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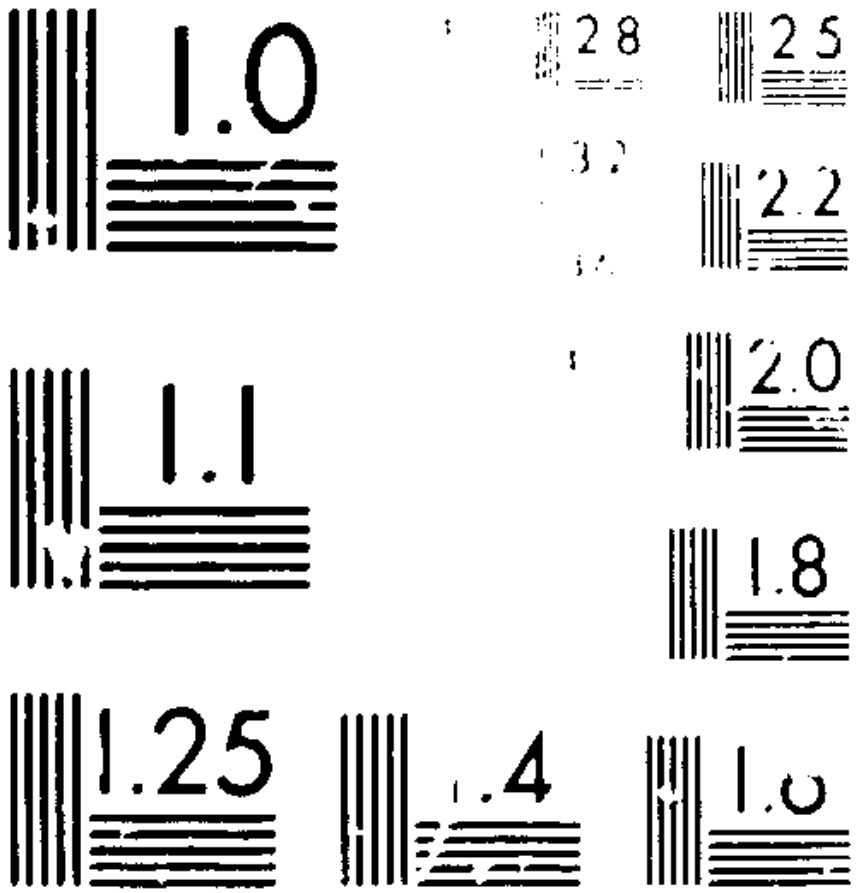
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Distr.
LIMITED

UNIDO/IS.273
30 December 1981

UNITED NATIONS INDUSTRIAL
DEVELOPMENT ORGANIZATION

ENGLISH

THE POTENTIAL OF GENETIC MANIPULATION FOR THE IMPROVEMENT OF VACCINES AGAINST ANIMAL DISEASES IN DEVELOPING COUNTRIES*

prepared by

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V.81-33838

INTRODUCTION

Any assessment of the priority for attempting to control or eradicate an animal disease in a developing country must take into account two objectives:

1. To diminish or remove a disease handicap to the country's animal production.
2. To control disease of international importance so as to gain acceptance of products of animal origin in world markets.

The principal causes of animal disease in developing countries are bacterial, viral and protozoological pathogens plus external and internal parasites some of which are vectors of disease or others, by the burden of their infestation prevent the host from thriving. The contribution of the constraints on animal production of inadequate feed and feed supplements must also be taken into account. This broad base of the handicap to animal production and its constraint, must be appreciated in discussing what might be achieved by concentrating on one or other important pathogen.

VIRUSES

In the context of the potential of the application of genetic engineering (genetic manipulation, recombinant DNA technology, recDNA technology), the diseases for special consideration are those caused by viruses. There are a number of reasons for this. Virus diseases are important being characteristically more infectious than bacterial or protozoal diseases. Many viruses have a great ability for survival and so to surmount natural barriers between countries and continents thus complicating international trade. Of specific relevance is that genetic

engineering is more applicable and potentially more advantageous in the manipulation of viruses compared with bacteria or protozoa.

POTENTIAL ADVANTAGES OF recDNA TECHNOLOGY

Recombinant DNA technology if used in the preparation of viral vaccines should result in a product superior to those prepared by standard methods. Although no vaccine prepared by the expression of the specific immunogenic protein in a recipient bacterium is yet in commercial production, one can confidently speculate about the advantages of the procedure. These are:

1. The antigen is separated from the infective component of the virus thus obviating the risks of spreading infection during the manufacturing process by the handling of large volumes of the infective agent.
2. No inactivating process is required and any deleterious effect of that procedure on the antigen is avoided.
3. No test of innocuity of the vaccine is required, at least, in terms of residual infectivity.
4. The technically demanding large-scale culture of mammalian cells is not required, nor is the costly and sometimes sensitizing medium.
5. Any short-comings in potency may be overcome by scale of production.
6. Refrigeration to the same extent as for conventional vaccines may not be required for preservation of the potency of the vaccine during storage and distribution.
7. Production costs are likely to be cheaper rather than dearer, one saving being that high cost disease security buildings and effluent disposal plant are not required for a vaccine production unit.

There are other possibilities which are sufficiently attractive to warrant research. For example, it should be possible to prepare vaccines against pathogens for which vaccines cannot readily be manufactured by conventional methods. This is the case with infectious hepatitis in man. A number of viruses causing disease in animals are antigenically labile with numerous immunologically different strains, for example, foot-and-mouth disease, African horse sickness and bluetongue. The synthesis of a novel protein by the assembly of nucleotide sequences might provide an antigen giving wider coverage against antigenic variation than could be provided from a selection of virus isolates.

THE MAJOR DISEASES OF LIVESTOCK

In listing the so-called major diseases of livestock, it is important to understand the criteria being used in selection. For example, rinderpest is a disease of cattle of great antiquity and it was formerly the cause of disastrous losses in Asia, Europe and Africa. The success of programmes for its control and eradication has been such that it is no longer considered to be important in many previously affected countries. Nevertheless, no list would be complete without it. There is still sufficient endemic disease present for it to constitute a threat, especially in Africa. Some diseases have an importance within a limited geographical area and other diseases, although widespread, do not have too serious an impact on animal production. There are also those infections that are ubiquitous but the importance of which becomes greater as animal production becomes more intensive and the major diseases are controlled. Examples are mastitis, enteric infections and respiratory infections caused by a variety of bacteria, mycoplasms and viruses. Taking these considerations into account, an attempt to summarise the situation is given in Table 1. There now follows a series of notes on each of the diseases cited.

Foot-and-Mouth Disease

Foot-and-mouth disease (FMD) is the cause of severe economic loss due to its immediate effects on the diseased animal population and due to the severe constraints that its existence engenders on international trade in animals and products of animal origin. Its importance is compounded by being highly infectious with seven distinct immunological types each possessing a spectrum of antigenic variation. The major countries or regions of the world which are free of the disease are Canada, the United States of America, Mexico, the countries of Central America including Panama, the Caribbean, much of Western Europe, Japan, Australia and New Zealand. The disease is endemic in South America, Africa, much of Asia, and still in a few European countries.

The use of FMD vaccine in well-organized programmes of control in Western Europe reduced an annual incidence of some thousands of outbreaks a year in the late 1950's/early 1960's to the virtual elimination of the disease within ten years. During the last few years it has become an inescapable conclusion that of the few outbreaks of FMD that have occurred, some have been due to residual infectivity in inadequately inactivated vaccines. This provides an incentive for the use of recDNA technology for the preparation of an absolutely non-infective product.

The market for FMD vaccine in South America, Africa and Asia can be measured in hundreds, if not in thousands of millions of monovalent doses. In most of the endemic areas, it is necessary to use a trivalent vaccine which has to be administered two or three times a year. It cannot be concluded that a recDNA vaccine would make it possible to adopt a less frequent schedule of vaccination, although this could be a consequence of high potency being achievable by an increased antigen content, provided good expression can be readily obtained of all the necessary antigens. It must be emphasised, however, that a genetically

engineered vaccine must be at least as good as the standard inactivated virus vaccine based on cell culture for production of the antigen.

Most information on the FMD situation in all its aspects is available for the countries of South America due to the coordinating, technical assistance and training activities of the Pan American Foot-and-Mouth Disease Center, Rio de Janeiro, Brazil. Although FMD vaccine had been used on a small scale in Argentina, Uruguay and Brazil in the late 1940's and in the 1950's, it was not until the 1960's that national programmes of control began to become established in the majority of the countries. These programmes were subsequently greatly strengthened by the financial support of the Inter-American Development Bank. During recent years it has been possible to begin to see the impact of these programmes. Chile is now in a very favourable situation with only a very few outbreaks restricted to cattle imported for slaughter during the last three to four years. The incidence of FMD in Uruguay is kept down to a relatively low level in much of the country, excepting the areas in the neighbourhood of its border with Brazil which forms no geographical barrier. Great improvement has been brought about in Argentina during the last two years in the effectiveness of the FMD vaccines by the Government's imposition of more realistic standards of quality control. A number of areas in a number of the countries of South America can be identified as being free of FMD and there is a growing recognition of the importance of regional coordination, one of the primary aims of the Pan American FMD Center. This is now further exemplified by the active existence of the South American Commission for the Control of Foot-and-Mouth Disease (COSALFA) and the recently created Animal Health Program of the Inter-American Institute for Cooperation on Agriculture (IICA).

Current progress in the development of a genetically engineered FMD vaccine

During the last three years a number of the research institutes and vaccine production companies in this field have begun work on the production of a genetically engineered FMD vaccine. Messenger RNA has been translated into DNA, the nucleotide sequence of the immunogenic viral protein (VP1 in Europe, VP3 in the USA) has been expressed in E.coli, the resulting protein has been shown to stimulate a specific antibody response in susceptible animals. This work is in progress in Germany, France, England, Argentina, Brazil and the USA. Most progress has been achieved by the USDA Plum Island Animal Disease Center/Genentech collaboration with, so far as available information indicates, a substantial lead having been built up.

Rinderpest

Rinderpest was eradicated from Western Europe before the end of the last century, for example, from the United Kingdom in 1377. This was achieved by the compulsory notification of outbreaks, by control of animal movement, by control of importations, and by the slaughter of affected animals which was long before the aetiology of the disease was understood and the viral cause determined. In the endemic areas of Africa and Asia, the first possibility for the protection of susceptible cattle by immunisation was being investigated some eighty years ago using the serum-virus method. The further investigation of this by Edwards in India in the late 1920's led to the development of the goat virus vaccine, namely, a live vaccine using virus passaged in goats with a consequential loss of pathogenicity for cattle. The availability of this vaccine stimulated the initiation of control programmes in Asia and Africa but always complicated by unacceptable reactions in the more susceptible cattle, either because of breed or because of epidemiolcgical considerations. Other methods of attenuation were sought with

success using passage in rabbits, in chick embryos and in cell culture. The ultimate success was the production of the cell culture vaccine of Plowright and Ferris (1959). The subsequent mass vaccination on a continental scale that then became possible in the 1960's led to a great contraction of the endemic areas of the disease. These are now confined to northern equatorial Africa and to India. Furthermore, there is no reason why these remaining pockets of infection could not be eliminated with the correctly organized application of the required and known resources.

Rinderpest is caused by a paramyxovirus, the strains of which of whatever origin are immunologically homogenous. The present vaccine is effective and being a lyophilized product it has, thus, some tolerance with regard to the conditions for storage and distribution. There would appear to be no advantage in attempting to produce a rinderpest vaccine by the application of the recDNA technology.

Rabies

The virus of rabies affects wild animals, domesticated animals and man. Its epidemiology is characterised by distinct climaxes in a number of wildlife hosts with an identifiable geographical location. For example, fox rabies in Europe; Arctic fox, skunk, bat and raccoon rabies in North America; vampire bat rabies in Central and South America; mongoose rabies in the Caribbean and South Africa, etc. The most dangerous epidemiological situation for man is urban rabies in dogs.

From the point of view of animal production, the most important climax is that of the vampire bat and cattle, especially in South America. A recent assessment of the economic losses in cattle production due to bat transmitted rabies amounted to some US $ 28 million per annum.

Control of rabies

Since the days of Pasteur, vaccination in man has been predominantly used as post-exposure treatment. Pre-exposure immunisation is of more recent date and is now very effective by the use of cell cultures for production of the antigen. The pre-exposure vaccination of animals has a much longer history particularly in dogs and cats. Mass vaccination of dogs was first practised in Japan in the 1920's. Modified live virus vaccines, for example, the Fleury vaccines prepared from viruses passaged in chick embryos. In spite of inactivated virus vaccines and live virus vaccines being available for more than thirty years, the vaccination of cattle against bat-transmitted rabies in Central and South America has now been widely adopted. Such vaccine as is used in cattle would now appear to be the more potent cell culture vaccine. If this produces a more easily appreciable impact on the disease, the greater use of vaccine may be encouraged.

Genetically engineered rabies vaccine

Work is proceeding in a number of laboratories on what is a good candidate virus for the development of a genetically engineered vaccine. The advantage of rabies virus is its antigenic homogeneity. If this development is successful and if large volumes of potent vaccine can be relatively cheaply produced, the opportunity is provided for achieving much more effective control of bat-transmitted rabies in cattle.

Vesicular stomatitis

Vesicular stomatitis is a vesicular disease, mainly of cattle but also affecting horses and pigs, clinically indistinguishable from foot-and-mouth disease. It occurs only in the Americas and largely within the latitudes of the tropics, i.e.

in the southern States of the USA, Mexico, Central America, Panama, Colombia. Venezuela, Ecuador and Peru. From time to time extensions to the north or south occur with very infrequent outbreaks beyond the normal extremities of its range, i.e. in Canada and in Argentina. Vesicular stomatitis has a double importance, firstly, the necessity to make a laboratory diagnosis to ensure that it is not foot-and-mouth disease in the countries free of FMD; and, secondly, the fact that severe economic loss can be caused especially in dairy herds due to the frequence of vesicular lesions on the teats.

There are two immunologically distinct virus types, Indiana and New Jersey, with considerable antigenic variation within the Indiana type. The epidemiology of the disease is complex with the various modes of transmission not yet fully understood and with the persistence of antibodies in a wide variety of forest mammals, farm livestock and man in the endemic areas of the lowland forested tropics of the Americas.

Live virus vaccines and inactivated virus vaccines have been prepared and tested in the field on a limited scale but a general policy of vaccination throughout the endemic areas has never been pursued.

The ready availability of an effective vaccine would be an incentive for action and the potential of genetic engineering to achieve this merits consideration.

Bluetongue

Bluetongue is an insect-transmitted virus disease of ruminants, principally of sheep, which was apparently confined to Africa until the early 1940's, although it has since occurred in the Mediterranean, the Middle East, Southern Europe, Pakistan and India, and in the most important endemic area other than Africa,

namely, the USA where it can be found in sheep and cattle in most of the States. The virus was recently isolated in Australia and antibodies have been detected in the nearer territories of South-East Asia.

The virus is strongly polyvalent with twenty or more types. Vaccination is used in control with both live virus and inactivated virus products being available. The live, attenuated virus vaccine is the more frequently used. The problem of the multiplicity of virus types is overcome to a limited extent by, for example in South Africa, using three polyvalent vaccines each containing five of the virus types. The use of genetic engineering in this situation justifies investigation in the hope that a synthesised antigen might provide a wider antigenic coverage than any one field type. This is the subject of research in the USA and in South Africa.

Hog cholera

Hog cholera or swine fever is a highly infectious virus disease affecting solely swine. It has a world-wide distribution although it has relatively recently been eradicated from Australia (1962), Canada (1963), United Kingdom (1966), Japan (1975) and the USA (1976).

In the 1940's and 1950's the losses due to hog cholera in the USA were estimated to be of the order of US $ 30 million to 40 million per annum. Vaccination is used in the control of the disease. The older inactivated virus vaccine has been largely replaced by an attenuated live virus vaccine. There is no plurality of virus type and, for the same reasons as cited in the case of rinderpest vaccine, consideration of the application of genetic engineering for vaccine production has not an obviously high priority.

African swine fever

The virus of African swine fever has, presumably for centuries, successfully parasitised the indigenous wild swine population of Africa by the maintenance of infection in the absence of clinical signs of disease. This has been with the active participation of the soft tick Ornithodorus moubata. The most important of the wild swine in this context is the warthog, but the bush pig and the giant forest hog have also a minor role in the epidemiology of the disease. The presence of this infection of the wild pig population in Africa became apparent only with the introduction of the European domesticated pig into East and South Africa about the beginning of this century. From about 1910, outbreaks of disease with a mortality of up to 100 per cent began to occur in Kenya in the domesticated pig. As domesticated pigs were introduced into other African territories south of the Sahara, so did African Swine fever become a problem. It was not until 1957 that the first outbreak of the disease occurred outside the African continent. This was in 1957 in Portugal. The transport of the infection was accepted as being related to the inadequacy of the procedures for the disposal of food residues from aircraft flying between Angola and Portugal. It is not relevant to this report to describe in detail the further spread of African swine fever. It is sufficient to record that since the appearance of the disease in Portugal in 1957, it was reintroduced in 1960 when it spread to Spain and it has since occurred in France (1964), Italy (1967), Cuba (1971), Malta (1978), Dominican Republic (1978), Brazil (1978) and Haiti (1979). A feature of the extension of the disease out of Africa is that the initial very high mortality in swine has tended progressively to decline to the extent of the appearance of apparently healthy carrier animals. A baffling problem is how to stimulate protection by the classic immunological procedures. All attempts have been unsuccessful or impracticable. RecDNA technology may be invaluable in new attempts to understand the immunological enigma of the disease. Work on this aspect is in progress in Spain but

as yet its possible application for production of a vaccine has not yet been reached. Control and eradication of the disease is solely dependent on rapid diagnosis and "stamping out".

African horse sickness

African horse sickness is an acute virus disease of equines causing a high mortality and transmitted by Culicoides species. It has been known for about two hundred years in South Africa. From time to time epidemics have occurred outside Africa especially in the Middle East where in 1956/61 over 300,000 horses, donkeys and mules died. There are nine distinct virus types and protection is by polyvalent vaccination with a lyophilised attenuated live virus vaccine.

As postulated in the case of bluetongue vaccine, recDNA technology might provide superior synthesised antigens.

Equine encephalomyelitis

Venezuelan, eastern and western equine encephalomyelitis are caused by arthropod-borne viruses. "Eastern" and "Western" refer to the USA. Considerable variation in the severity of the clinical signs occurs with each of three viruses. The western virus tends to be the less severe, clinically; the eastern virus is the most severe, pathologically; and the Venezuelan virus (VEE) is the most important as regards the developing countries. Periodic epidemics have recurred in Colombia, Ecuador, Peru, Trinidad, and Venezuela. In 1969 VEE appeared in Guatemala and thereafter in the other countries of Central America (not Panama), Mexico and the State of Texas in the USA. Each of the viruses may infect man. The epidemics of VEE can be very serious where horses, donkeys and mules are part of the agricultural economy. One such epidemic in one part of Colombia in 1967 was reported as causing the deaths of 27,000 donkeys and 40,000 horses and mules.

Control of the diseases is by vector control and vaccination. Inactivated vaccines against the eastern and western viruses have been used for many years. The extension of VEE from Guatemala northwards stimulated the development of an effective attenuated live virus vaccine by passage of the virus in cell culture (virus strain TC-82). A characteristic of these viruses, perhaps especially of VEE, is the inter-epidemic phase when the disease is of low priority. This is currently the VEE situation and it is not presently possible to assign a high priority in the genetic engineering field.

Three virus diseases of lesser importance affecting farm livestock, excluding poultry

1. Malignant catarrhal fever

A herpes virus infection of relatively widespread distribution but probably of most importance in Africa where wild game, especially the wildebeest (but also the hartebeest and the topi) are the cause of the transmission of the disease to cattle. If the practices of keeping livestock permit, the separation of the game from the cattle by fencing is an adequate control procedure

2. Pulmonary adenomatosis of sheep or Jaagsiekte

This disease is a lung cancer of sheep which is probably caused by a virus. Research in South Africa seeks to obtain a greater understanding of the aetiology of the disease and to propose methods of control. The possibility of genetic engineering providing a method of vaccine production is a high priority.

3. Aujesky's disease or pseudorabies

This is a disease of swine caused by Suid Herpesvirus 1. It is endemic in Europe and has become increasingly important where swine production has become increasingly intensified. It now occurs in the USA, South America, Australasia and Asia.

Recent studies of the benefit-cost analysis of programmes to eradicate Aujesky's disease have failed to establish a priority for such action, at least in the United Kingdom. Genetic engineering might provide the means to produce an effective vaccine.

Diseases of Poultry

Newcastle disease

Newcastle disease which is widespread in its distribution causes serious economic loss due to mortality and loss in egg and meat production. To these losses must be added the cost of control programmes especially if slaughter is practised with payment of compensation. Estimates of such losses are available for recent incidents, namely, U.K. - 1967/70, £20 million; Southern California, USA - 1971/74, US$ 56 million; Singapore - 1973, US $ 34,500,000.

Although differences between strains of Newcastle disease virus occur, for example, in virulence, there is no evidence of any plurality of antigens of significance in immunisation. Live and inactivated virus vaccines are available but experience indicates that no one vaccine is ideal for all situations and geographical areas. There may, therefore, be justification for turning to genetic engineering with the objective of producing massive quantities of antigen for preparation of a vaccine of higher potency than hitherto attainable by standard methods.

Marek's disease

Marek's disease is caused by a herpes virus and is characterised by the production of virus-induced tumours. It was earlier known as fowl paralysis. Also "acute leukosis" has been shown to be an acute form of Marek's disease. Its distribution is widespread but with the development of a live

virus vaccine, firstly produced by attenuation in cell culture and, later by passage in turkeys, it can be readily controlled. There is no obvious high priority to use genetic engineering for the development of a superior product.

Bacterial diseases

The bacterial diseases of greatest importance as far as their control and eradication are concerned are tuberculosis and brucellosis. Of secondary importance are clostridial infections, anthrax, bovine pleuropneumonia and leptospirosis.

Tuberculosis

There is no satisfactory method of immunisation for the protection of domesticated livestock against tuberculosis. There is a high priority for those responsible for recent advances in immunology to look again at tuberculosis and, in this reappraisal, genetic engineering may be relevant.

Brucellosis

The eradication of brucellosis does not depend, in the final result, on vaccination. The available vaccines, either strain 19 or strain 45/20 are reasonably adequate for their assigned role. Both, however, have disadvantages which would probably be eliminated by genetic engineering..

Clostridial infections

The Clostridial infections are caused by spore-bearing anaerobes and the specific diseases are best known as tetanus, butulism, gas gangrene, lamb dysentery, blackleg, braxy, pulpy kidney and struck. The animals most usually involved are sheep. The discovery of a means to protect animals or man against

infection with this group of organisms dates back to the last century. Behring and Kitasato (1890) first demonstrated the production of an antitoxin by the injection into animals of tetanus toxin. Similar advances were made with diseases also affecting animals but the most productive period was during the 1920's when most of the vaccines were developed which are now in successful current use, world-wide. These vaccines are effective and probably have the widest sale. It is not obvious how genetic engineering could improve what is a satisfactory situation but the mere following of an existing practice for some sixty years suggests that a new appraisal might be made with the potential of genetic engineering being borne in mind. The possible advantage might be in the synthesise of a novel antigen which might provide greater coverage than can be achieved by a multiplicity of vaccines.

Anthrax

A satisfactory vaccine is available and no improvement would appear to be necessary.

Bovine pleuropneumonia

In comparison with the animal diseases of the tropics and subtropics, bovine pleuropneumonia which is caused by Mycoplasma mycoides is of less than the highest priority. In the attempted development of a suitable vaccine one of the greatest difficulty has been the development of an adequate test of vaccine potency. Under these circumstances the possible use of genetic engineering is of low priority.

Leptospirosis

The presence of leptospirosis infection would appear to have more importance as an obstacle to the international movement of livestock than as an important indigenous disease.

Those circumstances, if substantial, provide no justification for becoming involved with genetic engineering.

Protozoal Diseases

Trypanosomiasis, Theileriosis, Anaplasmosis, Babesiosis and Coccidiosis are important protozoal diseases. Much further research is required before the stage is reached, especially with trypanosomiasis and theileriosis, before there is any prospect of identifying an antigen which, by genetic engineering, could be developed into an effective vaccine.

TABLE 1

Major Animal Diseases in Developing Countries

An assessment of the potential of genetic engineering for the improvement of vaccines

Disease	Category of Importance	Priority for genetic engineering in vaccine preparation
A. Viral Diseases		
Foot-and-mouth disease	1	High
Rinderpest	1	Low
Rabies	1	High - bat-transmitted rabie in cattle.
Vesicular stomatitis	2	Medium
Bluetongue	2	High
Hog cholera	2	Low
African swine fever	2	Unknown - high as a research tool.
African horse sickness	2	High
Venezuelan equine encephalomyelitis	2	Low
Malignant catarrhal fever	3	Low
Pulmonary adenomatosis	3	High
Aujesky's disease	3	Medium
B. Viral Diseases of Poultry		
Newcastle disease	1	Medium
Marek's disease	2	Low
C. Bacterial Diseases		
Tuberculosis	1	High
Brucellosis	1	Low
Clostridial infections	1	Low
Anthrax	2	Low
Pleuropneumonia	2	Low
Leptospirosis	3	Low

Table 1, Cont'd.

D. Protozoal Diseases

Trypanosomiasis Theileriosis Anaplasmosis Babesiosis Coccidiosis	)	These diseases, especially the first two, are of great economic importance in Africa. The progress of research has not yet arrived at the point at which vaccination is feasible. This will come but when it does, many consequential problems will have to be evaluated before deciding upon the correct strategy.