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DIARRHOEAL DISEASES CONTROL PROGRAMME

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Report of the First Meeting of the

SCIENTIFIC WORKING GROUP ON BACTERIAL ENTERIC INFECTIONS: MICROBIOLOGY, EPIDEMIOLOGY, IMMUNOLOGY, AND VACCINE DEVELOPMENT

(Geneva, 21 - 24 April 1980)

CONTENTS

The first meeting of the Scientific Working Group on Bacterial Enteric Infections: Microbiology, Epidemiology, Immunology, and Vaccine Development of the WHO Diarrhoeal Diseases Control (CDD) Programme was held in Geneva from 21 to 24 April 1980. The participants are listed in the Annex.

1. BACKGROUND

The participants were briefly informed about the evolution of the two components of the CDD Programme: the implementation, or health services delivery component, in which WHO was cooperating with Member States in the establishment of national CDD programmes within the context of primary health care, and the research component, which was designed to improve methods of delivery of treatment and control strategies and to develop new tools for prevention and treatment.[1] It was universally felt that the research component should have a problem-oriented approach, especially since the funds available were limited.

Under the research component, nine Scientific Working Groups and Sub-Groups had met on a one-time basis between August 1978 and March 1980 to review available knowledge in specific areas and to define global research priorities.[2-10] Similar meetings had been convened by the WHO Regional Offices to define regional research priorities. These meetings had laid the groundwork for the research component of the Programme.

In January 1980, the Programme's second Technical Advisory Group (TAG)[11] had recommended that the research component be managed on a permanent basis through a peer review mechanism using Scientific Working Groups (SWGs) and Steering Committees (SCs); global SWGs (GSWGs) should be constituted to manage basic research that could best be managed at the global level, while regional SWGs (RSWGs) or analagous bodies should deal with operational or applied research that was closely linked with national CDD programme implementation. The present GSWG was the first to be convened under this new management structure.

2. TERMS OF REFERENCE

The Group reviewed the terms of reference of SWGs and their SCs as recommended by the second TAG.[11]

2.1 Scientific Working Groups

The specific responsibilities of SWGs include:

- reviewing existing knowledge;
- designating areas where research is needed (i.e., gaps in knowledge);
- recommending approaches that should be adopted to fill the identified gaps, with due regard to their feasibility and cost;
- preparing a clear research plan that identifies the approaches and activities to be undertaken to provide new knowledge.

It was envisaged that while the final objective(s) of an SWG would rarely change, the feasibility and priority of various research approaches could be modified as progress was made, new information was obtained, and new problems emerged. Such decisions would be reflectd in the research plan, which was the basis for the activities of the SWG.

2.2 Steering Committees

The Steering Committee is responsible for the management and execution of the research plan and activities of its respective SWG. Its terms of reference include:

- identifying scientists/institutions to formulate and carry out research projects;
- reviewing the relevance, scientific quality, and budgets of all proposed research projects;
- identifying and developing research training opportunities within the research activities of the SWG;
- evaluating the technical and scientific progress of each research project supported by the SWG and recommending its continuation, revision, or termination;
- identifying and developing institutional strengthening opportunities to support the research activities of the SWG;
- preparing an annual budget;
- preparing an annual status report;
- coordinating the work of the SWG with other elements of the CDD Programme and with other research activities relevant to the work of the SWG.

The SWG agreed that its SC would initially consist of five members (Dr J.P. Craig, Dr J. Holmgren, Dr M. Merson, Dr S.C. Pal and Dr B. Rowe) while recognizing that it might be necessary to add additional members depending on the number of proposals received and eventually supported.

3. RESEARCH PLAN FOR THE SCIENTIFIC WORKING GROUP, 1980-1984

The Group developed a five-year work plan (Figures 1-4) for research. It recognized that not all the activities listed applied to all the bacterial pathogens under consideration by the Group.

4. RESEARCH PRIORITIES

The Group reviewed the research priorities recommended by earlier SWGs and Sub-Groups that were relevant to its work[2,5,6,8,9] and prepared a list of specific research topics that it felt should receive priority for funding by the SC in the next three years. These topics were ranked at three levels of priority based on the following criteria: the extent of the problem to be studied, the chances of early success in its solution given the limited funds available, and the availability of good research workers with an interest in the problem. (Note: these criteria and the priorities listed reflect the opinion of this specific SWG and are not meant to suggest universally applicable research priorities for adoption by other national or international bodies.)

The priority topics are listed below with their corresponding rank (1 to 3, in descending order):

Rank

4.1 Vibrio cholerae 01 - epidemiology and microbiology (see also 4.8)

4.1.1 Epidemiology of cholera. Some of the epidemiological characteristics of cholera require more extensive study, especially in endemic areas. For example, in parts of Asia (e.g., Bangladesh and India), the reasons for its seasonal pattern remain unexplained. On the African continent there have been few systematic studies of its modes of transmission, though those that have been carried out suggest that the disease may be spread by direct person-to-person contact. In most areas where the age-incidence of cholera has been studied, it has been found for unknown reasons that the disease is rare in infants. 1

4.1.2 Extra-human ecology. The ability of cholera vibrios to survive and multiply in different environments needs to be clarified. These studies should also investigate the differences in survival ability between the classical and El Tor biotypes of Vibrio cholerae 01, so-called atypical V. cholerae 01 (i.e., non-toxigenic or hypotoxigenic strains), and non-01 V. cholerae. Special attention should be paid to the possible association between V. cholerae 01 and plants, aquatic organisms, sediments, or other specific microhabitats. Such studies should also assess the effect of specific environments on the virulence factors and antigenic and biochemical characteristics of V. cholerae 01. 1

4.1.3 Phage-typing schemes. Experience with other enteric bacteria has shown that precise phage-typing schemes can be useful in studying their epidemiology. Therefore, the current phage-typing schemes for V. cholerae 01 should be reassessed and further developed with the aim of achieving a scheme that is internationally acceptable. 2

4.1.4 Atypical V. cholerae 01. It needs to be determined whether the so-called atypical V. cholerae 01 strains that have been isolated from the environment in a number of geographical areas are capable of causing disease in man. If evidence of their pathogenicity is obtained, the mechanisms of pathogenesis should be elucidated. 3

4.2 Vibrio parahaemolyticus

4.2.1 Pathogenesis. Although it has been demonstrated that disease is associated with the heat-stable haemolysin, the mechanism(s) by which this organism causes diarrhoea is not known. Attempts should be made to determine the factors responsible for the organism's adherence to the bowel mucosa and the production of diarrhoea, with special attention to the possible role of enterotoxin(s). 2

4.3 Non-01 Vibrio cholerae and group F vibrios

4.3.1 Pathogenesis. These organisms have occasionally been reported as causative agents of diarrhoea but their overall significance as pathogens remains to be established. If they are found to be of importance, there will be a need for studies of the pathogenic mechanism(s) involved, especially with regard to the identification and characterization of cholera-like and other enterotoxins. 3

4.4 Enterotoxigenic Escherichia coli (ETEC) - epidemiology and microbiology (see also 4.8)

4.4.1 Enterotoxins and enterotoxin tests. The current tests for the detection of ETEC enterotoxins - heat-labile (LT) and heat stable (ST) - are not suitable for routine use in most laboratories; this applies especially to the ST enterotoxin, for which an immunological method is needed. Simpler tests are needed for the detection of these toxins, especially ones that do not require tissue culture or animal facilities (bioassay). 1

Rank

Recent work in ETEC-infected pigs indicates that there is a second type of ST enterotoxin (STb) that has not as yet been identified in ETEC-infected humans; the possible importance of STb in human ETEC infection needs investigation.

4.4.2 Epidemiology. While there is good evidence that ETEC are important causes of diarrhoea in many developing countries, there have been few systematic studies of their epidemiology. Studies are needed to define the modes of transmission, the frequency of serogroups related to toxin type, and the relationship between ETEC disease in man and animals. 1

4.5 Enteropathogenic E. coli (EPEC)

4.5.1 Epidemiology. Outbreaks of infantile enteritis due to EPEC, once common, are now rarely observed in the developed countries. The reasons for this decline, and the role of EPEC as a cause of sporadic or epidemic infantile enteritis in developing countries, require study. 2

4.5.2 Pathogenesis. Little is known about the pathogenesis of EPEC diarrhoea or the virulence factors of EPEC. Preliminary evidence suggests that a "toxin" may be responsible for the disease and a possible adhesive factor has been described. Research into these areas should be extended. 3

4.6 Enteroinvasive E. coli (EIEC)

4.6.1 Epidemiology. Available data from a few countries indicate that EIEC are restricted to a limited number of serogroups. Studies are needed to confirm this observation in other geographical areas, especially in developing countries. These studies should also define the etiological importance and epidemiological features of EIEC. 2

4.7 E. coli with other pathogenic mechanisms

Pathogenesis and epidemiology. Recent evidence suggests that there may be at least one other mechanism (i.e., cytopathic) by which E. coli can cause diarrhoea. Further study is needed to evaluate this and other possible mechanisms; once their role in diarrhoea has been confirmed, the epidemiology of the responsible strains should be defined. 3

4.8 Cholera and ETEC diarrhoea - immunology and vaccine development

4.8.1 Immune mechanisms and protective antigens

4.8.1.1 Identification of protective antigens. There is a need for a better definition of the precise bacterial somatic structures and extracellular products that are important in pathogenesis and the establishment of immunity. These would include the factors involved in bacterial attachment to the intestinal mucosa, penetration of the mucosa, adherence to the brush border, and multiplication in situ. Such studies should also examine the importance of enzymes (e.g., mucinase, neuraminidase and proteinases) and known bacterial structures (e.g., flagella, flagella sheath, pili). This knowledge is essential for a more rational selection of candidate strains for the development of new vaccines. 1

4.8.1.2 Tests for antibody measurement. Tests should be developed for the measurement of antibody against the structures or products of the organism that are shown to play an important role in pathogenesis and/or the establishment of immunity. Simplified assays for the measurement of antibodies to cholera and ETEC enterotoxins in serum and other body fluids are also needed to expedite sero-epidemiological studies of the two diseases. 1

Rank

4.8.1.3 Measurement of acquired immunity. The natural course of disease and acquisition of immunity should be determined in epidemiological studies and in volunteers, with special attention to: (a) the extent and duration of immunity to the homologous organism; (b) cross-protection against heterologous organisms (e.g., does immunity to cholera confer resistance to E. coli LT disease?); and (c) the extent and duration of priming of the mucosal immune system for a secondary immune response (e.g., does E. coli LT diarrhoea prime effectively for booster with cholera toxoids or toxin subunits?). 1

4.8.1.4 Genetic determinants of virulence. Genetic analysis should be applied to these organisms to provide a detailed understanding of the factors associated with virulence and protection. Application of this knowledge should facilitate the rational identification of antigens that should be included in vaccines. 2

4.8.2 Methods of stimulating mucosal immunity

4.8.2.1 Methods to elicit an immune response. There should be a search for methods to elicit a mucosal immune response, through evaluation of various antigen forms, routes of administration, and adjuvants. 1

4.8.2.2 Methods to prolong the immune response. Better ways should be found to prolong both the immune response and the memory for response to boosters; the role of each in prolonging protection should be studied. 2

4.8.2.3 Methods to measure mucosal immunity. Studies are needed to define practical ways of measuring mucosal immunity in man. Such studies should include the examination of extra-intestinal secretions, such as saliva and breastmilk, to determine whether they reflect intestinal immunity. Studies of breastmilk antibody should also investigate its ability to provide passive immunity to the baby, a property that might be reinforced by planned immunization of the mother. 1

4.8.2.4 Studies of the immune response in population groups. Differences in the immune response to these organisms in different population groups, such as those living in endemic and non-endemic areas, should be investigated. The possible influence of age, nutritional status, genetic factors, and coexisting microbial and parasitic infections should also be assessed. 2

4.8.3 Development of animal models 2

There is a need for a more satisfactory animal model than those currently available for studies of immunity in diseases caused by these agents. the model should utilize the non-ligated bowel in intact adult animals. The availability of such a model would greatly facilitate the pursuit of many of the above-recommended studies (4.8.1-4.8.2).

4.8.4 Testing of existing candidate cholera vaccines

4.8.4.1 B-subunit cholera vaccine. A vaccine made from the B subunit of cholera toxin has been prepared in Sweden and shown to be immunogenic and safe in volunteers in Bangladesh and Sweden. Appropriate pilot studies and a field trial to determine its protective capacity against cholera and ETEC diarrhoea should be carried out in an endemic area. 1

Rank

4.8.4.2 Living vaccines made from non-toxigenic V. cholerae. Two living non-toxigenic strains of V. cholerae have been developed in laboratories in the USA and proposed for use as oral vaccines. Small-scale studies in volunteers have been initiated. Appropriate testing of their immunogenicity, stability, and reactogenicity should continue, and pilot and large-scale field trials should be carried out if they are found safe, immunogenic, and stable. 2

4.8.4.3 Other existing vaccines. Other new cholera vaccines that have been developed need to be carefully assessed first in animal protection studies. Should they prove to be protective, they should be evaluated for their immunogenicity and reactogenicity in volunteers prior to field testing. 3

4.8.5 Evaluation of synergy 2

There is a continuing need for evaluation in experimental animals and in volunteers of the synergy between two or more immunogens administered concurrently. This will facilitate the development of combined non-living vaccines (e.g., vaccines against cholera or ETEC diarrhoea containing both somatic antigens and toxin-derived antigens such as B-subunits) and identification of the antigens that will be required in live vaccine strains.

4.8.6 Development of new, improved immunogens 2

Efforts should continue to develop new and improved immunogens, especially those falling into the following categories:

(a) non-living immunogens, including whole-cell vaccines, crude extracellular products, and purified somatic or extracellular products such as lipopolysaccharide or toxin-derived antigens;

(b) living vaccines, consisting either of naturally occurring non-pathogenic strains or laboratory-produced mutant or recombinant strains. Candidate live vaccine strains should have selective phenotypic markers to allow fo their differentiation from wild-type strains.

4.9 Campylobacter jejuni

4.9.1 Isolation and characterization. Present techniques for the isolation of C. jejuni require reduced oxygen tension and blood-containing media. Simpler isolation techniques need to be developed for routine use in laboratories. A typing system (e.g., serotyping or phage-typing) is also needed for epidemiological studies. 1

4.9.2 Epidemiology. Available evidence, mostly from studies in developed countries, suggests that C. jejuni can account for up to 15% of acute diarrhoea cases in some settings. There is a scarcity of information on its transmission, although the available evidence suggests that the disease may be a zoonosis. Studies are necessary to define both the importance and the epidemiology (reservoir, source, and mode of transmission) of the organism in developing countries. 1

4.9.3 Pathogenesis. C. jejuni can cause both watery diarrhoea and a dysentery-like illness, but the pathogenic mechanisms responsible are not known and require further study. 2

Rank

4.10 Salmonella (including S. typhi)

4.10.1 Virulence of multiple drug-resistant strains. Evidence from recent epidemics, mainly in developing countries, suggests that strains with plasmid-mediated multiple drug resistance may be more virulent. The validity of this apparent relationship and the reasons for it need investigation. 2

4.10.2 Epidemiology of typhoid fever. Endemic typhoid remains an important and little studied public health problem in developing countries. Studies are required to clarify the reasons for its age distribution, its mode(s) of transmission, and other epidemiological features. 2

4.10.3 Evaluation of the efficacy and cost/effectiveness of a new oral typhoid vaccine. A live oral vaccine has recently been developed at the Swiss Serum and Vaccine Institute in Berne. In its first field trial it was found to be highly efficacious for at least two years. Further trials of this vaccine are indicated to determine an optimal vaccination schedule. It will also be important to determine the cost/effectiveness of administering this vaccine should it continue to prove efficacious. 1

4.10.4 Immunity in typhoid fever. Although the clinical picture of typhoid fever has been well described, the mechanism by which man acquires immunity to the disease is not clear. Available evidence suggests that immunity may be cell-mediated, but the precise mechanism and way to measure it need to be determined. 2

4.11 Shigella

4.11.1 Pathogenesis. While it is clear that shigellae are entero-invasive, recent evidence indicates that some strains can produce an enterotoxin. The role of this toxin, if any, needs to be defined in relation to the clinical spectrum of the disease. There is also a need to determine the mechanism by which shigellae penetrate intestinal cells. 2

4.12 Yersinia enterocolitica

4.12.1 Epidemiology. Most of the epidemiological data on Y. enterocolitica are from developed countries, where the organism appears to cause about 1 to 3% of acute diarrhoeas and the disease is a zoonosis. There is also evidence that human cases are caused by strains of specific serotypes and that some of these serotypes have a particular geographical distribution. There is a need to determine the epidemiology (reservoir, source, mode of transmission, and serotype prevalence) of this organism in developing countries. 3

4.12.2 Pathogenesis. Y. enterocolitica causes a range of clinical syndromes which are age related; they include diarrhoea, mesenteric adenitis, and immunological phenomena (e.g., reactive arthritis, erythema nodosum). There is evidence that some strains produce a heat-stable toxin and are invasive. The relationship between these syndromes, their age distribution, and their pathogenesis need to be studied. 3

4.13 Other organisms 3

Other organisms (e.g., Klebsiella, Aeromonas) have occasionally been reported as causes of acute diarrhoea. The frequency with which these organisms cause diarrhoea needs to be determined, and the characteristics of the pathogenic strains require clarification.

Rank

4.14 Interruption of transmission 1

Many studies that have been carried out to determine the role of water supplies and latrines in reducing the incidence of diarrhoea have been inadequately designed epidemiologically and have not differentiated between the known etiological agents. Once there is a better understanding of the modes of transmission of the bacterial enteric pathogens (4.1.1, 4.1.2, 4.4.2, 4.5.1, 4.6.1, 4.9.2, 4.10.2, 4.12.1), specific cost/effective methods of interrupting their transmission through environmental intervention should be studied. Single and multiple approaches to reducing transmission need to be examined, with special emphasis on the role of modifications in water supply, water usage, defaecation practices, and personal and domestic hygiene.

4.15 Pathogen removal by water treatment processes 2

Although there is information about the ability of the common water treatment processes to remove some of the enteric pathogens, other treatment technologies and the effects on other pathogens require further study. For example, the effect of storage in reducing the bacterial contamination of otherwise untreated rural water requires evaluation. In particular, the specific effects of storage, coagulation, slow sand filtration, and chlorination on the survival of C. jejuni require study.

4.16 Pathogen removal during excreta treatment and re-use processes 3

Except for C. jejuni, there is sufficient information about the ability of conventional sewage treatment processes to remove the major bacterial enteric pathogens. There is an important need, however, to assess the extent to which appropriate technologies having wide applicability in the developing countries are able to destroy these pathogens. Technologies requiring such evaluation include (a) for site sanitation: twin-pit latrines, twin-soakaway pour-flush latrines, and batch double-vault composting latrines; (b) for night-soil and sludge treatment: systems based on storage, drying, and thermophilic composting; (c) for sewage treatment: waste stabilization ponds, aerated lagoons, and oxidation ditches. It is also important to study the survival of bacterial pathogens in agricultural or aquacultural excreta re-use systems.

4.17 Indicator organisms for diarrhoea pathogens in aquatic environments 3

The overall adequacy of E. coli as an indicator of the presence of bacterial enteric pathogens in aquatic environments in tropical countries needs to be assessed. If E. coli is found to be a suitable indicator, an improved and more convenient test should be developed for its enumeration, having an incubation temperature of 35-37°C (instead of 44.5 ± 0.2°C as at present) and a high degree of specificity for E. coli in tropical waters and wastes. The suitability of faecal streptococci as an indicator organism should also be studied; in particular, the significance of isolations of S. faecalis var. liquifaciens requires investigation.

5. IDENTIFICATION OF INSTITUTIONS TO UNDERTAKE RESEARCH

The Group discussed means by which institutions and research workers could be informed about the research programme and its priorities. It was pointed out that without any formal advertising the Secretariat had received 69 enquiries, 39 of which were in the field of bacterial infections and would be referred to that SC for consideration (the other 30 would be referred to the SCs of other GSWGs). It was agreed that the SWG's plan for support of research should be announced in WHO publications (e.g., Bulletin, Chronicle) and that announcements describing the research priorities of the SWG should be distributed with

the help of the Regional Offices and the WHO Programme Coordinators to institutions and research workers in the developing countries, as well as to national medical research councils and analagous bodies in developed and developing countries. Each SWG member agreed to prepare a list of institutions and workers in his Region who could be contacted as potential collaborators in the Programme.

On the question of the equitable distribution of funds between scientists in the developing and developed countries, the Group agreed that, where possible, priority should be given to the support of institutions in the developing countries, or to institutions in developed countries undertaking collaborative research projects with institutions in developing countries. The latter type of effort was strongly endorsed. It was acknowledged, however, that there would be a need to allot some research funds to institutions in developed countries where some of the more urgent basic research activities could more rapidly be carried out. In this regard, the Group felt that WHO should try to influence national research funding bodies in developed countries to give greater support to diarrhoeal diseases research projects in their respective countries. A wide geographical distribution of support to institutions was felt to be desirable but subject to the overriding consideration of quality.

6. APPLICATION FORMS FOR RESEARCH SUPPORT

The application form developed by the Secretariat was reviewed and adopted with some minor modifications. It was agreed that neither principal investigators nor other senior professional staff should receive a salary or salary supplements except in very special or unusual circumstances.

In order to facilitate the completion and consideration of application forms, the Group recommended that interested workers should be asked first to write a letter of intent to the Secretariat describing their proposed research project. The Secretariat could then, when appropriate, encourage the completion of an application form. It was agreed that a project receiving support from the SWG could receive additional support from other funding bodies, provided that this fact was reported to the SWG.

7. BUDGET

The activities that needed to be covered by the Group's budget (e.g., contracts, site visits, meetings, etc.) were discussed. There was a strong feeling that the undertaking of high-quality research in developing countries required that institutions in such countries receive grants for research strengthening, including core support for buildings and equipment, training, and salaries. It was recognized that present funds were inadequate for these activities, and that emphasis would have to be placed on the need for this kind of support during discussions with potential contributors to the Programme.

8. FUTURE MEETINGS

It was agreed that the dates and agenda of the 1981 SWG meeting would be set by the SC when it met in September 1980.

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FIGURE 1: RESEARCH PLAN 1980-84 - SCIENTIFIC WORKING GROUP ON BACTERIAL ENTERIC INFECTIONS: MICROBIOLOGY, EPIDEMIOLOGY, IMMUNOLOGY AND VACCINE DEVELOPMENT

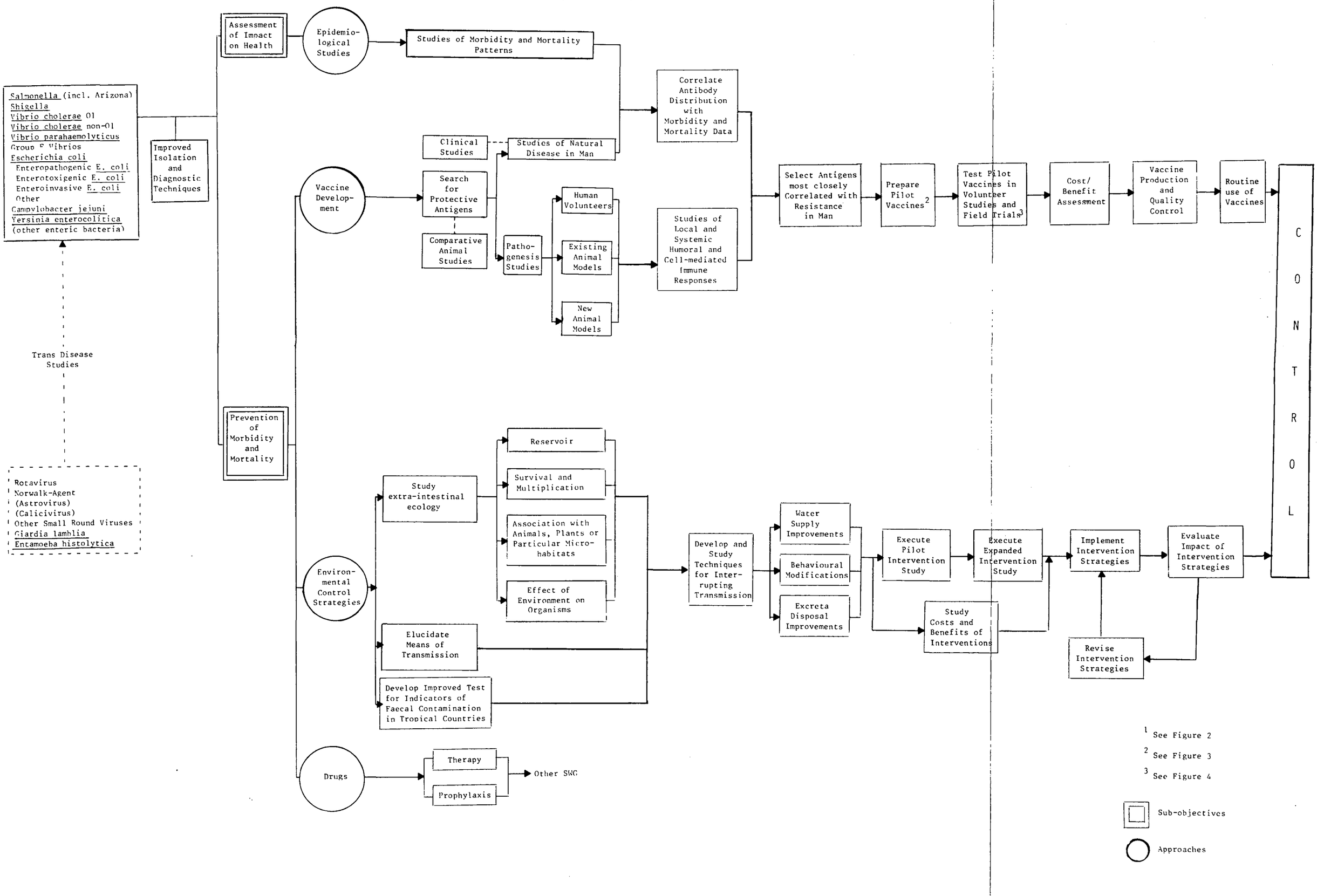


FIGURE 2: SEARCH FOR PROTECTIVE ANTIGENS

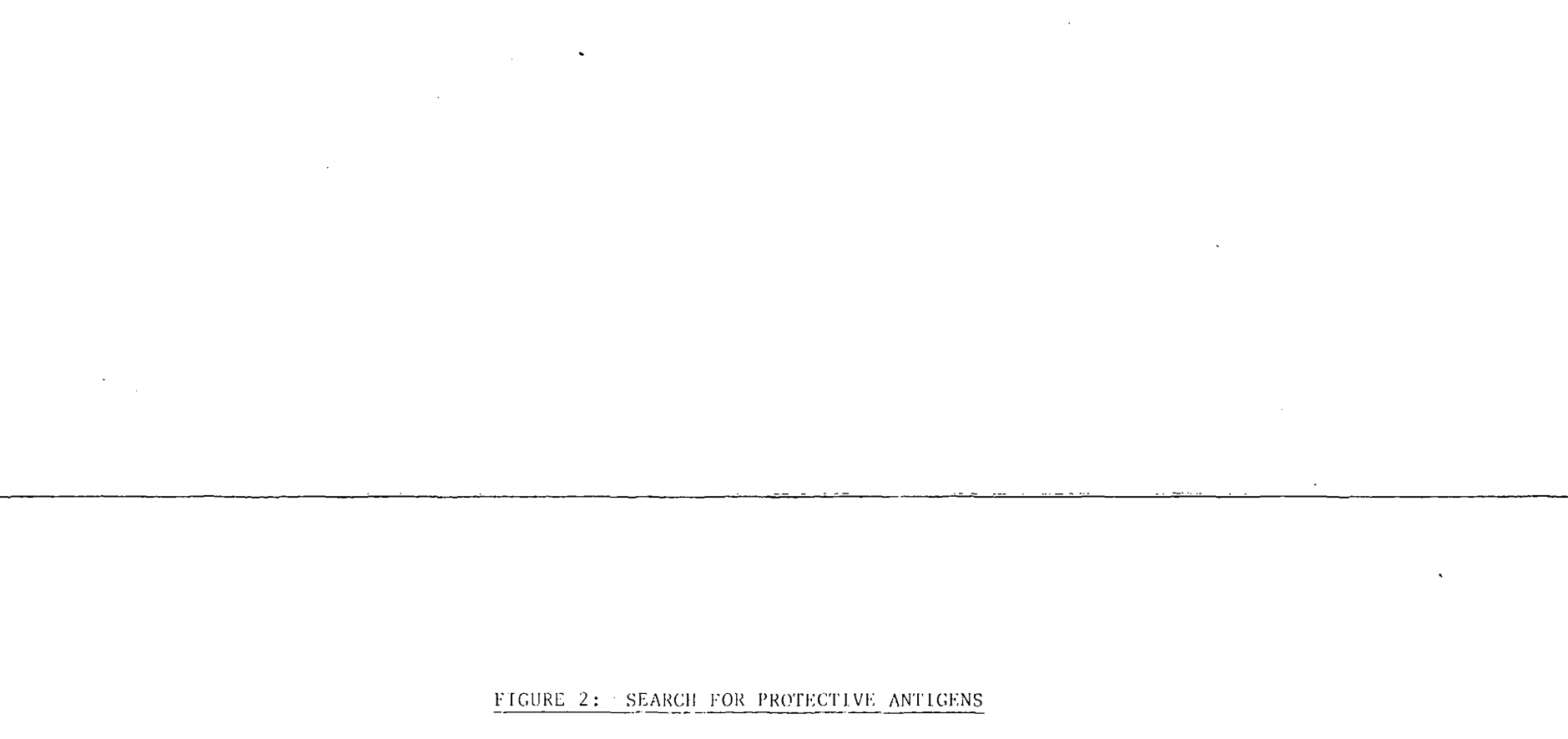
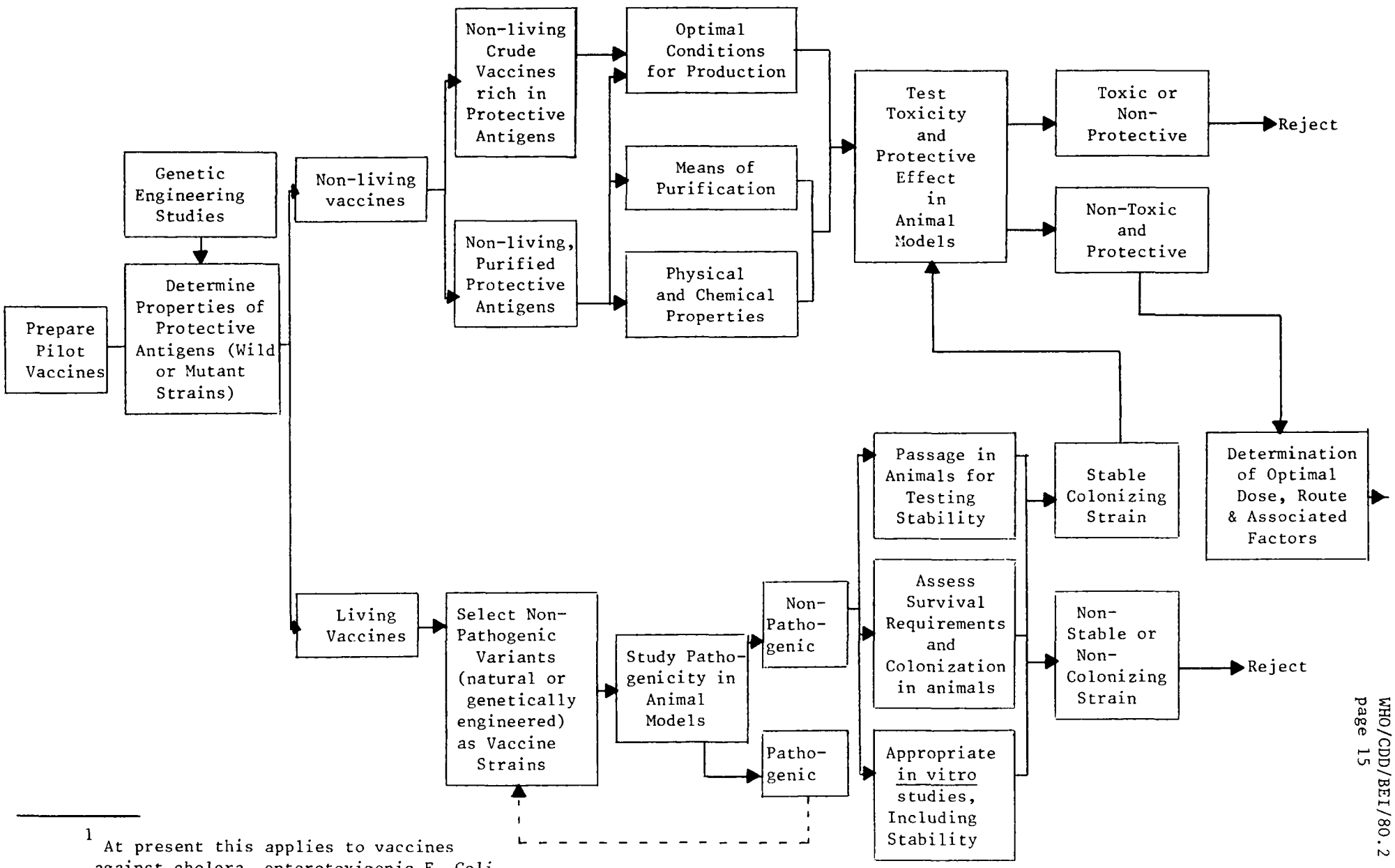
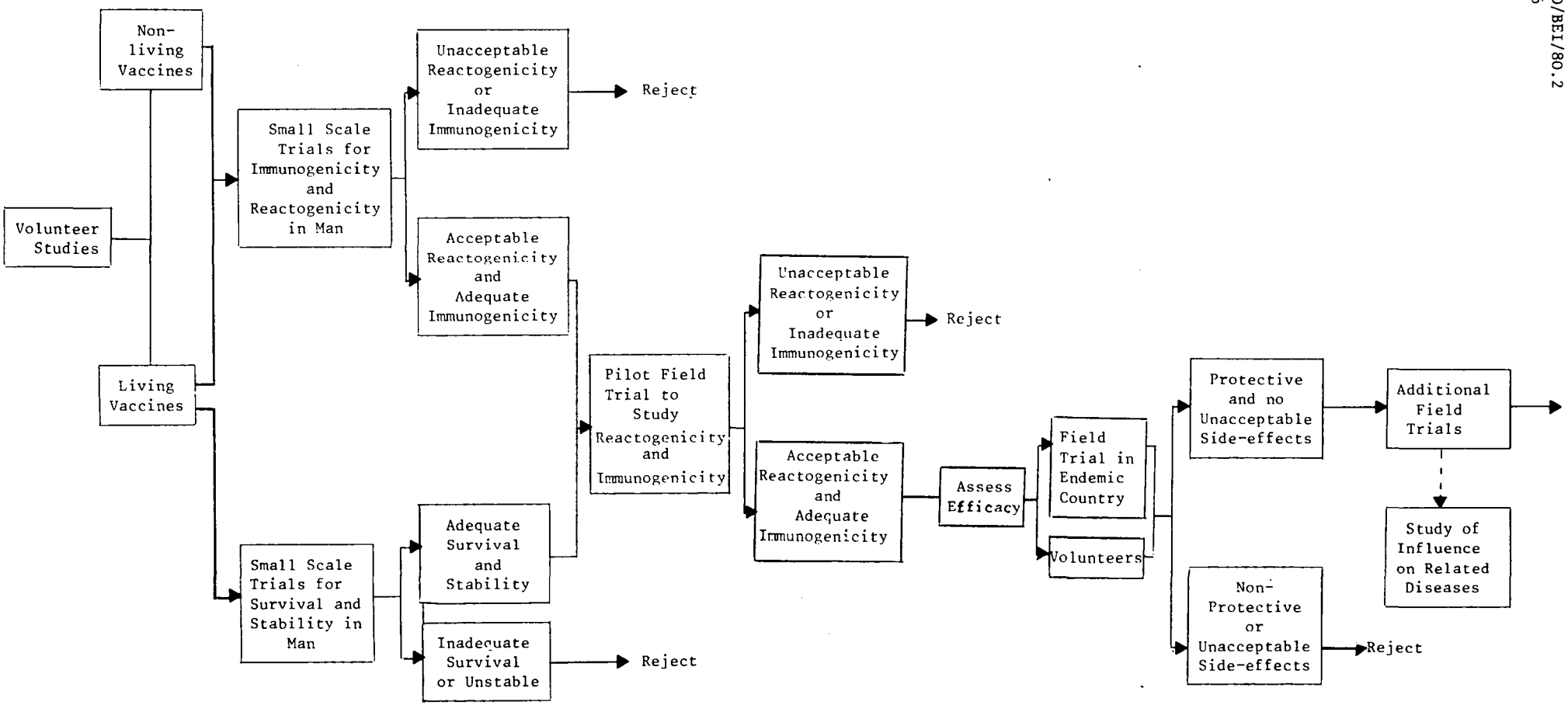


FIGURE 3: PREPARATION OF PILOT VACCINES [1]



[1] At present this applies to vaccines against cholera, enterotoxigenic E. Coli diarrhoea and typhoid fever

FIGURE 4: TESTING OF PILOT VACCINES IN VOLUNTEER STUDIES AND FIELD TRIALS



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