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Growing sustainable and resilient human vaccines development and manufacturing capabilities in Africa – challenges and opportunities

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Statement of the Problem: Africa currently produces only 1% of its vaccine needs, a situation that exposes African countries to a high risk of epidemics and pandemics, weakened national security, poor emergency preparedness and poor sustainability and supply assurance of vaccines. AVMI commissioned the Vaccine Manufacturing and Procurement in Africa (VMPA) study to assess the feasibility of establishing sustainable vaccine manufacturing capacity in Africa.

Methodology: This analytical assessment of vaccine manufacturing capacity and procurement mechanisms in Africa was designed to answer four key questions related to understanding the vaccine market dynamics in Africa, the vaccine procurement & financing mechanisms, the technical feasibility of establishing sustainable vaccine manufacturing capacity in Africa, and the cost drivers and funding mechanisms in establishing sustainable vaccine manufacturing in Africa. 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 an expert Strategic Advisory Group.

Findings: In 2013, Africa vaccine market was approximately 5.5% of the global vaccine market, with an ever-increasing demand in terms of number of doses of vaccine and vaccine types. In 45 of the 54 African countries, UNICEF is the predominant procurer; the percentage of UNICEF vaccine sales in Africa compared to the total UNICEF vaccine sales globally is around 60%. Only eight companies in Africa have existing or potential vaccine manufacturing capacities, only one of which currently exports a WHO prequalified vaccine (Yellow Fever). There are huge obstacles for establishing sustainable vaccine manufacturing capacity in Africa, including industrial and commercial competition for routine vaccines, scientific, technical, managerial and financial challenges, compounded by the lack of an enabling ecosystem in most African countries.

Conclusion & Significance: Current vaccine supply in Africa is heavily influenced by funding sources and global community policies and incentives. While the potential for developing vaccine manufacturing capacity in Africa exists, current procurement and related practices could impede the utilization of any African manufactured vaccines and therefore require in-depth consideration for sustainability of local vaccine production. Active intervention to establish a conducive business environment is required for the development of a more comprehensive and sustainable vaccine manufacturing industry in Africa

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A potent candidate black water fever malaria vaccine in the offing, Ugandan case

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Introduction: Black water fever malaria, an acute hemolytic disease syndrome, associated with Plasmodium falciparum infection, occurring only in non – immune children and adults could, be a disorder of the Zinc finger gene and tumor necrosis factor alfa. It is characterized by haemoglobinuria, fever, jaundice and anemia. We now report that their immunity can be boosted with a combination of antihistamine and Zinc Sulphate to the effect of preventing further malaria attack for over a year.

Case History: 120 children aged three months to twelve years, were followed for hemoglobinuria without a known haemoglobinopathy, with symptoms of fever, vomiting, abdominal pain, passage of dark red urine, and loose stools, epistaxis and body weakness, after treatment with chlorpheniramine and zinc sulphate in addition to anti malarials. There was a positive family history of leprosy one case and congenital malformations, ranging from cervico-facial-ano genital sinuses and tags, in 96 cases, polydactyly, in one case, to Einhoms disease, in one case and or dactylitis, in one case. All the 120 had consumed silver fish contaminated with organophosphate poison. Physical examination revealed fever, pallor, jaundice, dehydration, renal angle tenderness, hepatosplenomegaly and congestive cardiac failure in all of them.

Method: Blood and urine samples were taken for examination and abdominal ultrasonography was requested.

Result & Treatment: Full haemogramme showed low haemoglobin, suggestive of severe anaemia, monocytosis, high total white and low red blood cell counts; positive rapid test for plasmodium falciparum and unspecified mixed species of plasmodium, and random blood glucose of varying degrees of hypoglycaemia. Urinalysis report revealed a positive Haem-test without the presence of Red blood cells. Renal parenchymal disease was detected on Ultrasonography in all of them. Black water fever malaria with severe anaemia and congenital pre-auricular sinus with renal disorder was diagnosed. In addition to general and specific care, oral chlorpheniramine, 0.35 mg/kg/day in three divided doses for five days, and oral Zinkid (zincsulphate), 0.4mg/kg twice daily for 14 days, were administered. They were discharged between November 2012 and April 2013, and 114 of them have not had recurrence of the disease to date with exception of six, four of whom turned up at 8 months of follow up, nine at 9 months, and the other, at 10 months, with Black water Fever Malaria syndrome.

Conclusion: Black water fever Malaria syndrome patients developed ample immunity to the disease to the extent of protecting 95% of them for more than a year against Malaria.

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IFITM knockdown/knockout technology for vaccine production

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Type I interferons protect cells from viral infections through the induction of a group of genes collectively named interferon-stimulated genes (ISGs). Among these ISGs, are the IFITM (interferon-inducible transmembrane) which have been shown to restrict the replication of several highly pathogenic human viruses, including severe acute respiratory syndrome (SARS) coronavirus, filoviruses (Marburg virus and Ebola virus), influenza A viruses (IAVs), and flaviviruses (dengue virus). The Genetics and Genomics group have identified these antiviral proteins in the chicken (chIFITM) and have shown that a reduction in chIFITM expression results in an increase in the virus titre in CEFs infected with avian influenza A virus (AIV) H9N2, suggesting that chIFITMs have a functional role in the control of viral infections. The observation may have useful implications in terms of vaccine production. To this end, a patent was filed relating to the modification and testing of avian IFITMs, and has now been granted in multiple countries (See attached Appendix 1). Many vaccines have been produced in embryonated hen's eggs or continuous avian cell lines for more than 30 years. (See attached Appendix 2). However, it is well established that the rate determining step in the manufacture of numerous vaccines is the induction of antiviral immune responses that prevents the replication of vaccine viruses. To generate chIFITM knock-down, we will use cutting edge genetic approaches such the CRISPR/Cas9 system which will directly target and knock-out chIFITM expression. We believe that this approach will overcome the rate limiting step in vaccine production, directly resulting in increased vaccine yields and improve the speed at which vaccines can be manufactured. We are currently in talks with major vaccine producers keen to adopt this internationally patented technology, to advance the field of both animal and human vaccine production. Discussions with HorizonDiscovery Ltd have been very positive. Using their extensive expertise in genetic modification using CRISPR/Cas9 technologies, we will be able to progress rapidly with this project. Data generated from the preliminary objectives of the project will be conveyed to GSK, Sanofi, and Ceva whom have indicated their significant interest in this technology, however, further proof of concept is required.

Objectives: The broad objective of the project is to observe the effect the knock-down of chIFITM genes expression, achieved via siRNA and CRIPSR/Cas9 transfection methods, has on viral titre in avian cell lines (commonly used for vaccine production) infected with Influenza A Virus. An additional objective of generating an IFITM-/- line of chickens will be addressed once the outcome of these early objectives are met. These would be exploited for both embryonated egg and CEF based vaccines. In addition, through analysing the genetic material of a wide variety of chicken breeds and outlying avian species that differ in levels of resistance to these viruses, we hope to identify versions of these proteins that give protection, in laboratory, commercial and "backyard" chickens. Analysis of these proteins in the chicken presents opportunities not just for a greater understanding of viral resistance, but also as tools to combat viruses in the poultry farming. It may be feasible to selectively breed for birds with improved resilience to viral infections; however, this requires the identification of resistance-associated factors and knowledge of how they act. The aim of our work is to understand the biology and any genetic changes of these genes in chickens. Specifically, the ability of IFITMs to protect the chickens against viruses will be examined. The output of this work will be in identifying versions of these proteins that give resistance to a number of avian viruses. Poultry breeders and farmers will then be able to select the protective version of the genes encoding these proteins in future breeding programmes. Developing efficient control strategies against these viral diseases will not only of benefit Western societies, but also alleviate poverty in developing countries, where these diseases are widespread, causing devastating effects on poultry farming.

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Immunological studies on Tetanus Toxoid

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Tetanus toxoid is one of the most successful vaccines used in immunization programme almost all over the world. Neonatal tetanus can be prevented by immunizing women of childbearing age with tetanus toxoid, either during pregnancy or outside of pregnancy. Tetanus vaccine is used either in mono or in combination with other antigens i.e. Diphtheria, Pertussis (whole cell or acellular), Hepatitis B, Haemophilus influenzae B, Inactivated polio vaccine etc. Tetanus toxoid is produced batch-wise using complex media, often containing poorly defined components. Therefore, batch related quality control to guarantee safety and potency is a statutory requirement.

In the new concept, quality control is seen as an instrument to monitor consistency of the critical steps in the production process and testing of vaccines. Monitoring consistency places emphasis on in-vitro methods, since in-vivo tests are less appropriates (expensive, time consuming and inaccurate) for this purpose. Immunochemical techniques may include the use of polyclonal antibodies for direct ELISA or monoclonal antibodies in capture ELISA and immunoblotting to indicate local differences in antigenicity.

There is no uniformity in the potency test of tetanus toxoid. Potency assays in animals may be seen as a way of estimating relative antigen contents parallel to the in- vitro estimations; e.g. by the flocculation tests or the Mancini test. In animal tests, however, it is the ability to provoke production of antibodies (immunogenicity) that is utilized and not just the ability to react with antibodies (antigenicity). This distinction might be carried even further. In challenge tests, the ability to create protection against toxin challenge is the reaction used (protective immunogenicity). In antibody production assays the ability to provoke production of antibodies reacting in a certain antibody detection system is used. In the past, the potency of tetanus toxoid was being expressed in Lf - units. United States Pharmacopoeia prescribed antibody induction method. British Pharmacopoeia, other European countries and World Health Organization recommended active challenge method for assaying the potency of tetanus component. However, Indian Pharmacopoeia prescribed both the methods viz. antibody titration method and active challenge method.

For the potency estimation of tetanus toxoid component in mono-valent or combination vaccines, the challenge test has been in use for many years. Despite the use of large number of animals (> 100 mice or guinea pigs) to test one batch of tetanus toxoid, this test has not been shown to correlate with immunogenicity in humans. However, toxin-neutralizing antibodies induced by the vaccine are generally accepted as correlates of protection. The three 'R's concept for the replacement, reduction and refinement of the use of laboratory animal testing is now widely accepted as not only need for ethical but also for scientific reasons.

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Increased coverage of influenza and anti-pneumococcal vaccines in the integrated care management of Albacete

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Vaccination is the public health technique that has saved most lives. In our environment we had fallen into stabilization and even a regression in the vaccination campaigns.

Objective: To increase the coverage of influenza and pneumococcal vaccination through a management intervention.

Method: A health management intervention is carried out with the participation of the managers of the Directorate of Integrated Care of Albacete to improve the coverage of vaccination against influenza and pneumococcus. This involvement has led to better coordination with primary health care staff and patient awareness. Awareness campaigns on prevention of health for patients and for toilets. The Medical Director met the Board of Directors formed by directors of primary care and insisted on the benefit of vaccination, also included the increase in coverage rates as the objective of the management contract of those years and in case of compliance Were given incentives. Also during the vaccination campaign they were informed week by week about the vaccination rates in each center.

Results: Vaccination rates increased significantly both anti-influenza and pneumococcal disease, affecting the manifestation of the diseases caused.

Conclusions: This involvement has led to better coordination with primary health care staff and patient awareness that vaccination has increased over previous campaigns.

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Targeting conserved broadly neutralizing epitopes within HIV-1 envelope gp41 MPER as vaccine immunogens for seronegative partners of HIV-1 discordant couples

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Introduction: The membrane proximal external region (MPER) of HIV-1 envelope glycoprotein-41 (gp41) is targeted by several broadly neutralizing antibodies whose conserved linear epitopes are promising targets for vaccine design. However, a formidable challenge has remained the difficulty to design and deliver MPER based immunogens for the efficient induction of such broadly neutralizing HIV-1 specific antibodies (bnAb). This is mainly because the linear bnAb MPER epitopes are poorly accessible to the immune system. The overall objective of this study therefore was the development and validation of an RNA coliphage Qβ display system for efficient presentation of conserved bnAb epitopes to the immune system

Method: To overcome the challenge of effective presentation of MPER to the immune system we have selectively engineered the surface of the RNA coliphage Qβ to to display 12 molecules of MPER per phage particle. The expression cassettes were used for the production of QβMPER recombinant hybrid phages after transformation of E. coli HB101 strain.

Results: Specific recognition of all the linear MPER based bnAb epitopes were confirmed in ELISA with QβMPER VLP as antigen and the bnAb 2F5, Z13, 4E10 and 10E8 as antibodies. Next the prevalence of MPER specific antibodies was determined in plasma from antiretroviral naïve HIV infected participants of the CIRCB AFRODEC cohort. The greater majority (84%) of participants' plasma showed MPER peptide specific reactivity with antibody titers ranging from 200 to 409600 comparative to background values with Qβ empty as antigen.

Conclusion: Thus, this novel QβMPER VLP can be used to monitor MPER- specific immune responses in clinical samples. In addition the QβMPER VLP can be used as immunogens either alone or in combination with other strategies for the induction of MPER specific immunity against HIV-1.

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