WORLD HEALTH ORGANIZATION
REGIONAL OFFICE FOR EUROPE

WELTGESUNDHEITSORGANISATION
REGIONALBÜRO FÜR EUROPA

ORGANISATION MONDIALE DE LA SANTÉ
BUREAU RÉGIONAL DE L'EUROPE

ВСЕМИРНАЯ ОРГАНИЗАЦИЯ ЗДРАВООХРАНЕНИЯ
ЕВРОПЕЙСКОЕ РЕГИОНАЛЬНОЕ БЮРО

IMMUNIZATION OF THE ELDERLY

Report on a WHO Working Group

Zagreb
5-7 September 1983

ICP/ESD 008
0310G
ENGLISH ONLY
UNEDITED

1984

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1. Introduction

The Working Group on immunization of the elderly[a] met at the Institute of Immunology in Zagreb, 5-7 September 1983. The members[b] were greeted by the director of the institute, Professor B. Popovic. The meeting was opened on behalf of the WHO Regional Director for Europe by Dr B. Velimirovic, who outlined the scope and the purpose of the meeting. Professor B. Popovic was elected Chairman, Dr P.H. Mäkelä Vice-chairman and Professor D.L. Miller Rapporteur.

The purpose of the meeting was to review, in light of the changing pattern of the age structure of the population in European countries, the appropriate strategy for the protection of the eldery against infectious diseases and the development of a rational immunization programme for this age group. The group was acquainted with World Health Organization activities, carried out mainly by the Regional Office for Europe, on health protection and promotion of the elderly of which this Working Group's meeting makes part.

The group was presented with working papers on the relevant subject and accordingly to its terms of reference discussed various aspects of immunization of elderly in detail (see working papers in Annex 1). The brief summary, conclusion and recommendations are given in this report.

1.1 Aging of the population

The process of aging of the population is a characteristic featue of modern society. This process is determined by changes in fertility and mortality, which were strongly influenced by fast social and economic evolution, as well as the development of medical science and practice. Most industrially developed countries had in the middle of the last century less than 5% of people older than 65 years in the entire population. Presently, this age group of population represents one tenth to one seventh of the total population, but about two thirds of total health care expenditure are directed to the needs of the elderly.

Therefore, the prevention and treatment of diseases in the elderly are gaining importance as public health problems.

In developed countries, which comprise 30% of the world population, persons over 65 years of age already numbered more than 120 million in the mid-seventies. It is estimated that, by the year 2000, this figure will be about 180 million. In a recent WHO survey on mortality projection, it is estimated that life expectancy in developed countries will increase by the year 2000 from the present 70-75 years to 75-80 years. In Europe alone, including the USSR, i.e. in countries covered by the WHO Regional Office for Europe, there is hardly a country where the proportion of the elderly is below 10%, so that, out of 750 million inhabitants, there are almost 95 million of those older than 65 years.

There is every chance in the contemporary world that a high proportion of boys and girls who have survived the first year of life will live to be 70 and 75 respectively. The death rate among those over 65 years of age in the overall mortality is constantly increasing. It is expected that, by the end of this millenium, only 10% of deaths out of the total mortality in developed countries will be in the population younger than 65, that almost every other 65 year-old human being will live up to 80 years of age, and that the population above 80 years of age will account for as many as 50% of deaths.

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[a] The "elderly", in this text unless otherwise specified, incorporates all persons aged 60 years or more. Definition of the elderly: the Group recognized that "the elderly" may be based on several independent criteria. Vulnerability to infection varies, for example, in relation to the operation of physiological defences (which decline at different rates in various racial groups and in individuals within groups) and immune mechanisms (which may be impaired by disease or medical treatments). It also varies with different infections. Thus, chronological age does not always correlate well with biological age and immune competence.

Nevertheless, for practical purposes, operational policies are most easily devised and implemented on the basis of crude chronological age grouping. For this reason, and in conformity with previous WHO practice, the following working definitions were accepted: middle age - 45-59 years; elderly - 60-74 years; aged - 75-89 years; very old - 90 or more years.

[b] See list of participants in Annex 2.

Public health importance of the changing of the age structure of the population stems from the fact that age, mortality and morbidity patterns are related to and are reflected in the requirements for the type and intensity of health care.

The principal public health problems of developed countries are gradually passing from the mother and child health care to the care of the elderly.

Among the most frquent causes of death of persons older than 65 nowadays are influenza and pneumonia as well as heart diseases and neoplasmas. Infectious diseases, because the immunity of older people is weakened, in many cases, become fatal.

1.2 Infectious diseases

Although communicable diseases are by no means as important at present as they used to be as causes of death, they still occupy a very high place, especially among the elderly, and are leading causes of death among those older than 65 years. For these reasons, there is a need to improve existing methods for prevention and treatment of infectious diseases and to develop new and more effective ones.

According to the present-day state of knowledge, the average biological life potential is still higher than that reached even in populations of the most highly developed countries. This means that there are promises of a still longer life. However, this will only be of much interest both to the society as a whole and to the people if they will be able to enjoy as healthy and as happy a life in old age as possible. The immunization of the elderly certainly has its role to play in achieving these goals.

1.3 Immunization

Immunization is one of the essential components of any effective health care system. Health care of the elderly is largely dependent on coordinated efforts of numerous components of health and social services and activities. A special role in this coordination of the overall health care and welfare of the elderly is given to the general practitioner and other health staff working in primary health care, which should comprise the immunization of the elderly as well as of the young.

More time and space should therefore be given to the training of all profiles of health workers, including medical undergraduate and postgraduate students, on vaccination and immunization programmes, as this is of special importance for preventing high morbidity and direct cause of death from infectious diseases, e.g. influenza and pneumonia. Control of infectious diseases in the elderly can essentially contribute not only to higher life expectancy but also to better quality of life. By developing more potent and more effective conrol measures such as immunization for the prevention of infectious diseases predominant among the elderly, it would be possible also to realize the slogan that life should be added to years.

2. Immunity in elderly

2.1 Immune response in the elderly

Aging and immunity

The immune response is strongest in young adults and weakest in infants and in the elderly. Physiological immaturity of the immune system in infants does not usually present a medical problem except in cases of obvious immunodeficiency. On the other hand, a poor immune response in the aged could be connected with the development of certain diseases which occur at this age. Defective immune function in the aged is indicated by greater susceptibility to infections and increased frequency of autoimmune diseases and malignant tumours. Elderly individuals tend not only to be more susceptible to infections but to have a more prolonged course of illness with higher complication and mortality rates.

It is difficult to ascertain whether the changes of immune response in the aged are the cause, consequence or are independent of other structural and functional phenomena which occur in parallel with aging, such as a decrease in hormone levels and membrane permeability, decreased numbers of post-mitotic cells, etc. (1). Research into age-related changes of immune response has been carried out on humans and in animals (mostly mice), but the data available are still incomplete and are often contradictory.

In principle, the age-related decrease of immune function could be caused either by changes in the immunocompetent cells themselves, or by changes in their environment or by both causes simultaneously (2, 3). On the basis of experiments with cell transfers, changes apparently occur both within the cells and their contact or environment. However, it would appear that only about 10% of the total age-associated diminution of immune function can be ascribed to changes in cell environment, and the remaining, about 90%, should be ascribed to functional diminution of the immunocompetent cells themselves. In old age, changes occur in the morphology of lymphoid organs, in the number and function of immunocompetent cells and in the intensity of immune response of the cellular and humoral type.

Morphological changes

The total mass of lymphoid tissue, which is greatest immediately following puberty, gradually decreases later on. Involution is most clearly marked in the thymus, while the lymph nodes and spleen in normal individuals remain unchanged, or are only slightly reduced (2, 3). In old age, the cortex of the thymus is greatly reduced and the level of the circulating thymus hormone is diminished (4). In the spleen, the amount of the white pulp is reduced and the amount of red pulp is relatively increased. Furthermore, the borderline between the red and white pulp disappears and in the spleen of older individuals usually there are no germinal centres (4). Although the lymph nodes usually only slightly decrease in size with aging, histological changes are clearly visible. The thickness of the cortical areas is reduced and these contain considerably fewer germinal centres. In the same way, the number of macrophages increases in the medulla, and the borderline between the cortex and medulla disappears due to diffuse infiltration of plasma cells. While with the aging process, the thymus, spleen and lymph nodes, and organized lymphoid organs decrease in size or undergo change, the amount of diffuse lymphoid tissue increases in the whole organism (4).

Immunocompetent cells

The number of lymphocytes appears to decrease continuously after middle-age and in the sixties, their number is reduced to 70% of that found in younger people. This decline is caused by a decrease in the number of T-lymphocytes (2). Individual variation, however, is very pronounced. Some investigations have shown the same absolute number of T-lymphocytes in all age groups (4) and that the membrane affinity of these cells for SRBC is unchanged with aging (5-7). The decreases in the number of T-lymphocytes observed in humans and animals do not appear to be sufficient to explain the age-related decrease of immune function caused by T-cells (2, 8). It is possible that aging affects only some subsets of T-cells and that this does not influence the total number of T-cells (7). The number of human B-lymphocytes does not appear to change with aging (4).

Cellular immunity

Although the evidence is to a certain extent contradictory, it seems that the capability to reject allotransplants is decreased with aging. Older individuals tend to show weaker reactions of delayed skin hypersensitivity to ubiquitous microbial antigens such as tuberculin (4), streptokinase-streptodornase, candida or trichophyton (2) but some retain normal cell-mediated immune rections. The aged also show a decreased ability to become sensitized to antigens contacted for the first time. It would appear that, in the aged, proliferation of lymphocytes is decreased in the thymus dependent zones of lymphoid organs.

The ability of "old" human and rodent lymphocytes to be activated in vitro with mitogens for T-cells is decreased (2, 4, 7-9), and the number of cells which enter the cell-cycle during stimulation with Con A is reduced (10). This diminished reactivity of human T-lymphocytes is not caused by weaker function of the monocytes but by changes in the intrinsic T-cells' properties (8). In old men, the production of and response to interleukin-2 by lymphocytes is decreased (8).

Humoral immunity

The total amount of serum immunoglobulins (4) shows little change with aging, except for slight IgM deficiency (11). However, the frequency of monoclonal immunoglobulin (7), autoantibodies (7) and autoanti-idiotypic antibodies (9) is increased with aging. The amount of so-called natural antibodies decreases, as well as the level of those antibodies which are directed against the thymus-dependent antigens (2). The amount of antibodies directed against the thymus-independent antigens does not change with aging (2, 3).

Phagocytes

Macrophage function such as phagocytosis, digestion of antigens and initiation of immune response does not change essentially with aging (2). According to some reports, the uptake of antigens in the liver is decreased and macrophages *in vitro* become suppressive (9). In older men, reduction of nitrobluetetragolium by polymorphonuclears is significiantly reduced and at the same time their ability to phagocytize bacteria is significantly diminished (7).

Other factors

Present knowledge of the diminution of immune functon in older individuals is deficient, and there are many discrepancies. These deficiencies are the result of insufficient data, great variability in the response of individuals of the same age and species, and the imperfect immunological tests vailable to determine a particular immune function or to recognize immunocompetent cells. It should also be mentioned that the frequency of inflammation, renal failure, diabetes, anaemia, vitamin deficiency, poor skin reactivity, reduction in non-specific defence, etc., increases with aging and that these factors can influence the quality of immune response. Consequently, it is not easy to say whether immunodeficiencies in the aging process are caused only by a weakening of the immune system, or also by the additional effects of the above factors.

Irradiation

Local radiation therapy can have far-reaching consequences for infection by damaging epidermal and intestinal epithelial cells, and thus protracting wound healing and promoting invasive growth of enterobacteriaceae. If substantial portions of haemopoietic bone marrow are included in irradiated fields, impairment of granulopoiesis may result which represents a severe danger for fatal septicaemia. The high radiosensitivity of lymphoid tissue concerning both T- and B-cell compartments is well known. As a consequence, cell-mediated immune reactions and primary humoral immune responses are markedly depressed. Recent study of the influence of radiation therapy on T-cell subpopulations in the blood of women with breast cancer has shown an impressive reduction of 70-80% in the absolute cell numbers of suppressor and helper T-cells (12).

Steroids

The profound and complex effects of glucocorticoids on the human immune system have recently been reviewed (13). Aplication of steroids in man results in a redistibution phenomenen: lymphocytes, particularly T-cells, and monocytes are shifted from the circulation to extravascular compartments such as to bone marrow. Neutrophils, on the other hand, are flushed from the bone marrow and are accumulated in the peripheral blood.

Functional alterations of lymphocytes by steroids concern their blastogenic responses *in vitro*, particularly after stimulation with Con A, or with allogenic cells in mixed leucocyte reactions. Furthermore, spontaneous and Con A-induced suppressor T-cell activities on B-cell maturation were found to be extremely steroid sensitive. Serum immunoglobulin concentrations are not decreased or only slightly in steroid-treated patients, in spite of accelerated protein catabolism.

Functions of monocytes and macrophages are heavily influenced by glucocorticoids: there is evidence for inhibition of the motility and bactericidal activity of macrophages, but not of neutrophils. In addition, the inhibition of the secretion of interleukin-1 and plasminogen activator are assumed to have an indirect effect on lymphocyte functions by selectively affecting early immunoregulatory events.

Thiopurines

The purine analogues 6-mercaptopurine and azathioprine are widely and effectively used for immunosuppression. Azathioprine is usually given in combination with corticosteroids. In man, short-term application induces little change in the numbers of peripheral B- and T-lymphocytes. The usual chronic application of conventional doses of azathioprine apparently has no influence on the humoral immunity. Delayed hypersensitivity and skin reactions are slightly or moderately suppressed, but not annihilated. After at least three weeks of treatment with 6-mercaptopurine, non-specific inflammatory reactions are weakened or abolished. Thiopurines, like other cytotoxic drugs, may lead to myelotoxic reactions with relatively long-lasting neutropenia and even affect erythropoiesis.

2.2 Immunodeficient and immunosuppressed elderly

Increased susceptibility

It is generally assumed that age-related changes in the immune system have clinical consequences, including chronic diseases, occurrence of autoimmune phenomena and increased incidence of neoplasms. Management of these disorders requires the application of cytostatic and immunosuppressive drugs and radiotherapy. The impact on the patient's immune system, already weakened by age and worn out by chronic disease processes, is a vicious circle resulting in a drastically increased susceptibility to infections (14).

Effects of immunosuppressive treatment

In addition to their desired cytoreductive, anti-inflammatory or immune-modulating action, cytostatic and immunosuppressive agents may produce adverse effects on the patient's defences, such as granulocytopenia, which is known to be the most dangerous single factor predisposing to infection, functional alterations of phagocytic cells, impaired immune responses and damage of skin and mucosal barriers (15). Some of these effects of irradiation and of immunosuppressive drugs on the immune system are briefly summarized in Table 1.

Table 1. Effects of irradiation and immunosuppressive therapy

Effect	Irradiation	Steriods	Thiopurines	Alkylating agents
Lymphopenia	+++	++	±	+
Decreased primary antibody response	+++	±	+	+++
Decreased secondary antibody response	++	-	±	++
Decreased delayed type reactions	+++	+++	+	+++
Neutropenia	+++	-	++	++
Anti-inflammatory	+++	+++	++	±
Disturbed wound healing	+++	++	-	-

Alkylating agents

A number of alkylating agents is currently used for immunosuppressive and cytoreductive purposes, such as cyclophosphamide, chlorambucil, melphalan and others. Cyclophosphamide, the best known representative of this group, is a powerful inhibitor of both humoral and cell-mediated immunity. In man, short courses of high-dose cyclophosphamide, approximately 7 mg/kg/day, completely suppress antibody synthesis, if given together with an antigenic challenge.

Infections in the immunosuppressed elderly

Mortality statistics show that with advancing age death rates due to infections increase rapidly. It is clear that the groups of advanced age include persons who are immunocompromised by chronic disease processes and by cytostatic or other aggressive treatment. One major cause of death from infection is pneumonia. However, no distinction is possible in crude mortality

statistics between deaths in which pneumonia is the underlying cause and those in which it is associated with terminal illness due to other causes. Healthy elderly people as well as elderly immunosuppressed patients are assumed to be at special risk of contacting pneumococcal pneumonia (16, 17).

Underlying diseases and patterns of infections in elderly

The most prominent conditions undermining the defences in patients of advanced age are B-cell neoplasms. Normal immunoglobulin levels and antibody responses are depressed in patients with chronic lymphocytic leukemia, non-Hodgkin lymphoma and monoclonal gammopathies such as Waldenström's macroglobulinemia and multiple myeloma. Typical infections in these patients are pneumonia and septicaemia caused by pneumococci, but also by Haemophilus influenzae and Klebsiella. Relapsing herpes zoster with tendency for dissemination and oral candidiasis are also often encountered. If the age- and disease-associated immunodeficiency is further aggravated by cytostatic teatment, incidence and severity of the infections are augmented. Moreover, the specrum of infective microorganisms is widened including Staphylococcus aureus, gram-negative bacterias, cytomegalovirus, pneumocystis and cryptococcus. Reactivation of tuberculosis is also reported to be important. In view of these consequences, the advantages and disadvantages of cytoreductive therapy in a given patient require careful evaluation. This is of particular importance for monoclonal gammopathies most of which are benign conditions needing no such teatment.

A similar pattern of infections is found in old patients who are on immunosuppressive therapy for rheumatoid arthritis or other autoimmune chronic inflammatory disorders. Elderly patients undergoing extensive surgery for various reasons comprise a separate high-risk group for infections, since it is known that anesthesia and surgery have a negative influence on non-specific and specific immune functions. Postoperative intensive care, which is necessary in many of these patients, carries a high risk for nosocomial infections: wound infections, pneumonia associated with insufficiently cleared bronchial secretions and urinary tract infections in connection with bladder catheterization, may lead to fatal septicemia. Staphylococcus aureus and E. coli appear to be among the most important organisms in these conditions, followed by Pseudomonas, Klebsiella and other gram-negative bacteria.

Immunoprophylactic measures in elderly immunosuppressed patients

Active immunization with killed vaccines may be beneficial particularly in elderly patients whose defences have not been destroyed by long-lasting immunosuppression: healthy old people were shown to produce good antibody responses to pneumococcal polysaccharide vaccine (16) and to varicella-zoster vaccine (17). In view of the disturbance of the host's defence system, the prerequisites for development of protective titres in severely immunosuppressed elderly are comprised but experience is still limited. In addition to pneumococcal polysaccharide and varicella-zoster, vaccines against hepatitis B, cytomegalo- and influenza viruses are currently being evaluated.

Passive immunization with polyvalent immunoglobulin preparations is applied regularly to many patients with chronic lymphocytic leukemia, particularly during the cold season. Hyperimmune globulins specific for hepatitis B or zoster-immune globulin are given to exposed persons. These immunoglobulin preparations have a short half-life of about three weeks and are expensive. These and other disadvantages have limited their application so far. It is possible that with new preparations for intravenous administration, reliable protection can be obtained in a number of conditions.

The effect of immunostimulatory agents on immunological reactivity in the immunocompromised elderly is still uncertain, because there are no conclusive studies that would support or reject an influence of such agents on the immune system in elderly patients.

2.3 Measurement of immune response in the elderly

Methods of measurement of the immune response

Clinical and laboratory methods are available for measuring natural or acquired immunity. The majority of laboratory assays available are for detection of a specific antibody; usually, the first to appear after immunization belong in the IgM class and are less persistent that the IgG.

The *in vitro* neutralization tests for detecting or quantifying antibodies after immunization are expensive and require well-trained personnel and large numbers of suitable animals. Therefore, many efforts have been made to develop simple, economical, sensitive and reproducible *in vitro* methods for detecting and quantifying antibodies. The most frequent tests are based on specific interaction between antigen and antibody to detect the presence of antibody. The results are highly dependent on the conditions under which the test is performed.

The *in vitro* technique for antibody determination is based on the reaction of antigen and antibody containing serum. Antibodies which precipitate with a soluble antigen: precipitins are demonstrated by gel diffusion and counter immunoelectrophoresis radial immunodiffiusion. Their relative insensitivity in quantification of specific antibodies precludes their usefulness.

Similarly, agglutination reactions, are used in assaying specific antibody production. The agglutination reactions are, however, more sensitive and can be performed directly or indirectly. A number of viruses are capable of agglutining erythrocytes of various species. Antibodies against such viruses can be demonstrated in the sera of patients by specific inhibition of agglutination.

Another property of immunoglobulin, useful in quantitating specific antibody, is its ability to fix complement.

Neutralization of pathogens is a very sensitive assay for specific antibodies; quantification of antiviral antibodies is particularly useful and sensitive.

More recently, a variety of other assays with increasing sensitivities has been developed (immunofluorescence, enzyme-linked immunosorbent assay (ELISA), radio-immuno assay for determination of specific antibodies).

Quantitative tests for measuring antibodies

The tests most usually used for measurement of antibodies are listed below:

- haemagglutination inhibition test (HI) for influenza A and B, rubella, measles, mumps;
- complement fixation test (CF) for influenza A and B, mumps;
- neutralization test for poliomyelitis, measles, rubella;
- indirect immunoflourescence assay (IFA) for rabies, pneumococcal infection;
- passive haemagglutination for tetanus;
- enzyme-linked immunosorbent assay (ELISA) for tetanus, rabies; and
- radio-immuno assay (RIA) for tetanus, pneumococcal infection.

Serological investigations

A few serological studies on the immune status of elderly with respect to several diseases, such as influenza, pneumococcal infection, poliomyelitis, tetanus or rubella, were done. At present, there is no known study on the prevalence of diseases such as measles, diphtheria, pertussis or mumps in older persons. Several serological surveys and attempts at immunization dating back before 1970 show the immune status of older people with respect to various viral affections before and after immunization.

In a study of antipoliomyelitis antibodies, it was shown that 27% were seropositive individuals for all three types of persons aged 71-93, while 3% were positive for measles (18).

More recently, the study of the antirubella antibodies of 80 persons, aged 50-90, has shown that 28% were seronegative between ages 50 and 60, 24% between 60 and 70, 5% between 70 and 80, and 20% between 80 and 90. It is questionable whether the relative loss of rubella antibody in old subjects is due to the decline in immunity in previously infected persons or owing to the fact that these persons had never been infected. However, the high titre observed at this age may be dependent on reinfection.

IgG, IgA and IgM concentrations in sera of 31 subjects over 70 years of age have shown a significant increase in IgA and a reduction in IgM, while there was a decrease in B-IgM cells and an increase in B-IgG cells observed in comparison with a youthful control group (19). Following diphtheria vaccination, the percentage of seropositive individuals was comparable in the two groups, whereas before vaccination 40% of the young people were positive as against 60% of the elderly people.

Only 62% of seropositive individuals for the three types of polio virus was found in the United Kingdom in the population over 65 years old (20). No serological study is available in France, but half of the cases of poliomyelitis reported since 1980 occurred between the ages of 30 and 60 years.

In a study of antitetanus antibodies in persons aged 66-90, 62% were found to be seropositive in Switzerland (21) and in France from 50% down to only 6.6% (22).

Assessment of immunological aging

The notion of immunological aging is quite imprecise since the different phases of life constitute a fluid process and there is no sudden transition from adulthood to old age.

The immune response to antigen stimulation following immunization shows contrasting results. Indeed, antibody production decreases with age but with variations depending on the antigen injected, the number of doses and the individual response. It is difficult to determine whether what is observed is truly the primary response or represents a secondary response.

Since intradermal tests are increasing in number, a multipuncture method, which is more acceptable to patients and enables the simultaneous study of delayed skin-hypersensitivity reactions for several different antigens including the control antigen, has been developed. A study of three groups of older people (age 75-84, 85-94 and 95 or over) compared with a group of adults demonstrated fewer positive responses, a lower mean antigen response to less than or more than three antigens and decreasing intensity of the responses to antigen with increasing age.

Immune normality in elderly

Not all old people are immunologically deficient compared to younger persons. There is a population of 80-100 year-old subjects whose immune systems appear to function absolutely flawlessly. The prevalence of these "immunologically normal" elderly in the population has not been determined. There is some evidence that "immunological normality" is correlated with longevity, whereas persons of the 60-70 years group with impaired immune functions (skin tests to recall antigens) show a shorter survival. On the average, with age, immune functions deteriorate while individual variations increase.

2.4 Immune response to tetanus toxoid and influenza vaccine

Immune response to tetanus toxoid

The best evidence of the immune response is serological conversion and effective protection against disease.

A study in France of a large group of persons over 65 has shown that the serological response was in accordance with the initial titre of the vaccine, the absorbent, the number of injections and the interval between them (22). Regardless of the titre of the vaccine used, the antibody response was identical when three doses were administered, but differences are seen when the vaccination schedule is reduced to two injections. The best results were observed in persons vaccinated with a highly antigenic vaccine with a titre of at least 30 LF.

In addition to the above study, the surveys have shown that most of the antitoxins have insufficient antigenicity for use in a single injection in older people. The seroconversion rates reported in the various surveys range from 42% to 50%. However, there are delayed responses to tetanus immunization (23). Seroconversion rate increased, e.g. from 39% after one month to 59% at five-months interval, and the antibody level rose from 76% to 100% when the interval was increased from one to five months (24).

The age-related study has shown a better response to vaccination in elderly people under 80 years old with definitely higher antibody titres.

Immune response to influenza vaccine

Comparison of influenza antibodies one year after vaccination in persons vaccinated only once or during three consecutive winters indicates that for the 40-90 year-old population, repeated immunization has no cumulative effect on the level of anti-A and anti-B antibodies. The results are different for persons over 60 years of age in whom repeated immunization has no cumulative effect on the level of anti-A antibodies but a noticeable one for anti-B.

The pre-immunization immune status with respect to the influenza virus strains contained in the vaccine depends on the prior circulation of that strain. This is the case for the A/Brazil/78 (H1N1) strain for which a high proportion of the elderly people were seropositive, owing to its circulation some 25 years earlier.

As a whole, 75-95% of subjects, depending on their age, responded to influenza immunization for the A-virus, while only 65% responses to the B virus and 57% remained below the protective level.

3. Influenza

3.1 Epidemiological surveillance

In general, surveillance involves a complex study of the infection as a dynamic process involving etiological agent, host, environment and all conditions which may influence the process of spread of infection. The aim is to create an efficient system of measures to control, eliminate or eradicate the infection.

As far as influenza is concerned, some most important elements of surveillance are below.

Main sources of surveillance data

Regular reports

Mortality reports include the number of deaths attributed to influenza, pneumonia, bronchitis and other acute respiratory diseases.

Morbidity weekly reports of all acute respiratory infections including influenza (ARI) are provided by primary health practitioners by age group and admissions to hospitals.

Work and school absenteeism reports include the number of people absent from work or school due to ARI.

Laboratory reports

Virus watch programme is a continuous programme following the circulation of influenza virus and other respiratory viruses throughout the year including the nonepidemic period. The material is collected from selected sentinel stations or spotters and in cases of ARI outbreak from any place of its occurrence. Antigenic, biological, ecological and pathological properties of isolated influenza viruses are studied.

Serological investigation, paired acute and convalescent sera taken at a 7-14 day interval, are investigated for a four-fold or greater rise in antibody titre. Unpaired sera (a group of acute and a group of convalescent sera) are used to make a more rapid diagnosis of an influenza outbreak.

Serological surveys

Serological surveys carried out annually, in which sera are obtained from healthy persons of all ages and tested for the presence of influenza antibodies with different antigens, are used to estimate the level of collective immunity of the population.

Immunization

Influenza immunization is usually recommended in the late autumn or the beginning of winter, several weeks before the influenza season (depending on the geographical and climatic conditions of the country), using vacccines containing killed combined (types A and B) virionic vaccine containing antigenic strains. Groups of the elderly for whom vaccine is particularly recommended include:

(a) acquired or congenital heart disease associated with pulmonary congestion;

(b) chronic pulmonary disease associated with compromised respiratory function;

(c) chronic renal disease, especially with azotemia;

(d) chronic metabolic disease, such as diabetes mellitus;

(e) immunodeficient or immunosuppressed conditions, including malignant tumours, leukemia, etc., under therapy; and

(f) chronic severe anaemias, such as sickle cell disease.

Information dissemination

Weekly reports of ARI incidence are analysed and distributed rapidly to all components of the epidemiological service, including national and local health authorities, clinicians, and laboratory and public health workers. The weekly report includes:

- data on general and age-specific ARI mortality and morbidity in the country, regions and districts;
- commentary on the epidemiological situation in ARI;
- information on the recent influenza situation in the world; and
- results of the work of virological laboratories.

The results of serological influenza surveys should be published annually and distributed to all concerned as above.

Prediction of epidemics

Influenza epidemics can be predicted as follows.

Short-term prediction includes the continuous evaluation of the results of laboratory investigation, i.e. virus isolation and serological investigation, supplemented by the evaluation of mortality and morbidity reporting and comparison of the actual figures with the situation in he previous seasons.

Long-term prediction takes three sources of information into consideration for the prediction of influenza epidemics for the coming season: (a) the antigenic types of recently isolated influenza viruses; (b) the immunity of the population, naturally or artificially induced, estimated according to the results of previous serological survey; and (c) influenza incidence in the southern hemisphere.

Interpretation and guidance for vaccination

The aim of surveillance is to create an efficient system of measures to control, eliminate or eradicate the infection. It is not possible, however, to influence substantially the spread of influenza at present, because there is practically no way of isolating the source of infection and

no way to interrupt transmission. However, we are able to change some population groups from susceptible to immune to a limited extent. The clinical and epidemiological impact of this effort is usually not enough to persuade the public or health workers of its efficacy.

There are many negative factors influencing the practical effectiveness of influenza surveillance:

- the differential (etiological) diagnosis of ARI in the field is unreliable which increases the difficulty of evaluating the preventive effect of vaccination or chemoprophylaxis;
- problems concerning the composition of the vaccine as well as the route of administration, the role of humoral and secretory antibodies; and
- the problem of resource allocation, even in the case of good vaccine, and of sufficient time and personnel for vaccination of persons who are at greatest risk.

As far as the immunization of the elderly against influenza is concerned, it is necessary to consider the following:

- vaccination against influenza is not compulsory, some older people accept, some of them do not like "new" things at all;
- preventive vaccination programmes which are successful are carried out mostly in children because, apart from other reasons, paediatricians are more oriented to prevention than general practitioners; and
- mass vaccination campaigns have been used with success in adults (like tetanus immunization), but in the case of influenza, it is difficult because of scarcity of vaccine and its short-lived effect.

3.2 Early warning of outbreaks by excess mortality monitoring

Analysis of excess mortality

Monitoring of excess mortality is of a great value for the early warning of influenza epidemics because, although it lags about two to three weeks behind increases in influenza morbidity, it serves as the primary quantitative indicator of the increase of the rate of infection (24).

Excess mortality is defined as the difference between the observed number of deaths and the expected or prognosticated number of deaths in a given interval, e.g. a month.

Due to the great differences in the expected number of deaths from one age group to another, excess mortality must be expressed relatively, i.e. against the expected number of deaths in single age groups. The percentages of excess mortality in different age groups and different areas can thus be compared.

Excess mortality, as an absolute indicator, may often lead to the wrong conclusion, especially when mortality is analysed by age group. There are significant differences in mortality among different age groups - in the young age groups death rate is very low and among persons over 65 years of age it is very high. For example, in Yugoslavia in December 1972 excess mortality amounted to:

- 200 in the 45-64 year age group;
- 620 in the 65-75 year age group; and
- 950 among those over 75 years of age.

Expressed relatively, excess mortality was:

- in the 45-64 year age group 24.4%;
- in the 65-75 year age group 27.2%; and
- in the over 75 year age group 39.3%.

This means that in December of 1972 mortality in the 65-75 year age group was 2.8% higher than in the 45-64 year age group and 14.9% higher among persons over 75 years of age than in the 45-64 year age group.

The number of deaths from all causes and the number of deaths from pneumonia and influenza in Yugoslavia in an 11-year period (1960 to 1971) have been analysed. An increase in mortality never occurred except during influenza epidemics. Mortality from all causes was much higher than mortality from pneumonia and influenza. Thus, for example in March 1964, the number of deaths due to all causes was 7334, and the expected number of deaths was 3500. At the same time, about 800 persons died of pneumonia and influenza, while the expected number of deaths from these causes was approximately 100 persons. Analysis has shown that the greatest excess was due to cardiovascular and bronchopulmonary deaths. However, they could not account for the whole excess of 3800 deaths. Similar conclusions have been reached from analysis of the excess death rate and causes of deaths in another influenza epidemic which occurred at the end of 1969. These data indicate that excess mortality from all causes is the best quantitative measure of influenza epidemics.

Correlation between excess mortality and influenza morbidity

One of the classical descriptions of epidemics, which is often associated with influenza, is "high morbidty, low mortality" (25). However, one should always bear in mind that morbidity in an influenza epidemic may be so high that even a low mortality involves a great number of deaths (26). Every influenza epidemic in a population leaves behind a sharp peak of deaths from various causes. By analysing the causes of deaths and influenza epidemics a close correlation between excess mortality and influenza epidemics can be detected.

The expected mortality from all causes is generally in good accord with the observed number of deaths, except in those months when there is an increase in influenza morbidity. In the 45-64 year age group excess mortality was clearly noted during the four greatest epidemics in 1970, 1972, 1973 and 1975 which occurred in Yugoslavia. During three smaller epidemics (1971, 1976 and 1978), there was no excess mortality, or it was only minimal and could be considered as an accidental deviation. In the 65-75 year age group, excess mortality was noted each time there was an excess of deaths from all causes and when there was an increase in influenza morbidity. The same excess mortality was also noted in the over 75-year age group. Excess mortality, with regard to the cause of death, was found to be associated with acute respiratory, cardiovascular and bronchopulmonary diseases in all the three age groups observed.

During the influenza epidemics at the end of 1972 and the beginning of 1973 in Yugoslavia, the reported excess mortality amounted to 71%. At the beginning of 1975, reported excess mortality was 40%. In 1976, reported excess mortality was 27%, and in the 1978 epidemic excess mortality of 26% was observed.

The reported number of cases is certainly in every country smaller than the actual number of persons affected by influenza. However, the difference between these two numbers is believed to be more or less the same in all epidemics. The correlation between the number of cases and excess mortality was found to be highly significant statistically. It was observed that the percentage of excess mortality increases exponentially with the increase in influenza morbidity. The studies performed elsewhere, e.g. in the USA (27), confirm the above observations. It is therefore considered that the above method should be generally accepted and excess mortality analysis used as a rapid and most reliable quantitative indicator of the magnitude of influenza epidemics.

3.3 Immunization of the elderly against influenza

Studies of age-related mortality during pandemics of influenza have shown that the highest death rates occur in elderly persons (1). Although this excess mortality is most striking when a major antigenic shift occurs in the influenza virus, it is also evident in interpandemic years. In outbreaks of influenza A and B in the institutionalized elderly, mortality can be substantial (up to 30%) (28). An especially high rate of mortality has been reported among the elderly with underlying chronic diseases (29-31), ranging from 157 to 615 per 100 000 in persons aged 45 years and over (29).

The high proportion of influenza-associated deaths involving persons older than 65 years clearly indicates a need to give high priority to ensuring that such persons receive protection before influenza epidemics. Annual immunization of this high-risk group has been justified on both epidemiologic and economic grounds (30, 32).

Immune responses to influenza vaccines in the elderly

The efficacy of influenza vaccines is usually estimated on an immunological basis by the seroconversion rate and the percentage of vaccinated subjects showing an antigen agglutination

antibody titre thought to be protective (40). In principle, it has been found that there are no substantial differences in antibody responses between young and elderly populations to different subtypes of influenza viruses (33, 34).

In another study (5), 65% of elderly persons developed four-fold or greater responses to a split-product vaccine and 65-86% of recipients of whole-particle vaccines (H3N2 antigens) seroconverted (35, 36). However, response of the elderly to A(H3N2) antigens may be less frequent and of lower magnitude (37). A high rate of seroconversion in the elderly was reported in trials with vaccines containing A(H1N1) antigen (37-39). Whole-particle and subunit vaccines were similar in their antigenicity. Nasal secretory antibody responses in the elderly were also similar to the responses of younger subjects (33, 40).

Very limited information is available on cell-mediated immunity of the elderly to influenza. The available data (34, 41) suggest that there may be some important differences in cell-mediated immunity responses of the elderly in comparison with younger subjects in response to influenza vaccines.

Side effects

Most studies have shown that influenza vaccines are safe and well tolerated in elderly persons. Local and systemic reaction in the elderly occur with much the same frequency as in younger adults. Split-product and whole-virus vaccines appear nearly equivalent in terms of side effects and antibody repsonse (37, 38). In addition, so far no unexpected side effects, such as exacerbation of underlying diseases, were observed during the early or late observation period (37). Comparison of the effects of repeated vaccination on the kinetics of antibodies and on tolerance of the vaccine has shown that after a single injection, local and systemic reactions in children, adults or elderly persons were minor and short lived. Among several hundred individuals vaccinated twice, reactions were noted in 1.7%. There were 2.2% systemic reactions in adults and elderly persons immunized three times. No systemic reaction was observed in the few persons who were vaccinated during four consecutive autumns.

Vaccine effectiveness

Influenza vaccines tested in controlled trials in elderly populations have generally been effective. It has been shown (42) that vaccine efficacy relates to the pattern of vaccination: individuals who received a single does of A2 vaccine in two consecutive years of study were considerably better protected than those who had received vaccine in only one of the years. The rate of febrile illnesses in the former group was more than 90% below that of the vaccinated control group. Those given one does were only about half as well protected.

Some reduction in the duration of fever resulting from the use of the most recent vaccines even in the face of antigenic drift of the influenza A-type virus has been demonstrated (30). A clinical study among a geriatric population showed that influenza infections followed a milder course and brought about fewer complications among vaccinees and the mortality rate was 20 times less (43). In another study, vaccination in a geriatric hospital reduced the influenza attack rate from 36% to 10% in 1977 and from 25.7% to 5% in 1978 (44).

In non-institutionalized elderly persons with underlying diseases, vaccination with closely matched vaccine significantly reduced influenza hospitalizations and death compared with non-vaccinees (29).

However, several studies have failed to show protection from influenza vaccines. A major reason for the lack of effectiveness was that the vaccine virus did not match the epidemic virus (45, 46) or was not potent (6). Vaccine protection could not be shown in persons over 65 years of age who did not have underlying disease (4). In another similar study (47), a trivalent (A/Victoria/75 (H3N2), A/Scotland/74 (H3N2), B/Hong Kong/73) vaccine administered to a "regular vaccinee" geriatric group in 1976 failed to reduce the incidence of epidemic influenza (A/Victoria/75 infection), although it did confer protection in younger groups of subjects with less prior vaccine experience. Although most findings suggest that inactivated vaccines confer substantial protection against influenza in elderly subjects, further controlled studies are required to elucidate the optimal usage of the vaccine for the protection of the elderly.

Improvement of technology and an understanding of the genetic basis of virus growth in recent years has enabled the production of purer (free from egg proteins) and more standardized (using single radial diffusion) inactivated influenza vaccines. But much more should be done to increase efficacy of influenza vaccines.

It has been shown that antibody of persons naturally infected with influenza reacts serologically more often and to higher titre to cell-grown virus rather than egg-grown virus. This implies that influenza vaccine viruses grown so far in eggs may not exhibit the optimal antigenic determinants to induce protective antibody.

Furthermore, although immunization remains the major public health control measure for influenza in the elderly, additional control measures such as antiviral agents are required. The recent WHO informal consultation on clinical use of amantadine/rimantadine (Vienna, August 1983) has recommended rimantadine prophylaxis for elderly and high-risk individuals especially for those who reside in nursing homes and similar institutional settings, whether or not they have received influenza vaccine when influenza A activity is suspected or detected in the institution or community.

Rimantadine can be administered during the period of greatest risk for acquiring infection, generally the 4-6 week period following an outbreak, although occasionally, depending on circumstances, shorter or longer periods of prophylaxis may be advisable. The recommended prophylactic dose of rimantadine is 200 mg/day. Studies have demonstrated that this drug will prevent 70-90% of influenza A.

Vaccination strategy

The primary goal of the influenza vaccination policy, past and present, has been the reduction of excess death (49-51). In several countries (Canada, France, the Federal Republic of Germany, the United Kingdom, the United States and the USSR), vaccination is recommended for older persons, particularly those over 65 years of age. In the USA, the Immunization Practices Advisory Committee recommends annual influenza vaccination for all persons over 65 years of age and for persons younger than 65 years with chronic underlying illnesses (48). In spite of repeated recommendations in the USA, an average of 9500 excess deaths annually was estimated in this high-risk group from 1968 to 1976 (27). During this period, fewer than 20% of the elderly population received influenza vaccine (52, 53). Given the observed two-fold or three-fold excess influenza mortality during the epidemics, one half to two thirds of these deaths may be considered potentially preventable by providing influenza vaccination universally to those at highest risk.

The clinician plays a critical role in implementing this policy by recognizing and vaccinating patients at greatest risk. Various strategies for efficiently increasing the delivery of vaccines have been proposed.

Since nursing home residents are an easily accessible high-risk population, Fedson (54) has recommended focusing vaccination efforts in nursing homes and hospitals. Larson et al. (55) have suggested a strategy of sending "reminder postcards" to all high-risk patients in a practice. It is clear that the control and prevention of influenza should be a high priority in the elderly, but the choice between different strategies depends on health care and morbidity patterns of a particular population.

4. Pneumonia

4.1 Pathogenesis and immunity

Incidence

Pneumonia may afflict persons of any age, but both its incidence and its mortality rate are highest late in life. In the USA in 1974, "influenza and pneumonia" ranked fourth among the causes of death of those 65 years of age and older - the only category of disease of infectious origins among the ten leading causes of death. A retrospective study of pneumococcal bacteremia, most commonly a sequel to pneumonia, showed its incidence to be two and a half times higher among those in their 60s than in persons of all ages.

Reasons for the increased incidence of and mortality from pneumonia in the aged are only partially understood. Changes affecting both natural resistance to infection and the immune mechanisms evoked in response to specific pathogenic microorganisms doubtless play a role. Alterations in the structure and functional capacity of the lower respiratory tract are associated with the increasing incidence of pneumonia with advancing age (56). Musculoskeletal changes reduce vital capacity and the forcefulness of cough; neuromuscular alterations affect flottal closure and the cough reflex, increasing the frequency of aspiration; and alveolar edema resulting from cardiac failure impairs pulmonary clearace of bacteria, increasing the likelihood of pneumonia.

It is unclear what role, if any, alterations caused by advanced age in cellular immunity play in the pathogenesis of acute pneumonities of diverse causes in the elderly.

Continuous exposure of the respiratory tract to the external environment and the diversity of microorganisms capable of infecting makes prevention of pneumonia difficult. All agents causing respiratory infection, however, are not equally invasive. It is appropriate to direct prophylaxis, when possible, against those giving rise to the greatest number of illnesses and deaths.

The normal mammalian respiratory tract is highly resistant to infection with most bacteria but becomes vulnerable to such infection following injury to the lungs by physical, chemical or viral agents. Aspiration of gastric contents and of material fed to supine patients are doubtless important factors contributing to the increased incidence of pneumonia in the elderly and debilitated (56, 57). Among the viruses, infections of the aged with those of influenza are among the most important causes of morbidity and mortality, especially in persons with chronic underlying illness. In addition, the pulmonary injury of influenza predisposes to secondary bacterial pneumonia, most commonly pneumococcal, less frequently staphylococcal.

Despite such demonstrated efficacy, influenza vaccines are greatly underutilized. A high proportion of patients dying of "influenza/pneumonia" had been hospitalized in the previous year, and this suggests that those in this category be given influenza vaccine immediately prior to discharge from the hospital (58).

Among the bacterial pneumonias, those acquired outside of hospitals are caused most commonly by Streptococcus pneumoniae. Although antimicrobial drugs have brought about significant reduction in the mortality of pneumonia caused by the pneumococcus and by a number of other bacteria, there is no convincing evidence that a decline in the incidence of such infections has resulted from their use. The fatality rate from bacteremic pneumococcal infection is still unacceptably high. Eight studies from four countries in the past two decades have shown it to exceed 25% following treatment, with penicillin or with other antibiotics, of persons over 50 years of age or of those suffering from a variety of chronic illnesses (59–67). The group at high risk of death from bacteremic pneumococcal pneumonia is quite similar to that at high risk of death from viral influenza.

Study of the survival curves of untreated patients with bacteremic pneumococcal pneumonia and of similar patients treated with antipneumococcal serum or with penicillin shows little difference in the first five days following the onset of illness. This observation suggests that death results from early irreversible physiologic injury of the patient, injury not influenced by antimicrobial therapy. Two thirds of all deaths among patients with bacteremic pneumococcal pneumonia treated with antibiotics occur in this five-day period. Because the nature of the physiologic injury resulting from pneumococcal infection is not understood and means to reverse it are not available, prophylaxis appears to offer the best way of reducing the incidence of fatal infections among those at risk (59). An additional reason for considering the prevention of pneumococcal infection is the gradual increase in the number of isolates showing augmented resistance to one or more antipneumococcal drugs (68).

4.2 Pneumococcal polysaccharide vaccine

Tetravalent vaccine of pneumococcal capsular polysaccharides was shown to be safe and effective in preventing type specific pneumococcal infection in military recruits in 1945 (69). In a similar study in an industrial population in which a trivalent vaccine was administered, the polyvalent vaccine was shown to be 85% effective in preventing bacteremic infection caused by types represented in the vaccine (70). In addition, in this population in which the preponderance of acute pulmonary infection was caused by the pneumococcal types represented in it, the vaccine was effective in reducing by 50% all radiologically confirmed pneumonia in vaccinees, irrespective of cause, over the two-year period of the trial. The successful demonstration of the efficacy of vaccines of pneumococcal capsular polysaccharides in preventing type-specific pneumococcal infection in these two studies was facilitated by the high attack rates of disease, the access of participants in the trials only to participating hospitals and the high level of cooperation of physicians involved in their care.

Studies of pneumococcal vaccine in the elderly, although less definitive, are consistent with its efficacy in this segment of the population. Investigations of the responsiveness of older persons to the vaccine suggest that the levels of antibodies achieved may be somewhat lower and persist for a shorter duration than in younger adults, although the differences are not

striking (71, 72). There is need for additional studies to determine the optimal age of immunization to provide maximal protection for the elderly. A trial with a trivalent vaccine in 5000 persons over 50 years of age showed a 90% reduction in vaccinees of bacteremic infection, caused by pneumococcal types in the vaccine, when contrasted with a similar cohort of unvaccinated controls (73). Some questions regarding the design of this experiment have been raised. In a later trial of a 12-valent vaccine in 6500 persons over 45 years of age and a comparable number of controls, there was too little bacteremic infection to permit meaningful analysis. Ambiguities associated with immunological diagnosis prevent firm conclusions (74). The results are consistent, nonetheless, with the vaccine's efficacy in preventing infection caused by the pneumococcal types represented in it. Further data are needed to assess more fully the efficacy of polyvalent vaccines in high-risk populations. Because the immunological behaviour of a vaccinee, with a nonbacteremic infection and a pneumococcal type represented in the vaccine, is unknown and can be learned only from studies routinely employing the invasive techniques of transtracheal or lung puncture, such investigations are unlikely to be done for ethical reasons. Study of the efficacy of pneumococcal vaccine in preventing bacteremic infection does not require the use of immunological methods to confirm diagnosis. Its incidence is such in most populations, however, that the enrollment of 100 000 or more participants would be required, and the economic and logistical problems associated with conventional randomized double-blind trials of such size are likely to preclude them. Alternative methods of analysis are available in the form of case control studies (75) and of studies by the method proposed by Broome et al. (76). Preliminary results of such studies are consistent with the efficacy of the vaccine.

Although 83 pneumococcal capsular types are known, all are not equally invasive. The composition of the 23-valent vaccine licensed recently in the USA is derived from the distribution of pneumococcal types or groups causing over 13 000 infections of blood or spinal fluid in all five continents.

4.3 Immunization of elderly again pneumonia

There is some difference in prevailing types of pneumococci, therefore, the vaccine should be composed so as to protect against those most prevalent. The antigens included in the vaccine represent the capsular types responsible for 80-90% of bacteremic pneumococcal infections worldwide. It is important to bear in mind that pneumococcal vaccine is the most complex vaccine ever developed for administration to man and that it is designed to prevent many immunologically distinct infections. This fact should be taken into consideration when planning immunization of high-risk groups as the efficacy of pneumococcal vaccine is likely to be less than anticipated. If one vaccinates a cohort of susceptible persons, who respond equally well to the polysaccharides in the vaccine and experience comparable exposure thereafter to all the types included in it, and if one hypothesizes further that the efficacy of each individual antigen in the vaccine is 99%, then the maximum attainable efficacy of the polyvalent vaccine will be 0.99^{23} or 79%, if the failure of one component is considered equivalent to failure of all. It is important that the above should be considered in making realistic predictions and later evaluations of the immunization programmes carried out with a polyvalent pneumococcal vaccine.

Like influenza vaccine and for some of the same reasons, pneumococcal vaccine is underutilized. Omission of the vaccine results, in part, from lack of awareness of the continuing high mortality from bacteremic pneumococcal infection in certain segments of the population and, in part, from the desire for more definitive data on the vaccine's efficacy in some categories of patients at high risk of fatal infection, including the elderly. Such data can be obtained only if more persons at high risk are vaccinated in the future and are compared with their unvaccinated counterparts by means of case control and cohort studies, as noted earlier. Because many patients dying of pneumococcal pneumonia have been hospitalized in the five years before their deaths, it was proposed that, when hospitalized, those identifiably at high risk be vaccinated prior to discharge if they have not been immunized previously (77).

Vaccines are not available to prevent most other forms of bacterial pneumonia, including those caused by staphylococci, group A streptococci, the enterobacteria, *Pseudomonas aeruginosa* and *Legionella* spp. A tetravalent meningococcal vaccine, including the polysaccharide of group Y (78), and a vaccine of the capsular polysaccharide of *Haemophilus influenzae* type b are available, but the related organisms are insufficiently studied as causes of pneumonia in the elderly. However, in some areas and at the time of epidemics of cerebrospinal meningitis due to group A and/or C and Y, combined polysaccharide vaccine could be applied. The combined vaccines for elderly are still to be developed.

5. Tetanus

5.1 Tetanus as a problem of the elderly

Incidence

More than one million people die from tetanus in the world every year, most of them in developing countries. By contrast, over the last 30 years (1951-1980), tetanus morbidity has markedly declined in all developed countries (79). Among the most important contributing factors are the increasing proportiong of births with medical aid, the extension of routine active immunization, prevention of accidents, and better wound care.

In the USA, over the last 60 years tetanus mortality rates diminished by more than 38 times. This occurred in all age groups, especially in the 0-9 year and 10-19 year age groups. However, the trend came to a halt in adults as the immunization programme failed to reach them (80). Case fatality rates among tetanus patients have remained about 70% for newborns and above 72% for persons over the age of 60 years.

During the period 1951-1970, the loss of life due to tetanus among the European population, exceeded 3000 per year; but over the last decade (1971-1980), the number of such deaths has fallen to less than 1000 per year (81). In some regions, where tetanus used to be a severe problem (e.g. Moldavian SSR) due to immunization programmes, the mortality rates dropped 105 times over a period of 14 years (1961-1974) (81).

Selective studies on immunity to tetanus in developed countries have shown that from 80% to 98% of children in the 0-15 year age group had a protective level of antitoxin in their serum, while only 50-75% of those over the age of 50, as well as women, afforded such protection (81).

In all developed countries, there has been a trend of gradual increase of overall tetanus fatality rates (over 60%) owing to the shift of the high-risk groups towards the elderly.

Experience in many countries has shown that planned active immunization is a very effective measure in combating the disease. Only persons who are actively immunized and have a protective level of antitoxin in their blood can be guaranteed from any risk of contracting tetanus.

Estimation of prevalence

A mathematical model (2) has been developed to determine the risk for non-immune population. It is estimated that risk (R) varies greatly depending on the character and quantity of open wounds and environmental conditions (contamination of soil with Cl. tetani and season).

However, as the risk (R) is universal and unpredictable in every individual case of injury, the only guaranteed way to avoid it is active immunization of every individual.

At present, high-risk groups of the population in developed countries are concentrated among the elderly and women.

In order to ensure maximum safety and effectiveness of immunization programmes, they should be monitored with serological estimation of the level of circulating antitoxin, as well as allergy studies to prevent possible severe post-vaccinal complications.

5.2 Immunization of elderly with tetanus toxoid

Tetanus toxoid

Tetanus toxoid has been proven of high effectiveness and the elderly develop, in general, a good immune response to it. In a recent study of tetanus immunization among older subjects in France, the effectiveness of three toxoids containing respectively 10LF (Tetavax Nerieux), 30LF (Tetavax Nerieux), both adsorbed on aluminium hydroxide, and the third one containing 30LF adsorbed on calcium phosphate (IPADT Pasteur) was determined.

The subjects, over 65 years of age consisting of 182 women and 63 men, were divided into two groups:

- the first group received three injections, two injections one month apart, the third injection four months later; and
- the second group received two injections at an interval of five months.

Blood samples were taken before immunization, one month after each injection and 6, 9, 21 and 33 months after the third injection in the first group and the second injection in group two.

Regardless of the titre of the vaccine employed, the antibody response to all three toxoids is the same, when three injections are given. There is a difference, however, when two injections are given; better results are obtained with tetanus vaccine containing 30LF adsorbed on alumium hydroxide.

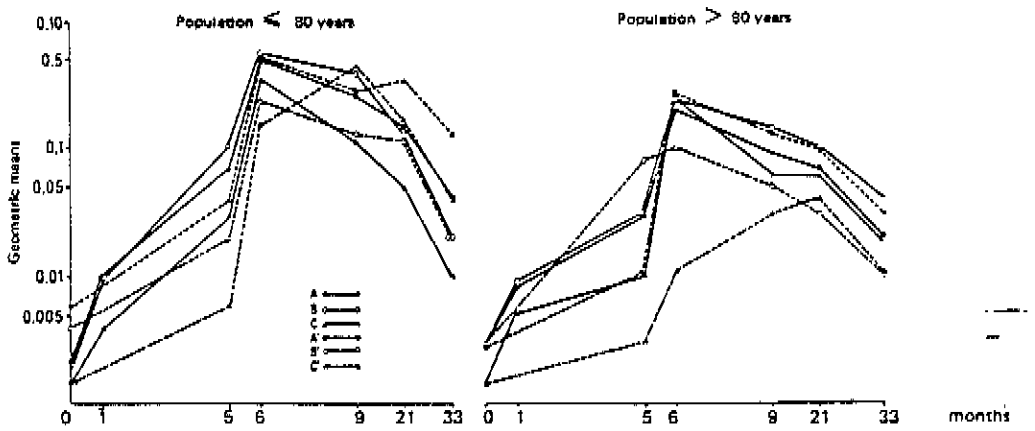
Despite the increased antibody titre found one month after the second or third injection, depending on the group, a rapid drop in the antibody levels was observed, especially following vaccination with vaccine adsorbed on calcium phosphate.

Nevertheless, although the post-immunization antibody levels were stable for at least one year, titrations done 28 months after the second or the third injection showed a large drop in the percentage of protected subjects.

Furthermore, the study of the results in the group which had three injections, as compared with those in the second group, showed that the injection given one month after the first seems to have had little effect on antibody production.

Better responses were achieved among people under 80 years of age. The geometric means of antibody titres were considerably higher.

Fig. 1. Tetanus immunization in elderly - geometric means of antibody as related to age



Immunization programmes

Effectiveness and safety being proven for tetanus toxoid as well as long-lasting immunity indicate that the problem of the protection of the elderly lies entirely on the sound programme and the logics of the application of this relatively safe and rather potent antigen for protection of the newborn and all ages. It was proposed at a number of international conferences on tetanus that every 10 years or so adults should be revaccinated in order to keep the level of individual immunity high enough because so called "natural immunity" in tetanus if of low occurence in developed countries. The matter depends on the ability of health administration to execute such programmes and to obtain the cooperation of adults and elderly people to participate in them and to be vaccinated.

6. Hepatitis B

Prevalence

Hepatitis type B(HB) is present in all parts of the world. It is transferred by the inoculation of blood or blood products containing hepatitis B virus (HBV) (i.e. Hapadnavirus type 1) and to lower extend perinataly and through sexual contacts (83). The prevalence of HB infection can be estimated on the basis of the detection of HBV markers, primarily the surface antigen HBaAg. There are three zones of HB prevalence in the world, namely: low-prevalence zone (HBaAg incidence of 0.1-0.5%) covering northern and western Europe, North America and Australia; intermittent-prevalence zone (HBsAg incidence of 1-5%) covering the Middle East, southern and eastern Europe, South America and the USSR; and high-prevalence zone (HBsAg incidence of 6-30%) covering most of Africa and Asia (84).

Hepatitis B vaccine

Hepatitis B vaccine has been shown effective and it is indicated for persons at high risk for HB infection irrespective of age. These groups include health care and laboratory personnel, close contacts of HBV carriers, the newborn of chronically infected mothers, homosexual men, drug addicts and prostitutes. Also included are patients requiring multiple blood transfusions, such as patients with anaemia, malignant diseases, or patients under cytostatic or immunosuppressive therapy and haemodialysis patients.

Whereas the majority of candidates for hepatitis B vaccination are young, there is also a high proportion of older individuals who need to be vaccinated with hepatitis B vaccine because they are immunocompromised. Immunization of immunosuppressed elderly against hepatitis B virus is indicated. Only limited data exist about the vaccination of elderly persons. In healthy probands, it was found that older individuals, particularly males, tended to respond to the vaccine less adequately than younger persons (85). Significant reduction of the response rate in vaccinees over 50 years of age (65% versus 95%) has been observed in another study (86). Conflicting results were reported about the influence of age to the immune response in dialysis patients. These patients are known to have immunodeficiency and respond poorly to the vaccine. In most studies, a response rate of 50-60% was found in these groups of patients (87).

In two clinical trials (85, 88), a significant difference of the immune response according to the age of the patients has been reported. In two other trials, a clear age-dependency of the immune response of dialysis patients could not be found (86, 87). Rapid advance in the field of synthetic and recombinant vaccines has already resulted in creation of new generation hepatitis B vaccines which are presently included in the WHO programme on vaccine development.

7. Typhoid

7.1 Incidence

Typhoid incidence is high in most developing countries and low in developed ones. Most European countries have reached the threshold of incidence where the self-control process begins (89) and, therefore, immunization of the population at large is not justified. Sanitary improvements and a gradual decrease in the prevalence of chronic carriers due to population dynamics have slowly led to the elimination of the disease. However, endemic typhoid persists in areas like the Middle East, North Africa and South America, and this provides a reservoir from which the disease may be reintroduced in Europe.

The high-risk groups in European countries are mostly those (including elderly) who visit such areas where they may be exposed to infection.

The vaccines presently available are parenteral vaccines, which have proved to be about 80% effective but which are relatively reactogenic (90). Less reactogenic live vaccines have been developed and are being tested for effectiveness (3). S. typhi 21a vaccine has proved to be non-reactogenic, safe and effective, but its optimum formulation and standardization still has to be proved by controlled field trials and laboratory studies which are sponsored by WHO (91).

7.2 Immunization of the elderly

Since typhoid is a serious clinical illness, elderly persons visiting endemic areas are exposed to high risk and need to be protected by an effective and preferably non-reactogenic vaccine.

8. Cost-effectiveness of immunization of the elderly

Cost and coverage

Application of immunization to the elderly requires sound health care budgeting and effective use of available resources. The cost will depend on the cost of vaccine and the coverage. However, various schemes of immunization and different immunization programmes for the elderly will differ. Therefore, there is a need to perform an analysis of the cost effectiveness of recommended immunization strategies in order to obtain the best results for the lowest cost (92). The cost of immunization can be decreased by applying it to well defined high-risk groups and by combining various health activities, using public information, communications and other means to increase community participation and thus the coverage.

Besides cost-benefit analysis, due attention must be paid to the assessment of health benefits of immunization derived from disease prevention, elimination of sequelae and death, and improvement of the quality of life.

Immunization against tetanus, since the toxoid is inexpensive and very effective while the disease is highly lethal and there is no known immunity, is very cost effective and brings great health benefits.

Immunization of the elderly against influenza and pneumonia, if applied to high-risk groups taking into consideration the epidemiological patterns of these injections in specific conditions, is also cost effective.

Immunization against hepatitis B, due to the high cost of presently available vaccine, may not be the most cost-effective approach for control. However, since the cost of the vaccine may be expected to decrease, it may prove highly cost effective in view of the chronic and incapacitating effect of this illness including its role in the etiology of liver cancer.

Immunization of high-risk groups of the elderly, such as tourists, against typhoid is justified and also cost effective, in view of the low cost of the vaccine and the severity of the illness.

Since the strategy adopted for immunization of the elderly may differ from country to country, the assessment of the cost of immunization should be calculated, taking into account local conditions and the epidemiological situation.

9. Conclusions

9.1 General

The problems of infectious diseases in the elderly and the need to develop and implement immunization programmes relevant to their prevention are not widely recognized. At present, it is often difficult to reach the elderly and other risk groups among adults with any vaccination programme. It is essential, therefore, to seek ways to change attitudes by:

(a) defining the reasons for the difficulty;

(b) education of doctors, particularly geriatricians;

(c) encouraging strong and consistent support from public health administrators;

(d) demonstrating convincingly that influenza and pneumococcal pneumonia are causing significant excess mortality;

(e) demonstrating that this mortality can be influenced by vaccination; and

(f) developing strategies to reach the public appropriate for different countries/populations, e.g. postcards to all target persons, newspaper, radio and television reports/advertisements, and old people's health clinics (comparable to child health clinics).

The cost effectiveness of vaccination in the elderly has received little attention, and further research is needed to develop reliable and useful models.

9.2 Immunity in the elderly

Immune functions generally decline with age and involution of the thymus, a decrease in thymic hormones and T-lymphocytes. Both cell-mediated and humoral-immune responses are altered in the elderly and the loss of immunocompetence is accompanied and aggravated by chronic diseases and infections. There is great variability, however, in individual responses.

B-cell neoplasms, in particular, further undermine defence mechanisms in elderly patients. The use of cytostatic or immunosuppressive drugs and radiotherapy for treatment of these and other malignancies tends to damage both specific and nonspecific defences, thereby further enhancing susceptibility to infection. Extensive surgery and anaesthesia also adversely affect immune functions and predispose to local and systemic infections which may lead to fatal septicemia.

When immunocompetence is abolished by disease or treatment, active immunization may be ineffective, and passive protection with immunoglobulins may be indicated. Immunoprophylaxis should be considered in elderly patients prior to surgery.

9.3 Influenza

Mortality from influenza is recognized as highest in the older age groups. Groups at particular risk include elderly persons who have such conditions as:

(a) acquired or congenital heart disease associated with pulmonary congestion;

(b) chronic pulmonary disease associated with compromised respiratory function;

(c) chronic renal disease, especially with azotemia;

(d) chronic metabolic disease, such as diabetes mellitus;

(e) immunodeficient or immunosuppressed conditions, including malignant tumours, leukemia, etc., under therapy;

(f) chronic severe anaemias, such as sickle-cell disease; and

(g) persons living in nursing homes and similar institutions.

These persons may gain greater benefits from vaccination because they tend to experience more severe illness and treatment costs for them are higher.

Although immunization remains the major public health control measure against influenza, prophylactic antiviral drugs (e.g. rimantadine) may have a role, particularly when influenza A activity is suspected or detected in residential institutions for the elderly.

Relative excess morbidity from all causes is the most reliable quantitative measure of influenza epidemics. Relative excess mortality is a valuable means of defining those age groups and other groups of the population at greatest risk of death from influenza.

Further research is required in the following areas:

(a) the more accurate definition of the incidence and consequences of influenza in the elderly through epidemiological and serological surveys;

(b) the relation between humoral and cell-mediated immunity and susceptibility to influenza following natural infection or vaccination;

(c) the efficacy of current vaccines in reducing mortality through large-scale field trials in the general population; and

(d) the development and assessment of more effective inactivated vacccines and of live vaccines for the protection of the elderly.

9.4 Pneumococcal infections

Pneumonia is a major cause of morbidity and mortality in the elderly in developed countries, although the incidence is variable in time and place.

Diagnostic difficulties preclude precise definitions of the incidence of pneumococcal pneumonia in population studies. Existing evidence suggests that it is about 5 per 1000 per annum in persons aged 60 years and over. During influenza epidemics, secondary pneumococcal pneumonia is common.

Case fatality rates in bacteremic pneumococcal pneumonia treated with antibiotics remain substantial, being in excess of 25% in persons over 60 years of age. The relatively recent appearance of antibiotic-resistant pneumococci, particularly penicillin-resistant strains, may adversey affect the present chemotherapeutic control of pneumococcal disease.

Pneumococcal vaccine has been shown to be safe and to reduce the attack rate of pneumococcal bacteremia and pneumonia in young adults, and studies in older populations are consistent with these findings. The specific polysaccharides incorporated in current 23-valent vaccines include the types responsible for approximately 90% of bacteremic infections.

Ethical, logistical and financial considerations limit the possibilities for further randomized control trials on a scale sufficient to confirm vaccine efficacy in the elderly. Cohort and/or case control studies offer feasible means of obtaining contributory evidence of vaccine efficacy.

Groups at special risk of fatal pneumococcal infection include elderly persons who have such conditions as:

(a) acquired or congenital heart disease associated with pulmonary congestion;

(b) chronic pulmonary disease associated with compromised respiratory function;

(c) chronic renal disease, especially with azotemia;

(d) chronic metabolic disease, such as diabetes mellitus;

(e) immunodeficient or immunosuppressed conditions, including malignant tumours, leukemia, etc., under therapy;

(f) chronic severe anaemias, such as sickle-cell disease;

(g) asplenia and splenic dysfunction;

(h) chronic hepatic disease;

(i) chronic alocholism; and

(j) persons living in nursing homes and similar institutions.

9.5 Tetanus

In virtually all developed countries, tetanus now has its largest incidence in older adults. The incidence of tetanus is not evenly distributed geographically, and most cases occur in farmers, gardeners, housewives and pensioners. Case fatality rates have increased, despite advances in therapy, mainly because of the change in age distribution. Active immunization with tetanus toxoid with reinforcing doses at 10-year intervals provides reliable protection against the disease.

9.6 Hepatitis B

Hepatitis B vaccine has proven effective and without serious side effects in the newborn, children and healthy young adults. However, response rates are age dependent and, especially in persons over 50 years of age, serological response rates and anti-HB levels are lower.

The immune response to hepatitis B vaccine in patients on long-term maintenance haemodialysis, who are considered to be immunosuppressed, is drastically reduced. No more than 50-65% of vaccinated patients show an antibody response, and anti-HB concentrations are generally low. In older dialysis patients, the immune response is impaired, probably mainly by the immunosuppressive effect of their disease as well as by age. More frequent injections may increase the response rate in the immunosuppressed elderly.

9.7 Typhoid

Typhoid incidence is low and declining in developed countries, and conditions do not justify general immunization of the elderly population. Elderly persons visiting endemic areas are liable to exposure to infection, and immunization may need to be considered in such persons.

10. Recommendations

10.1 General

WHO should encourage health authorities in Member States to develop and implement immunization policies directed to prevalent preventable infections of the elderly.

Health authorities in Member States should promote educational programmes to increase professional and public awareness of the danger of infection in the elderly and to promote the use of vaccines, particularly against tetanus, influenza and pneumococcal infection and tetanus, as a part of routine health care for persons over 60 years of age.

10.2 Specific

Influenza

High priority should be given to ensuring that elderly persons receive annual vaccination prior to the influenza epidemic season. Inactivated influenza vaccines containing antigens representative of recently isolated strains are recommended for persons over the age of 60 years, particularly those in the high-risk groups listed above. Antiviral drug (e.g. rimantadine) prophylaxis should be considered as an additional control measure against outbreaks of influenza A in institutions for the elderly, irrespective of previous influenza vaccination.

Research institutions should be encouraged to address urgently critical issues related to vulnerability of the elderly to influenza.

Pneumococcal infections

Polyvalent pneumococcal vaccine may be recommended in persons over the age of 60 years, particularly in the high-risk groups listed above.

Tetanus

Immunization against tetanus must be offered to all older adults as part of routine health care.

Hepatitis B

Passive-active immunization is recommended in haemodialysis units where HBsHg-positive patients are treated.

Typhoid

Immunization using an effective, non-reactogenic vaccine should be considered for elderly persons visiting endemic areas.

Combined vaccines

Combined antigens should be developed in order to simplify vaccination schedules and to adopt the most cost-effective strategy for protection of elderly by immunization.

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Annex 1

LIST OF WORKING PAPERS

ICP/ESD 008/6 Immune response in elderly by Professor D. Dekaris

ICP/ESD 008/7 Immunodeficient and immunodepressed elderly by Professor A. Morell

ICP/ESD 008/8 Measurement of immune response in elderly by Dr N. Ajjan

ICP/ESD 008/9 Epidemiological surveillance and prediction of influenza epidemics in Czechoslovakia by Dr V. Janout

ICP/ESD 008/10 Epidemiological surveillance and prediction of influenza epidemics in Yugoslavia by Dr N. Delimar

ICP/ESD 008/11 Vaccination of the elderly against influenza by Dr T. Bektimirov

ICP/ESD 008/12 Vaccination of the elderly against penumonia by Dr R. Austrian

ICP/ESD 008/13 Pneumococcal vaccines in the elderly by Dr T. Kereselidze

ICP/ESD 008/14 Experience in Finland with immunization in elderly against P. pneumoniae by Dr P.H. Mäkelä

ICP/ESD 008/15 Protection of the elderly against pneumonia with the 17-antigen pneumococcal vaccine by Dr J. Vodopija, Dr I. Zoric, Dr Z. Baklaic, Dr M. Svjetlicic, Dr M. Ljubicic and Dr F. Andrè

ICP/ESD 008/16 Experience in Canada with immunization of the elderly against influenza/pneumonia by Dr A.J. Clayton

ICP/ESD 008/17 Cost versus benefit in immunization against P. pneumoniae in developed countries by Dr J. Petres

ICP/ESD 008/18 Tetanus as a problem of the elderly by Dr B. Bytchenko

ICP/ESD 008/19 Immunization of elderly against tetanus by Professor B. Cvjetanovic

ICP/ESD 008/20 Tetanus: treatment or vaccination? A cost-benefit analysis by Dr B. Borcic

ICP/ESD 008/21 Immunization of immunosuppressed elderly against Hepatitis B virus (Federal Republic of Germany) by Dr W. Jilg

ICP/ESD 008/22 Immunization of immunosuppressed elderly against Hepatitis B virus (Yugoslavia) by Dr S. Smerdel

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