THE WHO REFERENCE CENTRES IN MICROBIOLOGY, BACTERIOLOGY, Virology AND BIOLOGICAL STANDARDS

by

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In the context of this paper, the term "reference" means the submission of a matter to some authority for discussion, information or consultation and the term "reference material" a standard preparation used for purposes of comparison. The term "designation" means the recognition by WHO of an institute, department or laboratory, normally located in an already established institution, as a reference centre which will carry out a number of specific functions assigned to it by WHO. It may or may not involve financial support. A reference centre may be jointly designated by WHO and any other competent and specialized international body, e.g. the Food and Agriculture Organization.

There are three types of Reference centres: International, Regional and National. The two first are designated by WHO as "WHO... Reference centres". The National centres are designated by the Government of the country concerned and may be recognized by WHO but no reference to WHO should appear in the title of the centre.

A WHO International Reference Centre (IRC) is an already established institution to assist in the development and maintenance of high standards of work in specialized fields, where such are needed. It provides certain services of international value to practice or research in medicine and public health and, in some cases, training. The aim of these services is to achieve improved precision, reliability, consistency, and comparability in practice and better results from national and international studies.

The functions of this centre may be indicated diagrammatically in the order in which these activities often develop:

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The establishment of standards and reference materials implies mainly the designation of particular materials to serve as international standards or as reference preparations (and definition of international units), the development of uniform nomenclatures and classifications and uniform techniques and methodology recommended for international use.

The International Reference Centre normally is only in direct relation with the Regional Reference centres and not with National Centres, unless there are no Regional centres (as in Influenza, for instance).

Besides the functions referred above, the International Reference Centre should also promote collaborative research studies or programmes of international importance which can be carried on entirely within the network of reference centres or with the participation of other laboratories or epidemiological and clinical groups. Examples of such activities are the WHO Influenza Programme or the Inter-laboratory Proficiency Testing Programme in Syphilis Serology.

A WHO Regional Reference Centre (RRC) has responsibilities similar to those of an IRC but restricted to those that it is fitted to accept, and limited to a group of geographically related countries. It collaborates with the IRC in its field by collecting certain data and materials, assisting in the development of classifications, etc., and has close contact with national centres for consultation. It deals with enquiries from the national centres and passes on to the IRC only those problems that it cannot resolve. Usually there is only one RRC dealing with a particular subject in a region.
As the National Reference Centres are actually not WHO Reference centres, they will not be considered any more in this paper; they are entitled to receive from the RRC (and in certain cases from the IRC) samples of standard materials and related information on the methods of use of such standards and may pass these on to other national institutes and industries.

It should briefly be mentioned that there is another type of designation by WHO: "WHO Collaborating Institution or Laboratory". These collaborating laboratories will work with an IRC on some task requiring international collaboration, or directly with WHO in collecting information or materials, or in carrying out certain reference duties more limited than those entrusted to a reference centre. They could also co-ordinate or undertake a specific research project.

In most cases, WHO gives certain financial support to these institutions designated as WHO Reference Centres or Collaborating Laboratories.

A list of the WHO International and Regional Reference Centres in the fields of Microbiology, Bacteriology, Virology and Biological Standards is presented as an Annex.

The activities of the WHO Reference Centres, both International and Regional, are very large and cover different aspects of research and services. A brief summary of these activities in 1970 by subjects shows clearly how useful the work of the centres has been for the development of WHO Programmes in different fields.

**Bacterial Diseases**

The International Reference Centre for Streptococcus Typing, Prague, has been engaged in a programme of cooperative international studies of streptococcal infections and their sequelae (rheumatic heart disease and acute glomerular nephritis) in tropical and temperate zones. The International Reference Centre for Staphylococcus Phage-Typing, London, took part in a collaborative study of nosocomial infections. Both centres provide reagents and sera to national laboratories and assist in the typing of difficult strains.
**Tuberculosis**

The International Reference Centre for BCG Seed-lots and Control of BCG Products, Copenhagen, undertook quality assays of vaccine products from national laboratories and institutes in Argentina, Canada, Hungary, India and Senegal, and research studies on the in vivo properties of a number of widely used BCG strains. This Centre maintains also a routine quality control, on behalf of WHO, on the BCG vaccines purchased by UNICEF for supply to the WHO/UNICEF-assisted projects throughout the world and provides training or consultation for BCG production experts.

**Leprosy**

The progress of experimental infection in animals over as long a period as possible has been studied at the Regional Reference Center for Mycobacterium leprae, London, where several hundred normal and immunologically deficient mice inoculated in various sites have been followed over their life-span: a high proportion had shown macroscopic evidence of gross damage of peripheral nerves. At the Regional Reference Centre for the Standardization of Lepromin, Tokyo, research studies on the influence of prolonged refrigerator storage of lepromin suggest that freeze-drying is advisable when storage longer than three years is needed.

**Venereal Diseases and Treponematoses**

Several hundred gonococcal strains from different countries were examined at the International Reference Centre for Gonococci, Copenhagen, for the surveillance of changing antibiotic susceptibility among circulating gonococcal strains: more strains are tending to become less susceptible to penicillin and certain other antibiotics; however, appropriate dosage schedules can, in most instances, overcome this tendency and there are several additional antibiotics (erythromycin and kanamycin, for example) to which *Neisseria gonorrhoeae* is still susceptible. The reference centres had provided several hundred shipments of reference preparations, reagents and control sera to national laboratories; and the International Reference Centre, Atlanta, has continued the inter-laboratory proficiency testing programme in syphilis serology with the participation of twenty-five countries.
Smallpox

More than 350 lots of vaccine were tested by the Centres in Utrecht and Toronto which also provide advice on the production and control of freeze-dried vaccine. These centres are also carrying out comparative studies on smallpox virus strains isolated in different places.

Zoonosis

Experiments at the Reference Centres for Rabies, Philadelphia and Atlanta, have shown that rhesus monkeys can be protected with only one injection of the highly concentrated and purified tissue-culture vaccine being developed recently; this may lead to a radically improved treatment schedule for rabies. The FAO/WHO Brucellosis Centres in various parts of the world continue to provide reference services and training facilities; they continue epidemiological investigations on practical problems of brucellosis control as well as research studies on the characteristics of Brucella strains isolated from several animals and the infections they could produce in man. Similar studies have also been made by the WHO/FAO Leptospirosis Reference Laboratories.

Malaria

Observations on the North Korean strain of P. vivax made at the Regional Reference Centre for Malaria, Epsom, suggest that the duration of the incubation period is affected by the sporozoite dosage, i.e., the lower dosage, the longer the incubation period. The Regional Reference Centre for Screening of Potential Antimalarial Compounds, Liverpool, is testing new compounds, synthesized in Poland, mainly biguanides and amidine ureas against rodent plasmodia.

Parasitic Diseases

The International Reference Centre for Filarial Nematodes, London, which maintains a large collection of identified material covering all stages of filarial parasites, has undertaken a study to establish reliable criteria for the identification of these parasites in their vectors. The collection of trypanosome strains at the International Reference Centre, Tororo has been considerably increased and the strains were recently transformed from solid carbon dioxide at -79°C to liquid nitrogen at -196°C for better preservation; samples from 250 strains were distributed to institutes in several countries and the Centre carried out IgM and fluorescent antibody tests on more than 4300 dried-blood samples from human surveys in near countries. Leishmanin prepared at the International Reference Centre for Leishmaniasis, Jerusalem, is now available to research laboratories.
Biological Standardization

The custody and distribution of international standards and reference preparations, as well as the organization of international collaborative assays for their establishment, are mainly carried out through the three International Laboratories for Biological Standards in Copenhagen, London and Weybridge; similar preparations are also established as international biological reference reagents which are used in diagnosis for the identification of micro-organisms.

Virus Diseases

The large network of Regional Centres makes an invaluable contribution not only to WHO programmes but also to virology in general. They serve as sources of authoritative advice to national virus laboratories and as centres for training virologists in research and in diagnostic work and thus provide selected laboratories with prototype strains of virus, diagnostic and reference reagents, antigens and cell cultures. They have organized collaborative studies in the field of respiratory viruses, Rhinoviruses, Rubella, Poliomyelitis and Arboviruses. An international conference on influenza was organized at the International Influenza Centre, Atlanta, which reviewed the new knowledge about the antigenic and other properties of the Hong-Kong virus, the problems posed by the relative inefficiency of recent vaccines and the recent work on chemotherapy and chemoprophylaxis. Eighty-eight national influenza centres in 57 countries received reagents for the identification of influenza viruses and for use in serological studies; these reagents were prepared in the International Centre, Atlanta, and tested at the World Centre, London. Both Centres received for characterization some 700 strains of influenza virus A.

### BACTERIAL DISEASES

**Enteric Infections**

- *International Reference Centre for Enteric Phage-Typing*
  - Central Public Health Laboratory, London, England
- *International Reference Centre for Escherichia*
  - Statens Serum Institut, Copenhagen, Denmark
- *International Reference Centre for Salmonella*
  - Institut Pasteur, Paris, France
- *International Reference Centres for Shigella*
  - Central Public Health Laboratory, London, England
  - Center for Disease Control, Atlanta, Ga., USA

- *International Reference Centre for Vibrios*
  - Cholera Research Centre, Calcutta, India

**Meningococcal Infections**

- *International Reference Centre for Meningococci*
  - Laboratoire de Microbiologie, Centre de Recherches du Service de Santé des Troupes de Marine, Marseilles, France

**Plague**

- *International Reference Centre for Plague*
  - * Central Asian Institute for Research on Plague Control, Alma-Ata, USSR

**Streptococcal Infections**

- *International Reference Centre for Streptococcal Phage-Typing*
  - Central Public Health Laboratory, London, England

### LEPROSY

- *International Reference Centre for the Serology of Leprosy*
  - Department of Microbiology and Immunology, Ribeirão Preto Faculty of Medicine, University of São Paulo, Brazil

### Regional Reference Centres for Mycobacterium leprae

- Division of Bacteriology and Virus Research, National Institute for Medical Research, London, England
- Virology Section, Center for Disease Control, Atlanta, Ga., USA

### Regional Reference Centres for the Standardization of Lepromin

- Laboratory of Serology, National Institute for Leprosy Research, Tokyo, Japan

- Leonard Wood Memorial Laboratory for Leprosy Research, Johns Hopkins University, Baltimore, Md., USA

### MALARIA

- *International Reference Centre for Malaria*
  - Laboratory of Parasite Chemotherapy, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md., USA

### Regional Reference Centres for Malaria

- Horton Malaria Reference Laboratory, Epsom, England
- National Institute of Communicable Diseases, New Delhi, India

- *International Reference Centre for Avian Malaria Parasites*
  - Department of Biology, Memorial University of Newfoundland, St John's, Newfoundland, Canada

### Regional Reference Centre for Screening of Potential Antimalarial Compounds

- Department of Parasitology, Liverpool School of Tropical Medicine, Liverpool, England

### PARASITIC DISEASES

### Filariasis

- *International Reference Centre for Filarial Nematodes*
  - Department of Parasitology, London School of Hygiene and Tropical Medicine, London, England

### Leishmaniasis

- *International Reference Centre for Leishmaniasis*
  - Department of Parasitology, Hadassah Medical School, Jerusalem, Israel

### Soil Stomatisis

- *Snail Identification Centre*
  - Danish Snailfish Laboratory, Copenhagen, Denmark

### Trypanosomiasis

* Initiated in 1970.
TUBERCULOSIS

International Reference Centre for the Diagnosis of Tuberculosis
Tuberculosis Research Institute, Prague, Czechoslovakia

Regional Reference Centre for the Diagnosis of Tuberculosis
Department of Tuberculosis, National Institute of Health, Tokyo, Japan

International Reference Centre for BCG Seed-lots and Control of BCG Products
BCG Department, Statens Serum Institut, Copenhagen, Denmark

Regional Reference Centre for Bacteriology of Tuberculosis
National Tuberculosis Institute, El Algodonel, Caracas, Venezuela

VENREAL INFECTIONS AND TREPONEMATOSES

International Reference Centre for Endemic Treponematoses
Institut Alfred-Fournier, Paris, France

International Reference Centre for Gonococci
Neisseria Department, Statens Serum Institut, Copenhagen, Denmark

International Reference Centre for the Biology and Immunology of Treponemes
Johns Hopkins University, Baltimore, Md., USA

International Reference Centres for the Serology of Treponematoses
Treponematoses Research Laboratory, Statens Serum Institut, Copenhagen, Denmark
Venereal Disease Research Laboratory, Center for Disease Control, Atlanta, Ga., USA

VIRUS DISEASES

Arbovirus Diseases

International Reference Centre for Arboviruses
Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Conn., USA

Regional Reference Centres for Arboviruses
Department of Virology, Queensland Institute of Medical Research, Brisbane, Australia
Institute of Virology, Bratislava, Czechoslovakia
Laboratoire des Arbovirus, Institut Pasteur, Paris, France
Virus Research Centre, Indian Council of Medical Research, Poona, India
Department of Virology and Rickettsiology, National Institute of Health, Tokyo, Japan
Institut Pasteur, Dakar, Sengal
East African Virus Research Institute, East African Common Services Organization, Entebbe, Uganda
Department for Arboviruses, Institute of Poliomyelitis and Viral Encephalitides, Moscow, USSR

International Reference Centre for Cell Cultures
Animal Type Culture Collection, Reidston, Soma, USA

Enterovirus Diseases

International Reference Centre for Enteroviruses
Department of Virology and Epidemiology, Baylor University College of Medicine, Houston, Tex., USA

Regional Reference Centres for Enteroviruses
Enterovirus Department, Statens Serum Institut, Copenhagen, Denmark
Section de Virologie, Laboratoire national de la Sante publique, Lyons, France
Department of Enteroviruses, National Institute of Health, Tokyo, Japan
Department of Bacteriology, University of Singapore
Enterovirology Unit, Virology Section, Center for Disease Control, Atlanta, Ga., USA
Institute of Poliomyelitis and Viral Encephalitides, Moscow, USSR

Influenza

World Influenza Centre
National Institute for Medical Research, London, England

International Influenza Centre for the Americas
Virology Section, Center for Disease Control, Atlanta, Ga., USA

Mycoplasmas

International Reference Centre for Human Mycoplasmas
Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md., USA

FAO/WHO International Reference Centre for Animal Mycoplasmas
Institute of General Pathology, University of Aarhus Medical Faculty, Denmark

Respiratory Virus Diseases other than Influenza

International Reference Centres for Respiratory Viruses other than Influenza
Common Cold Research Unit, National Institute for Medical Research, Harvard Hospital, Salisbury, England
Laboratory of Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Md., USA

Regional Reference Centres for Respiratory Viruses other than Influenza
Fairfield Hospital Communicable Disease Centre, Melbourne, Australia
Institute of Epidemiology and Microbiology, Prague, Czechoslovakia
Respiratory Virus Laboratory, National Institute of Health, Tokyo, Japan
Infectious Institute of Virology, Moscow, USSR

International Reference Centre for Cell Cultures
Animal Type Culture Collection, Reidston, USA

Cell Cultures

International Reference Centre for Cell Cultures
Animal Type Culture Collection, Reidston, USA
Rickettsioses

Regional Reference Centres for Human Rickettsioses
Institute of Virology, Bratislava, Czechoslovakia
Rocky Mountain Laboratory, National Institute of Allergy and Infectious Diseases, Hamilton, Mont., USA

Smallpox

International Reference Centre for Smallpox
* Laboratory of Smallpox Prophylaxis, Research Institute of Virus Preparations, Moscow, USSR

Regional Reference Centre for Smallpox
Center for Disease Control, Atlanta, Ga., USA

International Reference Centre for Smallpox Vaccine
Virus and Rickettsial Diseases Laboratory, National Institute of Public Health, Utrecht, Netherlands

Regional Reference Centre for Smallpox Vaccine
Connaught Medical Research Laboratories, University of Toronto, Ont., Canada

Trachoma

International Reference Centre for Trachoma
Francis I. Proctor Foundation for Research in Ophthalmology, University of California Medical Center, San Francisco, Calif., USA

ZOOLOGICAL

Brucellosis

FAO/WHO Brucellosis Centres
Commonwealth Serum Laboratories, Parkville, Victoria, Australia
State Veterinary Serum Laboratory, Copenhagen, Denmark
Central Veterinary Laboratory, Ministry of Agriculture, Fisheries and Food, Weybridge, England
Centre de Recherches sur la Fièvre ondulante, Montpelier, Hérault, France
Veterinary Microbiological Institute, Athens, Greece
Indian Veterinary Research Institute, Mukireswar-Kumaon, Uttar Pradesh, India
Institute of Hygiene, University of Florence Faculty of Medicine, Italy
National Institute of Animal Health, Tokyo, Japan
Medical Research Institute, General Hospital, Mexico City, Mexico
Institut Pasteur, Tunis, Tunisia
Institute of Veterinary Bacteriology and Serology, Istanbul, Turkey
Department of Medicine, University of Minnesota Medical School, Minneapolis, Minn., USA
State Laboratory of Hygiene, Rijeka, Yugoslavia

WHO Brucellosis Centre
Gamaleya Institute of Epidemiology and Microbiology, Moscow, USSR

Leprosy

WHO/FAO Leprosy Reference Laboratories
Laboratory of Microbiology and Pathology, State Health Department, Brisbane, Australia
London School of Hygiene and Tropical Medicine, London, England
Israel Institute for Biological Research, Ness-Ziona, Israel
Istituto Superiore di Sanità, Rome, Italy
National Institute of Health, Tokyo, Japan
Institute for Tropical Hygiene (Royal Tropical Institute), Amsterdam, Netherlands
Division of Veterinary Medicine, Walter Reed Army Medical Center, Washington, D.C., USA

WHO Leprosy Reference Laboratory
Gamaleya Institute of Epidemiology and Microbiology, Moscow, USSR

Rabies

International Reference Centres for Rabies
Institut Pasteur, Paris, France
Pasteur Institute of Southern India, Coonoor, India
Institute of Poliomyelitis and Viral Encephalitides, Moscow, USSR
Wistar Institute of Anatomy and Biology, Philadelphia, Pa., USA

Regional Reference Centre for Rabies in the Americas
Rabies Laboratory, Center for Disease Control, Atlanta, Ga., USA

Serum Reference Banks
Institute of Epidemiology and Microbiology, Prague, Czechoslovakia
* National Institute of Health, Tokyo, Japan
Department of Epidemiology and Public Health, Yale University School of Medicine, New Haven, Conn., USA

* Initiated in 1970.