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Challenges and Prospects of Anti-Rabies Vaccines Production in Nigeria

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Abstract

Rabies is one of the oldest known viral zoonosis and remains a serious public health hazard, especially in the developing countries. It is the major viral disease in humans living in the tropics, but it is enzootic worldwide. Though its hundred percent preventable, it is estimated to cause 55,000 deaths annually, at a minimum, because appropriate therapy and preventive measures are not available in most developing countries. Exposure to rabid dogs is responsible for about 90% of reported cases of human rabies in the world each year. Effective control, prevention and eradication of rabies in man and animal can only be realized by immunization. Despite concerted efforts to develop and produce anti-rabies vaccines for protection of man and animal against rabies since 1919 in Nigeria, successful achievement of effective control and prevention of the disease through vaccination is greatly hampered by poor or lack of modern technology and facilities required for development and production of safe and effective vaccines. High cost of development and production, poor electric power supply, poor policy implementation by governments, poverty and gross lack of awareness are other major constraints encountered in rabies vaccinology in developing countries including Nigeria. Recent advances in tissue culture technologies, genetic engineering and peptide chemistry have made it possible to design and produce large quantities of pure antigens. This is a far reaching prospects for the development and production of life-saving vaccines for humans and animals. This approach aims at development and production of safe, effective, potent, and inexpensive anti-rabies vaccines with longer shelf life, greater quantity in terms of volume of vaccines produced and short immunization schedule than the trial and error approach by which vaccines were developed, produced and used in the past.

Keywords: Rabies; Anti-rabies vaccine; Production; Challenges; Prospects; Nigeria

Introduction

Rabies is a rapidly progressive and uniformly fatal viral meningoencephalitis in humans caused by the rabies or related group of Rhabdoviridae, in the genus *Lyssavirus* [1]. All mammals are susceptible to rabies, although canine rabies presents the greatest threat to humans, especially in Latin America, Asia and Africa. Despite the fact that rabies is under-reported worldwide, it is estimated to cause 55,000 deaths annually, at a minimum [2]. Exposure to rabid dogs is responsible for about 95% of reported cases of human rabies in the world each. It is the major viral disease in humans living in the tropics, but it is enzootic worldwide.

Over the years, several types of anti-rabies vaccines have been developed, produced and used for protection of man and animal against rabies. Pasteur's basic approach to vaccine development such as attenuation and inactivation are still key pillars of vaccinology. In modern technology however, purification of target microbial components, genetic engineering and enhanced knowledge of immune defence to enable creation of attenuated mutants, expression of vaccine proteins and polysaccharide [3] have evolved over the years. Five groups of fixed strains of rabies virus are used globally today to produce the diverse kind of rabies vaccines, particularly in cell culture, for human use [3]. The Pasteur-derived strains of rabies virus are the most predominantly used for the production of traditional vaccines of the Semple or Suckling Mouse Brain (SMB) types, but also for the production of modern cell culture vaccines such as Human Diploid and Purified Vero Cell vaccines (HDCV and PVRV) [4]. Generally, vaccines are categorized into: Attenuated or modified live virus (MLV) vaccine; Killed or inactivated virus vaccine; Vaccine grown in brain tissue of adult sheep, rabbit or brain of new born mice, rats or rabbits; Embryonated chicken or duck egg-based vaccine and modern tissue culture based vaccine (MTCV) [5]. Hunt [6] also described four basic types of vaccine in use today.

In Nigeria, the MLV Low Egg Passage (LEP) and High Egg Passage (HEP) flurry strain vaccines were first produced in chick embryo in 1956 and in 1970 for dogs and for cats respectively [7,8]. These are produced only by the National Veterinary Research Institute (NVRI) Vom in Plateau State, Nigeria, which is the national laboratory saddled with the mandate to develop and produce animal vaccines in the country. Despite these early interventions however, previous research finding have shown that dogs succumbed to clinical rabies after previous vaccinations [9,10].

Challenges

The greatest challenge in the industry of anti-rabies vaccine production for both humans and animals, especially in some developing countries, is little or non-availability of modern technologies in order to transit from production of nerve tissue vaccine (NTV) to the tissue culture (MTCV) [11] or sub-unit vaccines. For instance, due to presence of high content of myelin of the adult brain tissue in Semple vaccine (NTV) there is a high incidence of neuroparalysis after usage of the NTV [11,12]. NTV is not only paralyticogenic, it is less convenient, less immunogenic, more reactogenic, less tolerable and less acceptable. In addition, more number of doses is needed and the administration of which comprise comparatively a painful procedure. MTCV however is more antigenic, acceptable, well tolerated, and convenient with less

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reactogenicity [11]. Another constraint is that encephalitis in puppies aged below 3 weeks of age [13] and lack of immunologic response in puppies below 11 weeks of age were listed as the draw backs of the MLV vaccines. It was also said to have short shelf life [14]; and responsible for vaccine-induced rabies in dogs [8], which led to the withdrawal of such vaccines in most developed countries [15].

In Nigeria, another important constraint of rabies vaccine production is high cost of materials, reagents, biological, chemicals, consumables and other supplies. The cost of procurement and maintenance/servicing of equipment such as safety cabinets, dispensing/capping machines, freeze-drying machines, labeling machines, incubators and freezers, to mention a few, can be alarming. The costs of tissue culture used in the production of the tissue culture based vaccines can also be enormous. Acytlethyleneimine and betapropiolactone used for its inactivation are usually very high. In Nigeria, where embryonated chicken or duck eggs are utilized for the attenuation and production of both vaccine seed virus and finished vaccine, the eggs are relatively expensive, though affordable. As there are no facilities available to raise and maintain specific pathogen free breeder stock of poultry for this purpose, it then becomes mandatory to stock and maintain at least a flock of minimally-disease-free birds or procure the embryonated eggs from reputable sources.

As in most developing countries, there are serious challenges with provision of constant electric power, which is an inevitable requirement in any facility where vaccines are produced, stored, handled and transported on industrial scale in Nigeria. Where central nationwide (National grid) supply of electricity is not possible as is the case in many parts of Nigeria today, local generation of power becomes inevitable for production, storage and transportation of vaccine at adequate conditions. The cost of such local generation of power can most times be outrageous. This eventually translates to increase in cost of production and finally increase in the cost of the product.

One other basic difficulty is that the economic demand for vaccines bears no relation to the social pay-off [16]. From a commercial standpoint, the total vaccine market here, in Nigeria and abroad is small. The world's poor, whose children have the greatest need for vaccines, cannot afford to purchase them at market prices.

Cost of vaccines is another problem, as new vaccines require not less than \$300 - \$800 million to develop, and the companies doing the research and development must first recover this cost [3]. To alleviate this problem therefore, support from governments and donor agencies to purchase the vaccines for developing countries is necessary [17]. In addition, establishment of vaccine production facilities in developing countries or subsidizing the cost thereof for major manufacturers of vaccines situated in developed or developing countries is necessary, to ensure both availability and affordability of the product to targets. Generally, there is a growing demand for vaccine safety worldwide. One of the advantages of the newer molecular technology is improved safety, although zero risk is not possible [3].

In Nigerian situation, a study carried out by Adeyemi et al. [18], revealed an over 66.0% increase in the cost of anti-rabies vaccination in dogs between 1995 and 2002 in university of Ibadan, Nigeria, where over a period of ten years, vaccination coverage was only 10.5% as against 70% recommended by WHO [19]. From the same study, it was observed that the vaccination coverage was much lower than it was the previous 5 years. This, as in many other cases is an index of low patronage and usage of the available anti-rabies vaccines in the country,

including imported foreign and the LEP and HEP produced locally in the country. The sole cause of low patronage and hence low vaccination coverage is basically lack of awareness, poverty and sometimes lack of political will by government authorities.

Another major challenge to be contended with in anti-rabies vaccine development and production in developing countries like Nigeria is absence of enforcement of registration and compulsory vaccination of dogs, free or subsidized vaccine/vaccination cost, regular mass vaccination campaigns and creation of awareness on rabies among the populace [20,21]. These result to low patronage of vaccines, and adversely affect production turnover and impetus to embark on developmental research activities. Rabies Immunoglobulin (RIG) is commonly avoided by medical practitioners in Asian countries, leading to treatment failure in the fear of reactogenicity [11]. In some cases, especially in Nigeria, RIG is not available for procurement and use in post exposure management of rabies. These, unknown to the target population, will be presumed to be as a result of outright vaccine failure, leading to loss of confidence in the vaccines, medical personnel and facilities; and subsequently loss of patronage, which will directly be detrimental to any vaccine production industry. Vaccines produced on outdated technologies, such as adult animal brain cultures were used contain myelin, which can provoke a demyelinating immunological disease [21] in the recipients. Compared with modern rabies, cell-culture vaccines, the nerve tissue-based vaccines are more reactogenic and may cause severe, even fatal, encephalitis and polyneuritis. Furthermore, NTVs are less potent and require a higher number of painful doses.

Prospects for Vaccine Development

Recent advances in genetic engineering and peptide chemistry have made it possible to design and produce large quantities of pure antigens - the basic building blocks of vaccines [16]. This implies that, the advent of molecular biology and genetic engineering has played dramatic role on vaccine development [3]. This provides higher opportunities for construction of inactivated antigen and for rational attenuation of organisms through direct mutation. The first successful genetic engineering was with hepatitis B vaccine manufactured in a yeast recombinant carrying the gene for the S protein which replaced a vaccine based on purification of S particles from plasma of infected individual (Diamond, 2011). If scientists can find the antigen of the infecting organism that stimulates immunity, it will probably be possible to produce an effective vaccine (Freeman and Robbins, 1991). It has also been reported that physician-scientists are creating new DNA vaccines that hold great promise for fighting disease more effectively, with fewer side effects [22]. However, the new vaccines are expensive, and funding for the project can be hard to find [3,22]. These design approaches are replacing the trial and error by which vaccines were developed in the past [16].

New anti-rabies vaccine development is aimed at producing safe, effective, and inexpensive vaccines that can be given with a short immunization schedule. Several prospective vaccines are in various stages of development. A purified chick embryo cell vaccine [23] has been shown to induce antibodies in monkeys and to protect guinea pigs from disease after parenteral rabies virus challenge. The vaccine is inactivated using beta-propiolactone, and is purified and concentrated by continuous zonal centrifugation. This is becoming a standard technique for removing allergenic materials from vaccine preparations. Highly purified and concentrated forms of the standard duck embryo

vaccine (DEV) also were being developed [24]. These appear to be more immunogenic and less allergenic than their predecessors, allowing a reduced vaccination schedule. DEV has the advantage of being relatively inexpensive.

Tissue culture techniques have long been used in studies related to rabies virus, and there are now a number of continuous cell line (BHK-21, MNA VERO and CER) used in research on pathogenesis, vaccine production and diagnosis of rabies [25,26]. Cell culture rabies vaccines are cleaner, devoid of egg lipids and proteins. It is more potent with longer shelf life and will give greater quantity in terms of volume of vaccines produced. An alternative cell culture medium is a continuous, aneuploid cell line derived from the vervet monkey kidney, called Vero [21]. This process allows higher yields of vaccine antigens than the HDCV approach and may be cheaper and more appropriate for use in the developing world (Ghosh, 2005). The last mentioned category of rabies vaccines are currently produced and used in most developed countries, while the live attenuated dog and cat anti-rabies vaccines are still in use in Nigeria. However, [24] reported a finding that strongly suggests that attenuation of Flury virus results from the harmonic co-evolution of G and L elements could be important information for the generation of safer and more effective modified live rabies vaccines. For example, the Ethiopian Health and Nutrition Research Institute manufactured a safe Vero cell culture based rabies vaccine "ETHIORAB" [27] which is safe and showed rabies neutralizing antibody titre higher than the 0.5 IU/ml mandated WHO threshold [28]. This is an indication that there is very good hope for Nigeria and other developing countries to improve on the present position with regards to modern rabies vaccine production technologies for effective control of rabies.

Correction of discrepancy of the G protein produced using recombinant DNA technology [29] by site-directed mutagenesis appears to be possible [30-32], which suggests that it may be possible to develop a totally synthetic rabies vaccine using this technique. Such a vaccine would contain neither whole virus particles nor the reactogenic components of cell culture vaccines. Thus, inactivation procedures would be unnecessary, and less complex purification techniques might be possible. A recombinant vaccinia virus expressing the rabies G protein has also been developed [33]. Inoculation of mice with the altered vaccinia vector virus induced immunity that was protective even against severe intracerebral challenge with live rabies virus [31]. This is another promising vaccine candidate.

Nel et al. [34] documented the construction of four DNA vaccines from the glycoprotein (G) and nucleoprotein (N) genes from a South African Mokola virus for immunization against Mokola virus. Two of the single G-expressing DNA vaccines (based on pSG5 and pCI-neo, respectively) protected laboratory mice against lethal challenge; Serological detection of virus-neutralizing antibodies post immunization, which titre increased upon administration of booster dose, gives a good prospect for advances in production of anti-rabies as well as anti-rabies related viruses vaccines for both animal and human use. DNA vaccines have been tested for their efficiency in several animal species and it has been found to offer protection comparable with those obtained with the inactivated vaccines [35-37]. The results of the study conducted in mice, showed that a single administration of the rabies DNA vaccine may be as effective as at least five injections of the cell-culture-derived vaccine [38]. Vector vaccines were found capable of inducing an immune response in dogs [39,40]. A recombinant rabies virus vaccine carrying two identical glycoprotein (G) genes (SPBNGA-GA) has also been constructed [41].

Conclusion

Vaccines developed over the first 2 centuries since the lifetime of Edward Jenner has greatly achieved reductions of infections and disease wherever utilized. Leius Pasteur's early approach to vaccine development was attenuation and inactivation. But today, purification of microbial elements, genetic engineering and improved technical knowhow of immune protection gives room for attenuation of mutants, expression of vaccine proteins in live vector, purification and synthesis of microbial antigens and induction of a variety of immune response through DNA, RNA and proteins manipulations. Both infectious and noninfectious diseases are now within the realm of vaccinology [3,42-47]. These new developments however come with their attendant problems, in the production, regulation and distribution of vaccines. In the middle of the 20th century, cell culture was adapted to virus growth, attenuation and eventual development of numerous attenuated virus vaccines [3,48-50].

The idea of complete inactivation of microorganisms as a means of vaccine development started in the 20th century. Although it is clear that prospects for control of disease by vaccination are bright, but it is not without its attendant problems such as limited supply of vaccine – this occurs mainly in the developed countries because there are a few manufacturers, and regulatory pressures makes production more difficult. Consequently, the growth of new manufacturers in the developing countries of India, china, Brazil Indonesia, etc., will go a long way to reduce this gap [3,51,52]. Developing countries, including Nigeria therefore, have prospect improving animal anti-rabies vaccine through transfer of existing modern technologies of vaccine development and production for the effective control of rabies in the country.

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