The Mother of Birds Initiative:

Building biopharmaceutical sectors from the ground up with enabling technologies and local resources.

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Abstract

LMIC nations seeking to build new or improved biomanufacturing capacity to improve routine and emergency healthcare, face the question of whether to employ a *top-down* or a *bottom-up* development strategy. Should they be negotiating licences, tech-transfer partnerships and large-scale financing for local "fill and finishing" of imported bulk products, or take the more challenging path of researching, developing and manufacturing new products locally, from scratch? We discuss the bottom-up approach with the specific example of egg-based recombinant product biomanufacturing using emerging gene technologies. We describe a current project implementation in Ghana.

The COVID-19 pandemic has ushered in the Age of Biology. The centralised petrochemistry-fueled pharmaceutical industry of the 20th century is being transformed by recombinant DNA technology and vast amounts of readily accessible genomic information. A broad range of recombinant biopharmaceutical, nutraceutical and cosmeceutical products can now be manufactured using raw materials from agriculture, forestry, fishing, conservation and other biology based economic sectors. In this emerging arena, LMICs have a competitive advantage because significant proportions of their economies are already biology based. Re-imagining strategies for building stronger local healthcare systems using biotechnology is therefore a viable strategy for greater autonomy. So called vaccine nationalism has now become a pragmatic proposition rather than a political anathema.

"Common Health" ideas of the Colonial Era engendered international agencies like WHO and which primarily facilitated global distribution of industrially made patented medical products. This model has served the planet and saved millions of lives over the last century through research, innovation, and large-scale manufacturing in high-income countries (HICs). Healthcare is wealth-care and must occupy a significant proportion of any well-structured economy because of its unique positive feedback loop-- healthcare *production* supports healthy populations that are more productive and can thus afford better healthcare. Without strong, wealth-generating healthcare sectors, LMICs are doomed to cheap or counterfeit drugs and must go through complex international negotiations to obtain affordable drug pricing. They are net exporters of both valuable forex and wealth-generating potential resulting in a negative feedback loop of dependency on imports. To fulfil their destinies in the post-pandemic "common good" equation, LMICs can no longer rely on supplying the raw materials, skilled labour and bioinformation for industrial transformation in HIC economies. In Africa for example, the COVID-19 Pandemic brought the rude awakening that 1.2 billion people could not depend on altruistic agreements for emergency healthcare needs. At the outbreak of the pandemic, Africa was importing 99% of its vaccines and biologics (SABC News), with no significant capacity to manufacture countermeasures. With pharmaceutical manufacturing global supply and distribution chains everywhere disrupted, Africans were left in *un-quantifiable* peril.

For Africa, the top-down tech-transfer model has not been responsive enough to impact pandemic emergencies. Even where pre-existing pharmaceutical tech-transfer projects existed, it was not possible to pivot or repurpose them in time to respond to the COVID-19 emergency. The same was largely true for Ebola and Bird Flu emergencies. In contrast, by June of 2020, the UNECA COVID-19 Innovation Challenge had identified many homegrown innovations from all over Africa and beyond. Few if any of these received any attention or investment since habitual focus remained on large, "economy of scale" tech-transfer projects and this still remains true in 2023.

Top-Down versus Bottom-Up

For LMIC nations seeking to improve emergency preparedness and local disease priority management, development strategies can be *top-down* or *bottom-up*. Top-down tech-transfer approaches have been the basis of African industrial sector development in many fields including petroleum, textiles, automotive and mining (UNCTAD, 2021). These have created sophisticated but largely export-oriented industries. In contrast, for healthcare, the only exports are foreign exchange to buy medicines and brain-drain of the very human capacity and innovation needed to grow a wealthy health sector. The highly regulated biopharma value chain extends from disease identification to manufacture to clinical prescription. LMICs are often strong in discovery and clinical ends, but have missing links in the key steps of product development, scaling and manufacturing. As a result, their existing regulatory frameworks, whose main purpose is repeat-validating imported products, rather than ensure local manufacturing process and product safety are considered immature (WHO, 2021).

Enabling biotechnologies are emerging

A globally distributed *bio*-manufacturing network served health in the colonial world in the first half of the 20th century. It was based on hen eggs. The Pasteur Institute still owns and operates the Yellow Fever vaccine production facility in Dakar, Senegal which has protected millions of Africans against Yellow Fever since 1932. There are regionally important Pasteur Institutes in Tunisia, Egypt, Morocco, Vietnam and other former French colonies. There were British, Spanish and Portuguese equivalents also. Ironically perhaps, this industrial model is the one LMICs should learn from today-- a distributed network of small-scale manufacturing facilities supported by local agriculture and independent of forex fluctuations and import disruptions.

Today, many more natural systems could be used to manufacture biomedical products. Plants can be genetically programmed to produce valuable components of vaccines, therapeutics, nutraceutical and cosmeceutical products. A plant-based Ebola vaccine was already in development before the 2014 West African Ebola outbreak. There are long-standing research and development programs at the CSIR and University of Pretoria in South Africa for plant-based vaccines now actively seeking investment for commercialization. Plant-based production is low cost, and easily supported by the agricultural skills, logistics and inputs available in every country.

Insects are the venerable grandfathers of biomanufacturing. The Silk Road, still at the center of global geopolitics today, was founded on the humble labour of silk moth larvae in *village enterprises* thousands of years ago. American biotechnology researchers studying silkworm diseases in the early 1980's discovered that virus infected caterpillars could be used as factories to produce very pure protein biologics. The initial, exciting vision of "Village Vaccine" businesses based on age-old silk farming, was quickly co-opted by western biopharma research and converted to industrial insect cell-culture in steel vats, resulting in today's multi-billion dollar *Baculovirus* industry segment. There are now at least 5 FDA approved clinical products made with Baculovirus cell culture technology, including an influenza vaccine and a gene-therapy product.

Fertilised hen eggs have been used for making Influenza, Yellow Fever, Rabies and Measles vaccines since the 1930s. Today, influenza vaccine manufacturing is the largest global pharmaceutical enterprise and is still mostly based on culturing viruses in fertile hen eggs-- it is an agricultural business. In the USA, it has developed, tested and manufactured new, variant-specific, influenza vaccines annually since the 1940's employing the manual labour of rural American farmers. Today, starting from a nasal swab, the industry is primed to scale-up, manufacture and distribute a half-billion vaccine doses in just 28 weeks (Blyden and Christiansen 2011)! The manufacture of vaccines in fertile eggs entails their pre-incubation, inoculation with live virus, harvesting of fluids, purification, pasteurisation, and sterile filling and finishing. Automation of this process permits large-scale manufacturing of safe and efficacious seasonal flu vaccines annually in both northern and southern hemispheres. There are also many smaller businesses that produce veterinary and poultry vaccines using egg technology-- often manually-- that play a key role in protecting the global food supply.

An "Internet" of Biomanufacturing

The Mother of Birds Initiative (MOBI) consortium is implementing new egg-based biomanufacturing technologies and the resources to deploy them. Innovative molecular processes can produce high-value medical products in eggs, enabling a unique convergence of advanced gene technologies with 80 years of vaccine know-how and facilities automation (Adjanohoun 2018) and creating a powerful and cost-accessible solution for LMICs. Building a network of modular, multi-use, facilities capable of both *developing* and *manufacturing* new drugs and vaccines on-demand is the best solution to the problem of unpredictable bio-threats and regional variants. It is also the best manufacturing business model for emerging individualised medicine and gene therapies.

MOBI is developing an *EggPharm* modular manufacturing facility consisting of egg production, protein expression upstream process and downstream purification and fill and finish components. The first EggPharm is under development in Ghana, where an *existing* poultry vaccine manufacturing program at the CSIR-Agricultural Research Institute will (i) upskill expertise from poultry to human vaccines, and (ii) develop and manufacture recombinant subunit malaria and COVID-19 vaccines in an international partnership. The project includes technology and product development, facility design, process optimization and scale-up in collaboration with African private sector entities from inside and outside the continent. Partnerships with equipment suppliers, Universities and a pharmaceutical company will support the achievement of batch production of WHO-standard Active Pharmaceutical Ingredient (API). Anticipated outputs are: (i) The establishment of egg-based human vaccines manufacturing capability in Ghana, ii) Production of WHO-standard vaccine API for two vaccine candidates for testing and approval under emerging AU-CDC Regulatory Guidelines, thus achieving the goal of Technological Readiness Level 8 (NIH/NHLBI, 2019).

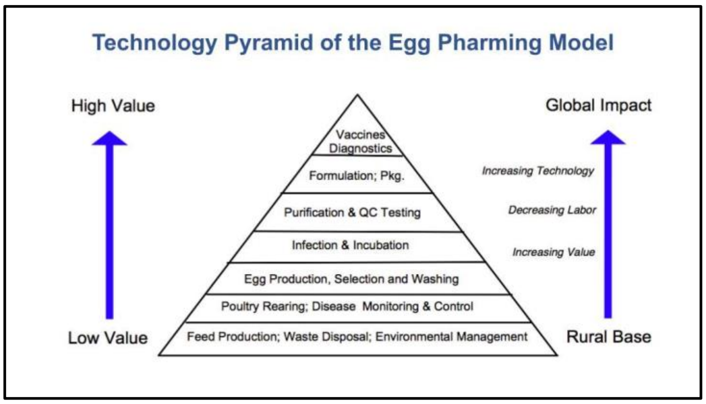

Figure 1. Building technology pyramids for healthcare biomanufacturing with eggs creates local opportunity.

MOBI calls for direct investment of pandemic preparedness funds to establish modular "EggPharms". Historical data from influenza vaccines benchmarks show that 60% of the cost of a flu vaccine dose is the cost of the eggs. Thus LMICs could redirect 60% of their expenditures on imported vaccines into their own economy as the first stage of biopharma sector development. Given that economic and food security crises go hand-in-hand with health emergencies, the added resilience is self-evident. A technology pyramid founded on local agriculture can offer return on investment at all stages, allowing projects to be built at whatever pace can be supported by socio-economic pre-conditions. Combined with new processing, and automation technologies, safe new routine and emergency vaccines and therapeutics could be made in eggs with similar timeframes as today's annual flu vaccines.

Policy recommendations / conclusions

LMICs should initiate complementary bottom-up strategies for homegrown healthcare production using biotechnology. Key steps in implementing a generic bottom-up approach are:

(i) Identify and acquire enabling technologies that can add value to locally available raw materials.

(ii) Up-skill local human resources to adapt and innovate with the new technologies.

(iii) Stimulate private and public sector partnerships that can build technology pyramids on top of agriculture, fisheries and forestry economic sectors--from foundation to high-value capstone products.

(iv) Integrate the biopharma value chain with food and other markets to enhance economic sustainability.

(v) Connect nodes at regional and national levels to share resources and capability for coordinated emergency countermeasures manufacturing.

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