in the context of Africa

- **Human resources:** The level of scientific expertise of staff is a major challenge for developing vaccines as well as for operating manufacturing facilities. Scientific knowledge is necessary to understand biological and chemical processes during the long manufacturing cycle times of the vaccine. The scientific network (technology institutes, academia, research centers and others) available in close proximity to vaccine production facilities is of critical importance. It is not only the scientific and technical knowledge and skills within the facility but also the connections and relationships with the science and technology in the surrounding environment that is factor of success.

- **Source of raw materials:** the sourcing of raw materials is always a long and tedious process. Every raw material has to be sourced from a GMP approved supplier. For example, the use of animal source raw material (e.g. calf serum, lactalbumin) needs to be manufactured in bovine spongiform encephalitis (BSE) free countries such as Australia and New Zealand. Master Cell bank and Master Virus Seed have to be fully characterized and validated in regards with the extraneous agents of the animal origin.

- **Manufacturing facilities:** Fully GMP compliant facilities (according to European and international standards) are required for the production of API, formulation, fill & finish, packaging and labeling.

- **Quality Management Systems:** A quality management system (QMS) is a collection of business processes focused on achieving quality policy and quality objectives to meet customer requirements. It is expressed as the organizational structure, policies, procedures, processes and resources needed to implement quality management. A quality system includes facility design, production and dispatch, without prescribing specific ways to establish these elements.

- **Logistics and Technical environment:** An appropriate level of technical skills to maintain the facilities, the reliability of power supply (water and electricity), the availability of essential spare parts, the cold chain management are critical especially in the context of the tropical climate of African countries.

- **Project management:** Project management is the process and activity of planning, organizing, motivating, and controlling resources, procedures and protocols.

Annex 5 Potential of vaccine development and manufacturing in Africa

African companies / Capabilities	Group 1: Companies with locally produced and marketed products			Group 2: Companies at late stage of vaccine development & manufacturing	Group 3: Companies at preliminary planning of vaccine development			
	Institut Pasteur Dakar (Senegal)	**Vacsera** (Egypt)	**Institut Pasteur** (Tunisia)	**Biovac** (South Africa)	**Institut Pasteur** (Algeria)	**Institut Pasteur** (Morocco)	**EPHI** (Ethiopia)	**Biovaccines** (Nigeria)
Research and early development	**Egg based vaccine technology**		**Viral vaccines: Rabies / Vero cell technology**				**Viral vaccines: Rabies/Vero cell technology**	
Pilot scale development				**Conjugate vaccines (Hib)**				
Industrial scale development (scale up and process validation)								
Industrial facilities in project	Conceptual design for YF production facilities							
Operational industrial facilities	Yellow Fever	Bacterial vaccines		Formulation, Fill & Finish			Viral vaccine: Rabies Fermi/sheep brain technology	
		Formulation, Fill & Finish						

Annex 6 Proposed next steps

The VMPA Study provides a detailed analysis of the current and planned vaccine development and manufacturing capacities, vaccine procurement and funding mechanisms, factoring in economic, technical, market and other elements at play. It is positioned as the first step towards informing the development of a strategic business framework for establishing sustainable vaccine manufacturing capacity in Africa.

The VMPA Study is intended to provide African and global stakeholders and policy makers with insights to facilitate evidence-based decisions on whether to promote and/or invest in local vaccine production in Africa. The next steps in the process should ultimately deliver a strategic framework for vaccine development and manufacturing in Africa, as a contribution to a sound, shared and comprehensive vaccine manufacturing strategy for Africa. This should incorporate the key components of an enabling ecosystem, for a viable, competitive and sustainable vaccine manufacturing industry in Africa.

Alongside this, it is also advantageous to consider scenarios and approaches for vaccine production in Africa, with respect to, for example, where such production should be, which vaccines should be produced, and what procurement mechanisms should be established to stimulate sustainable demand for local quality vaccines and facilitate operational economies of scale

Specific activities following on from the individual sections of the VMPA report could include the following elements:

1 Vaccine Market

- Assess the future market potential in regards to vaccine supply, demand and financing.
- Identify the most important vaccine preventable diseases and possible vaccines to be developed and produced to respond to Africa needs.
- Identify the profile of potential producer countries and strategies to be considered.

2 Vaccine Procurement

- Identify and consider possible alternative mechanisms and the feasibility of establishing such mechanisms to support vaccine manufacturing in Africa.
- To optimize the potential from African vaccine manufacturing, the challenges posed through limited capacity in procurement should be addressed in parallel with any manufacturing capacity development.
- When considering any alternative mechanism to the current arrangements, the basic premise must be that any alternative should be an improvement, offering additional benefits not necessarily achievable through simple improvements within the current system.
- Possible alternatives could incorporate a combination of current mechanisms and improvements and/or in addition could incorporate establishing new supportive and synergistic mechanisms.

3 Vaccine Manufacturing

- Conduct an examination of the unmet needs and priority vaccines to be potentially produced in Africa.
- This will provide evidence and the basis for an analysis of the critical factors required to create an enabling environment for a sustainable vaccine production.
- Develop a strategy with respect to vaccine production technologies and manufacturing for the next 10 to 20 years, identifying practical synergies, partnerships and technology transfer options.

4 Vaccine Manufacturing Costing, Funding and Finance

- Further consideration of current cost and funding mechanisms is warranted, along with the provision of evidence for the development of business models for vaccine production.
- Comparison and analysis of incremental versus 'big bang' manufacturing (gradual versus dramatic) approaches and 'regional hub' cost-benefit advantages is worthwhile.
- Once specific production platforms or vaccines are identified, it will be possible to conduct a detailed analysis of costs in specific geographies using identified drivers.
- It is necessary to explore various and diverse funding and financing options for optimizing both CAPEX and OPEX. Furthermore, by collating learnings from DCVMs, it should be possible to develop strategies for cost driver reduction.

Annex 7 Expert contributors

The advice and inputs from the experts, manufacturers and stakeholders who provided documentation and both written and verbal feedback to this study is acknowledged. All engaged persons, listed here alphabetically, provided inputs either through offering personal opinions as expert in their respective fields, or in their institutional capacity:

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