Report of the ad-hoc Consultation on Ageing and Immunization

21-23 March 2011
Geneva, Switzerland

Immunization, Vaccines and Biologicals

World Health Organization

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Contents

Introduction

An ad-hoc consultation on ageing and immunization was jointly organized and conducted by WHO staff of the Initiative of Vaccine Research department (IVR) and the Ageing and Life Course department (ALC). Dr John Beard, Director ALC co-chaired the meeting together with Dr Teresa Aguado, Coordinator of the Research and Product Development IVR.

Dr Beard welcomed the ad-hoc participants to the two and a half-days meeting on ageing and immunization. He reiterated that the mission of this broad group of combined experts on populations, gerontology, molecular biology and immunology, was to "think out of the box" in order to explore and advise on providing the bases for a future research programme on ageing and immunization. Dr Aguado emphasized the importance of the meeting as a generator of a research agenda which in turn can eventually lead to WHO recommendations for the vaccination of groups beyond infancy and with special emphasis on developing countries.

A list of participants is included (Annex 1).

The co-chairs presented the agenda (Annex 2), which was adopted by all the participants. Participants from the private sector agreed not to participate in the final discussion panel and final recommendations in order to avoid any WHO conflict of interests.

Note: Given time constraints, the draft agenda was presented and concluded in 3 sessions, but reported as in 4 sessions for a detailed description.

Overview

The improvement of child survival, reduced mortality rates and decreasing fertility rates worldwide, is one humanity's greatest triumphs, but this is now creating a significant new consequence: the ageing of the global population. By the year 2030 the percentage of the population that is elderly (≥ 60y of age) is predicted to represent over 25% of the total population, of which 75% will be living in less developed countries.

Ageing, and more explicitly, the natural decline of the immune system in the elderly, increases their susceptibility to infection and compromises responsiveness to vaccines. This is especially noticeable in frail patients, contributing significantly to their morbidity (i.e.: loss of independence, hospitalization, depression). Ageing has a major impact at the individual level, on the quality of life and also an economic impact at the societal level, presenting a major challenge to public health services.

Developing and implementing vaccines to control infectious diseases in the elderly will require a thorough understanding of the immunological mechanisms underlying immunesenescence across different populations and how this is influenced by environmental parameters, such as nutrition and exposure to infectious agents.

While a vast compilation of information on aging and immunization is already available from developed countries, evidence from developing countries is extremely limited and therefore is, urgently required. In addition, it is important to determine which types of immunization approaches could help to address vaccine "failures" associated with ageing. This will require identifying the key factors necessary for adequate protection during these years.

Objectives of the meeting:

The meeting sought to jointly combine expertise on populations and gerontology with molecular biology and immunology. It was expected that this would provide the bases for a future research programme that would inform WHO recommendations for the vaccination of groups beyond infancy, especially in developing countries.

The specific objectives of the meeting were:

1. to review knowledge on the types of adult and ageing populations at the global level

2. to review the main causes of morbidity and mortality in those populations, paying special attention to the infectious agents directly or indirectly responsible for disease

3. to review knowledge about immune deficits that determine the impairment/decay of protective immune responses associated with ageing (immunesenescence)

4. to propose solutions to correct/optimize these immune deficits

5. to review vaccines available to protect ageing individuals and to identify opportunities to extend protection

The expected outcome was a coordinated plan in the form of a research agenda to include:

a) developing a framework to study elderly populations globally according to socio-economical status and how socio-economic status influences the process of natural ageing

b) identifying the major vaccine-preventable diseases in the elderly, according to different population groups

c) preparing additional reviews to selectively address knowledge gaps in these areas

A summary of the presentations at the consultation are detailed in the following section.

Session 1:
Epidemiology of global elderly populations

Active ageing globally *(Alex Kalache)*

Dr Kalache detailed how the world's population is progressively ageing. Both Life Expectancy (LE) at birth and LE at age 60 have increased substantially over the last few decades throughout the world, while Total Fertility Rates (TFR) have dramatically decreased; in some 80 countries TFR is now below replacement levels. This will require very sensible and sensitive new policies designed for increasing the working population in good health

Ageing, even as it reflects progress in the 20th century, presents considerable challenges to the current century: *Developing countries are becoming older before becoming richer.* A 50% increase in the global population is predicted before 2050. This demographic explosion is concentrated mostly in developing countries, which will fundamentally shape the development of public health policy.

Healthy elderly people are important resources to their families, their communities, and to their societies. Investing in their health is cost-beneficial to society. For example, older women in Africa take care of the young orphans who lost their parents from AIDS. A recent study in Spain determined that 88% of the home health care is not done by non-professional remunerated healthcare workers, but mostly by elderly women. The elderly providers need to be in good health in order to fulfil these roles. This, in turn is a life course perspective - yesterday's children are today's younger adults, tomorrow's elderly people.

In 2002 WHO launched the conceptual framework entitled "Active Ageing", which was its most important contribution to the UN Assembly on Ageing, and an essential component of the Madrid International Plan of Action on Ageing that was adopted by the Assembly. "Active Ageing" was defined as " the process of optimizing opportunities for health, participation and security in order to improve quality of life as individuals age - thus, intrinsically embracing a life course approach." Dr Kalache emphasized that one of the ways to maintain health in elderly people - preventing morbidity, disability and premature death - is through targeted vaccinations. Existing vaccines which have proved to be cost effective require enhanced strategies for widespread use, while research is required to improve current vaccines and develop additional vaccines for ageing persons.

Infections in the elderly *(Karl-Heinz Krause)*

Dr Heinz-Krause showed that specific aspects of infections in the elderly include not only increased frequency and severity of certain infections, but also increased microbial colonization and altered microbial spectrum for a given infection and results in difficulties with the diagnosis. Additionally, antibiotic treatment presents specific considerations in the elderly. Infections in the elderly are not only relevant with respect to morbidity and mortality, but are also major factors leading to dependence and institutionalization. The most frequent bacterial infections in the elderly population are respiratory infections (bronchitis, pneumonia); urinary tract infections (cystitis, pyelonephritis); skin and soft tissue infections (cellulitis, diabetic foot infection); infective endocarditis; tuberculosis; digestive tract infections (post-antibiotic diarrhea, diverticulitis, cholecystitis, abscesses); central nervous system infections (listeria meningitis); foreign body infections (endoprothesis, indwelling catheters) and influenza. Nevertheless, Dr Krause pointed out that immunosenesence has some beneficial/protective input to take into account, e.g. H1N1 influenza affects in a lesser capacity to elderly, and possibly due to decreased inflammatory responses in the lung in elderly; the presence of antimeningococcal antibodies protects elderly from meningococcal meningitis, which is mostly seen in the younger population. Macro- and microscopic anatomical alterations and comorbidities are other factors that contribute to the immunodeficiency of the elderly.

Dr Krause reviewed that infectious disease in the elderly present distinct features in the developing world. The spectrum of infections in the elderly is often different from the one seen in the developed world and presents greater overall relevance. In addition, the general limited resources available for drug treatment, and the poorly controlled use of antimicrobial drugs leads to multidrug-resistant microorganisms.

The age of onset of the age-related increase in infection risk is not well understood, but might be earlier in the developing world. Depending on the type of infection and the type of analysis (frequency vs. mortality) substantially different results may be obtained. Clearly, malnutrition is a major contributor to the immunodeficiency of elderly patients in the developing world. Therefore, the frequency and severity of many infections are increased in the elderly, in particular in developing countries .The reduced nutrient uptake (due to less food access) reduces the body mass index (BMI) and correlates directly with infection risk. for example in sub-saharian countries such as Ghana, the average BMI of women older than 65 years of age is 19, when the recommended value is 25- 26.

There is clearly a lack of vaccines compared to the real need in the elderly. Yet, is also important to realize that decreased response to vaccination limits programs of vaccination in the elderly; thus vaccines with improved response rates in elderly are needed.

Epidemiology of infection in ageing population: questions for vaccines
(Gäetan Gavazzi)

In developed countries, a high presence of older residents in health care centers has consequences in terms of epidemiology of the infections. The acquired infections are community (up to 20-fold) or hospital acquired (up to 5-fold) and in a range between 5-30%, the elderly in long term facilities are the ones of highest risk of infection due to their own co-morbidities and the close relation with each other. Viral infections, are the most common within this population, with pneumonia and influenza being the most common and reaching up to 60% of the mortality. This is a number to be considered when making any decisions for designing new vaccines.

From all the vaccines available in developed countries to date, only vaccines against poliomyelitis, diphtheria, tetanus, influenza, pneumococcal and zoster are offered to the older people. A cluster of reemerging infectious diseases in adults such as measles and pertussis, or of higher severity in the older such as RSV, Clostridium and Norovirus infections, are suggested to be considered for new vaccines for high resources countries. They lack efficacy and effectiveness in this population and should be improved.

Taking into consideration that ¾ of the elderly population will be living in developing countries by 2030, suggested vaccines for this population must be considered. In this setting, among the vaccines already considered in developed countries, the focus should be centered on Malaria, Tuberculosis, Cholera, HIV and others that do not necessarily affect the elderly population but would be part of the strategies to prevent infections and cope with the challenge that the burden of infection in elderly represents for the global public health of each country .

Vaccine programme for life *(Jean-Pierre Michel)*

Dr Michel defended that targeting vaccines for older populations requires the establishment of a life course vaccine programme. Infectious diseases remain a significant cause of morbidity and mortality in adults aged over 60 years, and many of these diseases are vaccine-preventable (VPDs). There is a pressing need to promote a life-long vaccine schedule in order to increase vaccination against VPDs during the different stages of life. More explicitly, a very effective and well accepted vaccines together with specific guidelines for the vaccination of children will result in healthy ageing midlife adults, which together with preventive medicine and a continuation of the vaccine programme will improve their health in later life. Disability-free and healthy ageing are closely linked to childhood health and medical conditions in young adulthood. The mid-life vaccine gap drastically impacts health in later life, especially in unvaccinated and older populations. Scientific knowledge on immunesenescence will improve the vaccines and their life course programmes.

The expected benefits of vaccination in the ageing population are linked to the considerable negative clinical impact of VPDs in the unvaccinated population. When vaccinated, the mortality rate linked to preventable infectious diseases decreases, for example influenza vaccines diminishes all-cause mortality by 48–50% in community-dwelling older persons. Also, vaccine protection reduces complications and hospitalization, for example hospitalisations due to influenza or pneumonia were reduced by 27% in community dwelling older influenza vaccinees. Even more, vaccines in the elderly decreases antibiotic use, for example antibiotic prescriptions

were cut by 64% following influenza vaccination in a Canadian study; and therefore decreases antibiotic-resistant infections, for example pneumococcal conjugate vaccine diminishes nasopharyngeal carriage of penicillin-resistant streptococcus pneumoniae. In addition, the cost effectiveness of vaccines results in an improved quality of life of the vaccinated population, e.g. Herpes zoster vaccine increases quality-adjusted life years compared with no vaccination in older people.

With these arguments Dr Michel underlined the need for a preventive lifelong health perspective from childhood through to old age.

Vaccine preventable disability *(Janet McElhany)*

Influenza is the single most vaccine preventable disease and vaccination programmes are cost-saving in older people, but yet influenza is still causes serious outcomes in older people with 90% of all deaths due to influenza occurring in this population, and 3-4 hospitalizations for every influenza death. In addition, the response to the current vaccines is low in efficacy (70–90% for preventing respiratory illness in healthy adults compared to only 30–40% in older people).

Chronic diseases that increase risk for influenza are very common in older adults and all of the leading causes of catastrophic disability (defined as the loss of independence in ≥3 basic activities of daily living) have been linked to complications of influenza infection including pneumonia, heart failure, ischemic heart disease, strokes, cancer and hip fracture. This can be attributed to the loss of functional muscle strength (up to 5% per day) during prolonged periods of bed rest associated with these complications.

Aging affects cellular immune mechanisms and specific components of cellular immunity can be targeted to prevent disability in the development of new vaccines. New influenza vaccines are being developed but how does the reliance on antibody responses as a measure of vaccine efficacy limit our ability to test whether new vaccines can prevent disability? Current split-virus influenza vaccines provide a weak stimulus to the cytotoxic T lymphocyte (CTL) response, and hence T cell memory that is recalled during an influenza infection. Therefore Prof McElhaney proposes that correlates of CTL-mediated protection are needed to screen for enhanced efficacy of new vaccines.

Genetic alterations on ageing populations exposed to adverse environmental conditions *(Johannes Meij)*

Rapid demographic changes require focusing on old age under adverse conditions. Big emphasis on health care for younger people has resulted in rapid demographic changes. Currently, people over 50 years old are suffering from over mortality and this will require focusing on old age under adverse conditions.

After studying for more than 10 years a remote population located in Ghana and comparing them with the same age population living in the Netherlands, Dr Meij and their team found out that their immune status backgrounds are strikingly different. Analysis of cytokine production from blood samples of the Ghanaian population showed that their innate immune system is somewhat adapted to the conditions of

their way of life. Compared to the Dutch population in which cytokine production is normally reduced with age, the Ghanaians present an increase in pro-inflammatory response molecules to keep their immune system "awake" and more active and possibly help to survive the epidemiological threats to which this population is exposed to.

When a very common infectious source such as water is used as a model to study survival in this population, there is initially no difference between the source of drinking (boreholes or well/river sources). But when studying the haplotypes behind a ratio of high TNF activity and low production of IL-10, the study found a genetic background that increases the survival rate under unfavorable environmental conditions, and may predict survival. Similar results are shown in elderly that live in affluent conditions where innate immunity genes may predict survival at old age.

In terms of production of new vaccines, Dr Meij and his team is in favor of boosting the immune system at an older age, especially targeting the immune system to select pro-inflammatory host responses to overcome fatal infection and promote survival in adverse environments.

Session 2:
Immune senescence and evolving immune system

New tools for evaluation of antibody repertoires and affinity maturation following vaccination (*Hana Golding*)

The production of vaccines presents a paradigm shift: while whole viral particles, live or inactivated, vaccines are very potent but considerably unsafe, vaccines produced by subunit antigens present better safety issues but lower potency. In order to accelerate, prolong or enhance antigen-specific immune responses, it is common to include an adjuvant as part of vaccine formulation. Adjuvants activate early innate immunity and could overcome reduced immune responses in targeted populations such as the elderly. Therefore, when designing vaccines for the elderly, it is important to have in place broad analytical tools for better evaluation of the immune responses and to provide a link with vaccine effectiveness (correlates of protection).

Dr Golding group has developed several research methods for in-depth analysis of the humoral immune responses against influenza, and applied them in the evaluations of human responses to different vaccine modalities (with or without adjuvants) in different age groups: 1) Elucidation of antibody repertoires using "whole-genome-phage-display-libraries (GFPDL): frequency of clones binding to large conformational epitopes encompassing protective targets, 2) Surface Plasmon Resonance (SPR) to analyze antibody binding (qualitative and quantitative) to properly folded proteins from the influenza envelope globular receptor binding domain (HA1) and stem (HA2); calculate antibody affinity based on off-rate constants; , 3) ELISA-based antibody avidity assay (treatment with 7M urea)

The data presented were from analyses conducted with samples from several trials in which pandemic influenza vaccines (split virus or subunit, inactivated vaccines) were administered to different age groups including infants, children, young adults, older adults and the elderly.

T-cells and their niches in old age (*Beatrix Grubeck-Loebenstein*)

A well known sign of immunosenescence is the progressive reduction with age in the size of the thymus due to depletion of thymic cortex and medulla. This changes lead to changes in the size of T cell subpopulations from naïve to terminally differentiated effector T cells. This shift is accelerated by latent infection with cytomegalovirus and thymectomy.

Large numbers of effector T cells are believed to hamper the effect of vaccination and to support the development of age-related diseases. Prof Grubeck-Loebenstein and her group concentrated their research on the still controversial issue of whether the accumulation of effector T cells is due to continuous regeneration or decreased degradation. They have demonstrated that effector T cells are specifically enriched in niches such as the bone marrow, where they reside in a state of pre-activation. This is not due to an intrinsic resistance to apoptosis-inducing stimuli as suggested by others, as they also show that terminally differentiated effector T cells are particularly susceptible to apoptosis mediated by extrinsic and intrinsic factors. This susceptibility to apoptosis is partly due to a decreased capacity of the specific cell type to repair DNA damage, and also to changes in the important for longevity mTOR autophagy signaling axis.

The latter defect can be overcome by intensive IL-15 signaling, a characteristic feature of the aged bone marrow. Terminally differentiated effector T cells may therefore even represent a useful line of defense in old age in certain organs, which could theoretically be targeted with vaccines. They are still a biomarker of immunosenescence, as they could demonstrate an inverse relationship between the number of CD28-CD57+ T cells and the mobilization of memory T and B cells following immunizations in humans.

Age related decline in vaccine responses and the role of the thymus
(Richard Aspinall)

Characterizing the immune system of older individuals could help to understand the impact of changes in cell repertoire on the response to vaccines. The pool of naive cells in the elderly is smaller than that of young individuals, implying that the opportunity of acquiring new memory in response to new antigens is smaller too. Data show that a person over 65-years of age has a 1000-fold higher probability of dying of a vaccine-preventable disease than a younger one. In addition, older individuals show poor responses to vaccination with a clinical effectiveness of vaccines declining up to 30-40%. The major problem for the future is to produce an effective vaccine response in large proportion of individuals in the older population.

Reversal of the atrophy seen in primary lymphoid organs especially the thymus may improve vaccine responses in the elderly. A critical cytokine for the development and survival of T-cells in the thymus is IL-7. With age, some cells become senescence, the IL-7 production is reduced and the cells die. Injections of IL-7 in old experimental animals reverse the senescence situation increasing the production of new thymocytes: old mice that have been previously therapeutically treated with IL-7 and exposed to Influenza virus present a significant decrease of viral load of influenza in their lungs compared to control animals. Even more, Rhesus macacques treated with IL-7 intramuscularly show better antibody responses after being vaccinated against influenza.

A method of incorporating IL-7 easily into the body by using an aerosol would make the therapy accessible to humans. It is faster than intramuscular injection and it supports a high level of IL-7 distribution all over the body. This method could be the most efficient to reverse thymic atrophy and prolong immune functions. A challenge to this approach would include identifying individuals who would benefit from IL-7 treatment but Prof. Aspinall suggested that the TREC assay may provide a mean to achieve this goal.

Intrinsic deficiencies in human B cell functions with age *(Bonnie Blomberg)*

Decline in B cell (antibody) functions include a diminished ability to generate high affinity protective antibody responses to immunization against infectious agents or experimental antigens. By using peripheral blood-derived human B-cells from subjects of different ages, the laboratory of Prof. Blomberg has discovered that B cell numbers and percentages, especially switch memory cells (IgG+/IgA+/CD27+) decrease with age. Intrinsic functional defects within in vitro antigen- or mitogen- stimulated B lymphocytes during aging correlates with decreased activity of the enzyme required for the Ig class switch, the activation-induced cytidine deaminase (AID). This enzyme, also required for somatic hypermutation of the B cells to generate high affinity antibodies, is regulated by the transcription factor E47 which in turn is the one most affected by age..

Importantly, Prof. Blomberg provided evidence that AID analysis can be used to predict and monitor a B cell/ haemagglutination inhibiting (HI) response to the influenza (and likely other) vaccines .

These intrinsic defects in human B lymphocyte phenotype and function act as biomarkers and can predict vaccine response in the elderly as well as younger adults.

Dendritic cells in human ageing *(Silvia Della Bella)*

Dendritic cells (DCs) are potent antigen presenting cells (APCs) with the unique ability to prime naïve T cells *in vivo* and with a prominent role in the activation, polarization, and regulation of adaptive immune responses. They comprise a heterogeneous system of leukocytes widely distributed in all tissues, especially in those that provide an environmental interface. Distinct DC subsets have been shown to possess different morphology, phenotype and functions depending on their origin, state of activation and localization in different tissues and organs.

Prof. Della Bella has shown that during human aging DCs in multiple body compartments undergo numerical, immunophenotypic and functional changes that may contribute to the state of dysregulation and overall deterioration of immune function occurring in aged people. Decreased amount of DCs in frail /old individuals have been shown in the peripheral blood and in the skin. Age-related functional changes of DCs that may be detrimental to immune responses have been described in multiple tissues and they consist in overall constitutive increased DC activation associated with impaired responses of DCs to microbial (TLR-mediated) stimulation. Prof. Della Bella suggested that the constitutive increased DC activation occurring in aged subjects may be part of and contribute to inflammation, a state of chronic systemic inflammation observed in the elderly. Increased activation of DCs, together with inflammation, may sustain the development and progression of diseases that are augmented in the elderly including some autoimmune disorders, atherosclerosis, cancer and CNS diseases. Controlling the multiple causes that sustain inflammation may most likely, partially correct DC hyper-activation and its detrimental effects. On the other hand, the age-related impaired capacity of DCs to respond to TLR-mediated stimulation may be at least partially responsible for other aspects commonly observed in the elderly, such as increased susceptibility to infections,

increased severity and mortality of infectious diseases, as well as reduced efficacy of vaccination. Strategies aimed to optimize the routes of vaccine administration and promoting the use of adjuvants that stimulate DCs may help to increase vaccination efficacy and to partially overcome age-related DC impairments.

Chronic inflammation and immunosenescence *(Jean-François Nicolas)*

Aging is associated with chronic low-grade inflammation (inflammation concept). Inflammation occurs in blood and tissues and contributes to the pathology observed in different organs (including the immune system) during aging. Both innate and adaptive immunity are dysregulated and lead to the production of pro-inflammatory molecules and to the chronic activation of lymphocytes. Immunosenescence correlates with inflammation and is intrinsic to immune cells of elders but more importantly extrinsic, that is secondary to the (pro-inflammatory) environment of aged tissues.

Several mechanisms that develop to counter the inflammation may be responsible for immunosenescence including activation of T regulatory cells endowed with potent suppressive functions on both primary and secondary immune responses. Prof. Nicolas claimed that preventing chronic inflammation in elderly may improve immunosenescence and the quality of life.

Immune responses to respiratory diseases: Influenza, RSV, pneumonia and pertussis *(Janet McElhaney)*

Hospital admissions for viral and bacterial pneumonias are increasing in older people, claimed Prof. McElhaney. Better vaccines are needed to prevent or reduce risk of serious complications of acute respiratory illness.

A variety of strategies have been used to develop new vaccines but valid correlates of protection remains the greatest barrier to evaluating new vaccines for improved efficacy in older people. High levels of serum and/or nasal antibodies have been correlated with relative resistance to experimental challenge, whereas low serum and nasal antibody levels are risk factors for respiratory syncytial virus (RSV) infection and disease severity in older adults, but this is not an age-specific change. In addition, older adults have a greater rise in antibody titers to RSV post-infection than their younger counterparts.

Aging affects cellular immune mechanisms. A greater understanding of the advantages and limitations of different animal models are needed for their translation to improve vaccines for older people.

Immunosenescence and its impact on vaccination: influence of CMV infection *(Graham Pawelec)*

One of the difficulties in interpreting immunogerontological observations is the use of data from cross-sectional studies, which are likely to compare different young and old populations. Longitudinal studies seeking immune parameters associated with mortality in the very old, that is the Jönköping OCTO/NONA studies, lead to the development of the concept of an "immune risk profile" (IRP). The IRP takes into account immunological parameters including CD4:CD8 ratio of < 1, poor T cell proliferative responses, increased numbers of terminally differentiated CD8+ cells, low B cell numbers, and also the presence of Human Cytomegalovirus (CMV)-seropositivity .

The presence of CMV is usually asymptomatic, but reactivation in response to immunosuppression, inflammation, infection or stress can lead to overt disease and an enormous commitment of immune resources is required to control CMV. Prof. Pawelec and others question whether the presence of CMV is as harmless as it has been believed. Is the presence of CMV detrimental during response to vaccination? Both CMV infection and the IRP are associated with elevated markers of inflammation. Higher levels of inflammatory mediators such as CRP and IL 6 exacerbate the association of the IRP with frailty and death in the very elderly.

CMV infection is associated with the accumulation of the most differentiated CD8 cells and decreased CD8+ naïve cells. Furthermore, attrition of CD8+ T cell clones recognizing CMV, correlates with mortality in the very old. Age-associated decreases of naive T cells are seen only in CD8, not CD4 cells in CMV-infected people. But higher levels of CD8+ naive cells in people over 85 years does not represent any survival advantage as shown in the L85+ study in Leiden. Contrarily, a significant survival advantage was found for people with higher CD8+ effector memory cells and higher pro-inflammatory responses.

Interventions against CMV may improve immunity in the elderly. Once the causative link is convincingly shown, there is more of an incentive to treat with anti-virals (antibodies, pharmaceuticals, anti-sense interferenc), and to enhance responses to vaccination using higher immunogen dose, intra-dermal route, nasal route, or target negative regulatory cells, as well as by using immunomodulatory probiotics, eg. *Lactobacillus paracasei* and supplement with vitamins, minerals or a caloric restriction if appropriate.

Herpes Zoster (HZ)/HZ Vaccine: Tools for studying immune senescence *(Myron Levin)*

Herpes Zoster (HZ, shingles, zona) is a global disease and its relationship to aging is unquestioned. HZ is associated with significant morbidity. Not only does the frequency of HZ increase with age, but the prevalence, severity, and duration of HZ pain increases with age. Thus, HZ serves as a useful probe for the quality and quantity of immune responses in older people.

The origin of this disease of the elderly is in childhood when varicella (chickenpox) infection results in a viremia that seeds the skin to create the chickenpox vesicles. The axons of sensory neurons end at the base of these vesicles. The varicella-zoster virus (VZV) ascends in the sensory nerves to become permanently latent in sensory ganglia. HZ occurs when this latent VZV reactivates in a ganglion in an unlimited fashion that results in the destruction of neurons in the ganglion and associated neuropathic pain experienced in the skin innervated by that ganglion. The reactivated VZV travels back down the sensory nerve to the area innervated by the ganglion, producing the characteristic rash and additional pain. Since more than 90% of adults in the world are infected with varicella by age 30 years, each of these adults has the potential to develop HZ.

We now know that the likelihood or clinical reactivation is related to the loss of the specific VZV immunity that normally maintains latency. For that reason HZ is more frequent and more severe in immunocompromised patients. VZV-CMI is also lost with ageing allowing reactivation (or it allows VZV to propagate in the ganglion). Also, the lower the level of VZV-specific CMI at the time of reactivation, the longer it takes to develop an adequate response to the infection – i.e., more damage is done to the nerves and skin, thus explaining the increased severity associated with ageing.

The zoster vaccine boosts the VZV-specific CMI in older people and thereby prevents or attenuates a significant amount of HZ in vaccinated populations. However, the vaccine-induced boost is greatest in "younger" elderly. Thus the protection against HZ is greatest in those 60-69 year old and less in those in their 70's and older, although even in very old vaccinees the disease is often less severe.

There is a need for a HZ vaccine that will overcome the decreasing responsiveness with age. Attempts to do so with higher dose vaccines have not been successful. Additional approaches would be to utilize intradermal administration or to add an adjuvant. The latter approach must be done carefully, since there is a paucity of data on the use of adjuvants with live vaccines in general, and specifically to their use in older vaccines.

Session 3:
Using immunization to improve performance of the system

Protecting the elderly population in mouse and man: Learning from a novel TLR 9 –specific adjuvant *(Alexandre Von Gabain; Intercell)*

The major reasons to use adjuvants in vaccines are the lack of immunogenicity of the selected antigens, dose sparing and reduction of vaccine schedules (e.g pandemic flu). Additionally, some adjuvants could guide of the type of immunity into the desired pathway (e.g TH1, TH2 , TH17) and hopefully improve immunity in populations with reduced responsiveness (e.g in the elderly).

Prof. Von Gabain, CEO of Intercell, presented the properties of a new adjuvant named IC31®. This highly soluble compound simply mixed with the antigen induces activation of innate immunity and animal data, showed strong and long-lasting induction of specific T-cells, and also antibodies against many antigens.

Experiments with guinea pigs showed that IC31®adjuvanted to a novel Tuberculosis vaccine improves the vaccine efficacy and reduces the mortality rate due to this disease compared with the current BCG vaccine. In human trials with a TB subunit vaccine, IC31® has yielded induction of long term and high levels T-cell responses.

When used as adjuvant of Influenza vaccines, IC31® induced persistent mixed type 1/ type 2 IgG antibody levels in aged mice, most pronounced upon booster immunisation. In a ferret challenge study with H5N1, broad protection is induced in the absence of HI Abs, best attributed to T-cell immunity. However, there was no adjuvant effect of IC31® observed in young adults, most likely due to pre-exposure to the vaccine antigen.

IC31® boost the effect of vaccines and can be easily combined with registered adjuvants; for example Alum, MF59, but the use of this adjuvant is not possible for all vaccines due to the lack of an adjuvant effect in individuals with pre-exposure to the antigen .

Addressing the needs of the ageing population with new vaccines
(Marie-Jose Quentin-Millet and Martine Denis; SanofiPasteur)

The major areas of interest to strategically address the needs for the elderly at SanofiPasteur were presented. Firstly, it is important for the company to increase the immunization coverage for existing vaccines: influenza, pneumonia, DTP…, zoster (sp-MSD), but also to adapt the existing vaccines, especially the influenza vaccine, to the elderly by different formulations, schedules, immunization routes. In addition, new vaccines targeted for the elderly are part of their development portfolio.

The company presented their portfolio of vaccines for the elderly and indicated that new products on tuberculosis and pneumococcus are in Phase I clinical trials and a vaccine against *C. difficile* in Phase II stage of development. The most advanced program being the influenza program, with new vaccines that improve functional antibody responses in elderly subjects compared to standard vaccines. Different options were considered for increasing the immunogenicity of influenza vaccines: combination with an adjuvant, high dose of antigen (significantly higher functional antibody response in elderly subjects with the 60µg than with the 15µg hemagglutinin dosage), and intradermal injection (despite age-related changes that affect immune mechanisms in the skin, the intradermal route is well suited to vaccination of elderly subjects)

Prof. Quentin-Millet and Dr Denis explained that specific challenges of the target population are faced when developing vaccines appropriately for the elderly : partially effective and primed immune system, population often under medication, and difficulties in conducting trials within this population.

Adjuvants for improved vaccines for the elderly
(Giuseppe Del Giudice; Novartis)

In agreement with the other industry representatives, Dr Del Giudice mentioned that various approaches are being pursued to improve responsiveness to vaccines in the elderly, such as increased dosage of vaccine, intradermal administration, the use of strong adjuvants, the use of cytokine, and mucosal inmmunization. He underlined that when focusing on the elderly population, many of these approaches still need intensive work, and that most of the work is being done with the influenza vaccine and the majority of the work on adjuvanted seasonal influenza vaccines has been carried out with the oil-in-water MF59 adjuvant.

In reality, MF59-adjuvanted seasonal influenza vaccine has been licensed for elder individuals since 1997 and as of today it has been given to more than 50 million individuals. The vaccines has proved to be safe and more immunogenic than plain influenza vaccines. More recently, this adjuvant was used to develop pre-pandemic H5N1 and pandemic H1N1 vaccines suitable for all age groups. In a very large observational study carried out in Italy the risk of hospitalization for influenza-related disease in older adults (≥65 years of age) vaccinated with MF59-adjuvanted influenza vaccine (FLUAD®) was compared with that in elderly vaccinated with non-adjuvanted influenza vaccine (AGRIPPAL®). The results show that vaccination with FLUAD reduces hospitalisations by an estimated 23% compared to subjects vaccinated with non-adjuvanted vaccine. Vaccines against other diseases highly prevalent in elderly such as RSV, Group B streptococci, Pneumococci, Pertussis, Nosocomial infections as well as therapeutic vaccines against chronic infections and non-infectious diseases (e.g. CMV, Alzheimer…) can significantly benefit from the use of appropriate adjuvants.

Dr Del Giudice underlined that basic research on mechanisms of immunosenescence and ways to counteract them are still needed and active collaboration between academic institutions and industry may represent a successful way to proceed.

Vaccine design for the elderly
(Martine Wettendorf and Robbert Van der Most; GlaxoSmithKline)

GSK strategy to address the remaining unmet medical need is based on the combination of the right antigens and the right adjuvant system (AS) that can effectively stimulate the immune response and achieve enhanced and sustained protection

The current knowledge on mode of action of adjuvants suggests that adjuvanted vaccines can rescue the key features of immunosenescence. For instance, the AS adjuvanted vaccines such as the H5N1/AS03 pre-pandemic vaccine induced a significantly higher and persistent CMI response compared to the non-adjuvanted vaccine, indicating that it is possible to counteract the diminished T and B cell repertoire in elderly.

Also the value of adjuvant systems in restoring B and T cell responses was shown in the context of the Zoster vaccine candidate (gE AS01B), which presents higher immunogenicity than the current GSK Zoster vaccine Varilix.

In addition to the adjuvant policy followed by GSK, the company presented a new product in the pipeline, Boostrix, which fits into the line of the importance of adapting the existing vaccines for the elderly. Boostrix is a Tetanus-Diphteria and Pertussis vaccine immunogenic in adults 65 years of age and older.

New vaccines and immunization approaches for the elderly: MSD perspective *(David Kaslow and Eddy Bresnitz, MSD)*

Presentation by MSD centered the attention on whether immunoscenescence may start as early as adolescence. Data from the MSD Human Papiloma Virus Program clearly showed the impact of age on immune response in vaccinated young girls aged 9-23 years old. The decrease of response already at the age of 23 clearly may originate a debate on whether the statement of immunosenescence is a result of an advanced age.

A vaccine for use in the elderly is a research and development priority at MSD with a different primary global infectious disease targets according to target populations.

The main interest currently at MSD in relation to vaccines for the elderly lays on a MSD-sponsored observational study of vaccine responses in healthy elderly subjects. One of the primary objectives of this study is to develop statistical models that predict antibody responses of an elderly subject to selected protein-antigen vaccines – based on pre-vaccination (baseline) biomarkers and on early post-vaccination biomarkers. The second objective is to assess the generality of vaccine responsiveness within individuals by estimating relationships between the magnitudes of simultaneous vaccine responses within healthy aged subjects. By using this statistical models, MSD intends to give answers as to whether a determined biomarker provides an added value to age in terms of predicting hyporesponsiveness and therefore in developing and testing new vaccines for the elderly.

Potential Approaches to Elucidate Mechanisms of Immunosenescence
(Kushroo Shroff, Pfizer)

More people die from pneumococcal infections than from any other vaccine preventable disease. There is a significant burden of pneumococcal disease in adults >50 years of age. In addition to the disease burden in older adults, the case-fatality rate from IPD among hospitalized patients remains of great concern.

To counteract this unmet medical need, Pfizer presented data on a new Pneumococcal vaccine. A microengraving method for rapid selection of single cells producing antigen-specific antibodies was used to analyze T & B cell populations elicited by 13v Pneumococcal Conjugate Vaccine (13vPCV). The experimental approach has potential to define the qualitative differences between immune responses elicited in young and elderly people. Moreover, if the conjugated pneumococcal polysaccharide vaccine can safely generate high functional antibody responses, establish immunologic memory, and can be safe upon repeated administration in adults, it will have the potential to extend the duration of protection throughout the period of highest risk for the elderly population.

Ageing and immunity research at the National Institutes of Health
(Conrad Mallia, NIH)

In an attempt to broad the communication and knowledge about the research on mechanisms of immunsenescence and new immunization strategies at the National Institutes of Health in the USA, Dr Mallia presented an overview of the NIH Immune Aging Research programmes.

The NIH is studying how the aging immune system responds to infection and vaccination in order to improve the immune response in the growing elderly population. The supported research lines at the NIH regarding immune senescence are those related to hematopoiesis/thymopoiesis, T cell and B cell changes in aging, immune senescence and cancer, mucosal immune system changes with age, and in interventions to improve immune system in elderly (nutritional interventions such as zinc, Omega 3 and Vit E, caloric restriction). From all 27 NIH institutes and centers, the National Institute of Aging (NIA) and the National Institute of Allergy and Infectious diseases (NIAID) are the ones that concentrate most of this research work.

A co-supported NIA/NIAID program of rejuvenating aged immune system presents its ultimate goal on increasing the production of naive T cells in elderly and immunocompromised individuals. Additionally, the NIA is conducting an ongoing clinical trial to determine if administered growth hormone can improve immune function without adverse side effects.

Other NIAID supported targeted research programs with immune senescence components exist are:

- The cooperative centers for translational research in human immunology (CCHI) with a long term goal of facilitating translation of research into clinical applications in humans. The aging/immunity research areas include: innate/adaptive immune response to LAIV, TIV influenza vaccines, typhoid, yellow fever, smallpox vaccines, and the immune response to H. pylori infection.;

- The Human Immunology Project Consortium (HIPC), which provides profiles/signatures of the human immune system, in order to address the lack of human immune data. This program studies multiple types of normal and immunosuppressed populations and defines their profiles or signatures by looking at infection, vaccination, or adjuvant administration in different populations such as adults, children and the elderly.

- Protective Immunity in Special Populations Program. This program includes multiple types of healthy and immunosuppressed populations, and includes human samples and animal models to determine mechanisms of immunosuppression to ultimately provide better vaccines and immune-based therapeutic agents to protect against infection in these groups

- Vaccine and Treatments Evaluation Units which concentrates the clinical trials of Trials of seasonal vaccines, pre-pandemic vaccines and antivirals.

These programs have provided evidence of some possible strategies to enhance the immune response in elderly are by immunization at an earlier age for some pathogens, vaccinating with higher doses of antigen, and by enhancing the immune response through adjuvants or other immunostimulatory agents.

Session 4:
Measuring tools

Which parameters for analysis of immune senescence?
(Karl-Heinz Krause)

A distinct group of biomarkers of immune senescence is currently lacking. Only frequency of infections and decreased vaccine responses are the generally accepted surrogates for immune senescence. Reliable biomarkers would support the task of epidemiological studies when comparing immune ageing in different populations and countries. Also it would assist in the disease risk analysis on an individual and on a population level, as well as facilitating the assessment in terms of needs and types of intervention.

The potential biomarkers would best be analysed from blood samples and considerations on conservation and dispatch of the samples must be taken. On a worldwide scale, Prof. Krause's suggestions were centered on providing the samples mixed with solutions that avoid RNA degradation and/or the use of Dried blood Drops, and that their analysis is centralized.

Suggested potential immunesenescence biomarkers would be alterations in lymphocytes and myeloid cells, DNA/RNA changes and proteins. More specifically, cell biomarkers would include alterations in T- and B- cells, NK-cells, activation markers of dendritic cells and phagocytes. DNA/RNA biomarkers would include telomere length, mRNA expression profiles that would demonstrate variance in number /percentage of specific immune cell types and their activation state, and epigenetic analysis that would correlate with the possible presence of specific gene-silencing of immunosenescence. Proteins as immunosenescence biomarkers would include a panel of cytokines, C-reactive protein, specific antibodies e.g. anti-CMV and oxidized proteins.

Specificities of WHO-based approach to immunesenescence biomarkers must be of worldwide coverage and with limited financial means. They must be expert-based selected, with limited cost analysis but comparable in pilot studies with gold standard (e.g. flow cytometry) and logistically fitted.

It is possible to trace naïve T-cell pools in older adults?
(Pierre-Olivier Lang)

Predicting human phenotypes from genotypes is a newly emerging field, with particular interests for personalized medicine, in predicting outcomes of common diseases and/or in applying specific preventive interventions. Based on these perspectives, Dr Lang presented data showing that exclusive T-cell DNA rearrangements (signal joint TCR excision circles; sj-TREC) could be a promising biomarker for T cell ageing and could be easily estimated in drop blood samples.

The signal joint TCR excision circles sj-TREC analysis is used as a marker for recent thymic emigrants. These circles are a by-product of the initial T cell receptor gene rearrangement in naïve T cells. Quantification of of sj-TREC and T-cell population currently requires analysis on peripheral whole blood samples and FACS/QPCR methodology.

A new methodology to quantify T-cells has been developed with Dr Lang and colleagues that makes the use of dried blood samples possible and a simple QPCR mono assay using fluorescently labeled specific-sequence probes. The results are comparable to those obtained with the technique of reference which requires whole blood samples and combined FACS/QPCR analysis but it presents additional advantages: 1) the use of Dried blood samples implies reduction of infectious hazards and shipping-associated risks compared to venepuncture; 2) the analysis can be performed in long-term Dried samples presenting advantages in terms of sample storage and 3) the no need of an additional FACS analysis generates an economical methodology interesting for use in a global context.

When measuring sjTRECs compared to the total amount of cells in blood samples of healthy individuals of all ages, a large and highly statistically significant portion of the total age variance can be explained by the TREC measurement throughout linear regression model permitting TRECs to be considered as biomarkers of effective ageing. Nevertheless, the influence of diseases involving the immune system (HIV) or comorbid conditions that adversely impact the immune system (chronic heart failure or diabetes) on the accuracy of this method must still be addressed. These facts addressed, the TREC ratio could be evaluated in parallel with clinical endpoints and be explored as a predictive factor of cell-mediated immune response to vaccination, vaccine efficacy and effectiveness, and the ability of individuals with specific health conditions to deal with pathogens.

WHO's Study on Global Ageing and Adult Health (SAGE) - description of methods and sample
(Somnath Chatterji)

Dr Chatterji gave a detailed description of the significance of SAGE and its objectives. SAGE is a longitudinal study of aging in six countries (China, Ghana, India, Mexico, Russia and South Africa) with a total sample size of nearly 50,000 respondents. The objective of the study is to obtain reliable, valid and comparable health, health-related and well-being data over a range of key domains for younger and older adult populations in nationally representative samples.

The core SAGE collects data on respondents aged 18+ years, with an emphasis on populations aged 50+ years by using standardized survey instruments. The data collected examines health, health-related outcomes and well-being, and their determinants over time. With a first whole data collection completed, a follow up will be conducted every 2 years. SAGE intends to generate large cohorts of older adult populations to be compared with cohorts of younger populations for following-up intermediate outcomes, monitoring trends, examining transitions and life events, and addressing relationships between determinants and health, well-being and health-related outcomes .

In order to create a highly reliable database, methods are in continuous development, for example health status, self reported morbidity, risk factors, effectiveness of interventions. In addition, SAGE has also incorporated measured tests and collected dried blood spot (DBS) samples from all the participants. DBS samples are being stored frozen and are ready to be used. The first set of biomarkers to be measured will include Hb, HbA1c, hsCRP, EBV, HIV. Subsequent assays on HDL and total cholesterol, Triglycerides, IL6, will be added to the database and more assays are expected to be developed.

 Additional objectives of SAGE are to develop a mechanism to link survey data to data from demographic surveillance sites as well as to build linkages with other national and cross-national ageing studies. The programme clearly aims at providing a public-access information base for an evidence based policy debate amongst all stakeholders in the planning and decision-making processes about the health and well-being of older adults.

Discussion and Recommendations

This note does not capture every comment made during the consultation or the detail of the discussion session. Rather, it attempts to provide a synthesis of key issues that were raised by session that have implications for the strategic direction of WHO moving forward in the research agenda development.

Session 1: Epidemiology of global elderly population

In an attempt to discuss the different ways of ageing according to world region, health status and environment, the experts identified a number of particular elements, including impact assessment of ageing co-factors and global consensus on research data collection:

- The main issue during the discussion of session 1 was the need for **mapping of diseases affecting the elderly, and most specially in developing countries**. This was suggested to be assessed by monitoring the epidemiology of diseases of a) global/regional importance (e.g. diarrhoeal diseases, malaria…), b) chronic and acute and c) direct/indirect effects of infectious pathogens. As a initial point for the research agenda focus is to be given to selected key diseases, e.g. influenza, diphtheria, pertussis, as well as different study strategies according to global health status. For instance, assessing the effects on ageing of one single pathogen globally or assessing the combined effects of a group of pathogens in a given region.

- The need for the **assessment of the morbidity entailed by the diseases in the elderly population and the impact of the co-morbidities** (e.g. nutritional status, co-infections, psychological conditions affecting the immune system…) were largely discussed. Establishment of a relationship between disability observed in elderly and infectious diseases was highlighted to be weighted up in developed vs. developing country settings.

- The experts expressed their shared **concern and uneasiness with the current meaning of the terms "ageing" and "elderly"**. They all agreed that addressing immunosenescence by using the demographic cut off age of 65+ years is completely inaccurate in terms of biological immune development and environmental influence. A redefinition of ageing by immune competence rather than chronological should be considered.

The recommendations to address the needs mentioned above were:

1) to perform a meta-analysis of existing studies and new ones on ageing and immunization in order to acquire the information largely missing in low income country settings .

2) conduct consequent prospective studies.

Session 2: Immune senescence and evolving immune system

During Session 2 the experts concentrated their work on an in depth look into the underlying cellular mechanisms of immune senescence and identified some gaps to be part of the research agenda.

- It was noted that a **consensus of indicators (markers)** that facilitate defining immune senescence at the cellular level relevant to the human system is a priority. The experts expressed the need to define the immune senescence at the cellular level using markers for: **T-cells, B-cells, NK-cells and dendritic cells**. Quantification of naïve pools of cells and follow-up of their cohorts would contribute to define the starting point of immune senescence at the cellular level and its relationship with decreased protection against infectious diseases.

- **Additional markers** of elderly health status such as frailty were strongly suggested to be identified, specially those particularly important for the immune system such as **indicators of the inflammatory process and dermal alterations, as well as epigenetics and neuroimmunological indicators**. Studying the immune system in an integrated manner would be the accurate way to define immune senescence.

- It was suggested that the immune baseline parameters should be globally identified with the use of **simple assays that imply a consensus on the read-outs** for immune senescence.

The recommendations to address the above mentioned needs were:

1) Suggestion of creating a basic science consortium (periodic consultation: electronic, teleconferences, meetings) focused on tasks related to cellular parameters of the immune system

2) Need for cross-sectional studies on a number of agreed cellular parameters; e.g. thymus "status", production of selected cytokines…

Session 3: Measuring tools

During Session 3 the experts expressed the importance and the need to establish a good linkage between immune senescence and immune diagnostics.

- Importance of better diagnostic tests according to the **correlate of protection**, as defined by the different cellular indicators underlying immune senescence. Some of the mentioned tests were: protein chips for analysis of specificity of antibodies, TRECS, BRECS and methods of dendritic cell activity.

- Importance of better diagnostic tests for the **indirect measure of "ageing"**: frailty, inflammation.

- Importance of identifying the most **appropriate controls** given that "ageing starting point" may have to be redefined, particularly given the different conditions in developed and in developing countries.

- The need to aim at simple **methodology adapted for field setting** in low income countries was debated as a priority.

The recommendations to address the above mentioned needs were:

1) To create a basic science consortium focused on tasks related to methodologies. This consortium must agree on minimum requirements for reporting including standards, assays and controls.

2) Use of existing networks of laboratories with capacity building in low income countries, for example CDC, WHO.

In addition, during Session 3 the experts debated about the different possible analysis that can be performed on the collection of SAGE samples in order to obtain both epidemiological and scientific information on ageing and health-related issues. In light of that, the experts suggested to increase the collection of samples so that they are representative of a wide range of ages as well as global (developed, middle and low income countries). The different assays suggested were:

- Epidemiology data on mortality/morbidity on prevalent diseases: diarrheal diseases, urinary tract infections, Herpes Zoster

- Protein determination e.g. CRP

- Analysis of protective antibody levels on selected diseases

- TREC (T-cell receptors excision circles) measurement

- BREC (B-cell receptors excision circles) measurement

- Detection and analysis of cytokine levels and inflammation markers

- Detection of CMV presence in blood

- Parasite load detection e.g. presence of helminth infection

Session 4: Using immunization to improve performance of the system

A number of approaches are being explored to use vaccination more effectively in the elderly population, including tailoring vaccines for the elderly, using modified routes of vaccination and also modified schedules. Session 4 was employed by the experts as a platform to identify the gaps that need to be part of the research agenda. The suggestions/recommendations were:

- To clearly define the **"portfolios" of needed vaccines to protect the elderly** (type and number, schedule…) **and to identify unavailable vaccines** that are priority in the defined portfolio. Priority diseases identified were Tetanus, Diphtheria, Varicella Zoster, Influenza and Pneumococcal Pneumonia, globally, and Yellow Fever in selected areas.

- To **monitor responses to selected vaccines in adulthood (for instance after the age of 40)**, e.g. Tetanus. In this context, it was also suggested to follow vaccinated travellers responses, e.g. Hep A , Yellow Fever…in order to determine changes in responses with ageing and improving vaccine protection.

- **To revise information on persistence of antibodies** of selected vaccines in developing countries, e.g. Hepatitis B

- To explore the **significance of CMV** presence in relation to ageing (e.g. Pakistan study) and the relative interest in developing a vaccine against such chronic viral infection.

- To make use of **correlates of protection**, such as response to VZV, to follow immunity in different populations through life course

- To explore the **potential and safety of adjuvants** for specific vaccines for the elderly

- **To study "extreme" (very old, very sick, unvaccinated….) populations** in order to provide ageing baseline parameters.

- To explore the possibility of **immunizing at earlier age** for certain pathogens (e.g. Yellow Fever, HPV) that affect elderly populations as well as exploring the **boosting schedules**.

- To improve **adult vaccination and optimal coverage culture** giving importance to protecting elderly populations from cohorts that represent a risk e.g., children (measles), health workers (nosocomial infections)…

- **To promote life course vaccination** in order to promote healthy ageing by limiting the burden of illness linked to vaccine-preventable infectious disease.

Next steps in the development of a global research agenda

The next steps to eventually consolidate a global research agenda on ageing and immunization are the following:

- Major emphasis on identifying the **differences between developed vs. developing countries**

- Working in **partnership**: NIH, EU, private sector, academy, countries….

- **Positioning WHO departments of IVB/IVR and ALC** in the field:
    – Facilitate the developing of a global agenda
    – Assistance in networking with partners
    – Collaboration in selected studies

- Specific actions in the following year:
    – Commission a comprehensive review and critical appraisal of the evidence concerning the infectious disease burden in the ageing population of developing countries. This review will permit a) to identify the main causes of infectious disease morbidity and mortality in adult and ageing populations; b) to determine the prevalence and distribution of these conditions globally; c) to geographically map key viral and bacterial infections, as well as parasitic diseases, in the elderly of low- and middle-income countries. In particular, to assess the impact of global infectious diseases such as HIV, tuberculosis, respiratory and gastrointestinal diseases on the elderly population in developing countries; and d) to describe, and summarize the evidence for, hypothesized mechanisms that may explain high burdens of infectious diseases (e.g. malnutrition and environmental exposure).
    – Contribution to the SAGE study (see suggestion under section 3)

Annex 1:
Agenda

Day 1 - March 21, 2011

Time	Session/Speaker	Purpose of the session/ presentation
13:30 - 14:00	Registration	
14:00 - 14:15	Welcome address John **Beard**, ALC/WHO Teresa **Aguado**, *IVR/WHO*	To discuss the objectives of the consultation and the outcomes expected

Overall consultation co-chairs : J. Beard and MT. Aguado
Rapporteur: J. Thomas

Session 1:	**Global elderly populations: different ways of ageing according to world region, status and environment?**	
14:15 - 14:45	Alexandre **Kalache** Global Policies on Ageing, Brazil	Active ageing globally
14:45 - 15:15	Karl-Heinz **Krause** University of Geneva, Switzerland	Infections in the elderly
15:15 - 15:45	*Coffee break*	
15:45 - 16:15	Gaëtan **Gavazzi** CNRS, Grenoble, France	Epidemiology of infection in Ageing population: questions for vaccine
16:15 - 16:45	Jean-Pierre **Michel** University Hospitals Geneva, Switzerland	Vaccine programme for life
16.45- 17.00	Janet **McElhany** University of British Columbia, Canada	Vaccine preventable disability
17.00 - 17.30	Johannes **Meij** Leiden University, The Netherlands	Genetic alterations on aging populations exposed to adverse environmental conditions
17:30 - 18:30	**Discussion Session 1**	
18.45 - 20.00	*Buffet*	

Day 2 - March 22, 2011

Time	Session/Speaker	Purpose of the session/ presentation

Session 2: An evolving immune system:

1) an in depth look to the underlying mechanisms
2) using immunization to improve performance of the system
3) new vaccines and immunization approaches for the elderly. Today's perspective from the vaccine developers

Time	Session/Speaker	Purpose
08.30 - 09.00	Hana **Golding** FDA, USA	New tools for evaluation of antibody repertoires and affinity maturation following vaccination
09.00 - 09.30	Beatrix **Grubeck-Loebenstein** Institute for Biomedical Aging Research, Austria	T-cells and their niches in old age
09:30 - 10:00	Richard **Aspinall** Cranfield University, UK	Age related decline in vaccine responses and the role of the thymus
10.00 - 10.30	*Coffee break*	
10:30 - 11:00	Bonnie **Blomberg** University of Miami, USA	Intrinsic deficiencies in human B cell functions with age
11.00 - 11.30	Silvia **Della Bella** University of Milan, Italy	Dendritic cells in human aging
11.30 - 12.00	Jean-François **Nicolas** University of Lyon, France	Chronic inflammation and immunosenescence
12.00 - 12.45	**Discussion session 2.1**	
12.45 - 14. 00	*Lunch break*	
14.00 - 14.30	Janet **McElhany** University of British Columbia, Canada	Immune responses to respiratory diseases: Influenza, RSV, pneumonia and pertussis
14.30 - 15.00	Graham **Pawelec** University of Tübingen, Germany	Immunosenescence and its impact on vaccination
15.00 - 15.30	Myron **Levin** University of Colorado, USA	The essential role of specific cell-mediated immune responses in preventing herpes zoster in ageing individuals and the potential for boosting these responses with a zoster vaccine
15.30 - 16.00	*Coffee Break*	
16.00 - 16.20	Alexandre **Von Gabain** Intercell AG, Austria	Protecting the elderly population in mouse and man: Learning from a novel TLR 9 - specific adjuvant
16.20 - 16.40	Marie-Jose **Quentin-Millet** Martine **Denis** Sanofi Pasteur, France	Addressing the needs of the aging population with new vaccines
16.40 - 17.00	Giuseppe **Del Giudice** Novartis, Italy	Adjuvants for improved vaccines for elderly
17.00 - 17.20	Martine **Wettendorf** Robbert **van der Most** GlaxoSmithKline, Belgium	Vaccine design for the elderly
17.20 - 17.40	David **Kaslow** Eddy **Bresnitz** Merck, USA	New vaccines and immunization approaches for the elderly: MSD perspective

Day 3 - March 23, 2011

Time	Session/Speaker	Purpose of the session/ presentation
09.00 - 09.20	Khushroo **Shroff** Pfizer, USA	Potential approach to elucidate mechanisms of immunosenescence
09.20 - 09.40	Conrad **Mallia** NIH /NIAID, USA	Aging and immunity research at the National Institutes of Health
09.40 - 10.30	**Discussion Session 2.2**	
10.30 - 11.00	*Coffee Break*	

CLOSED SESSION: (Private sector attendance not permitted)

Session 3. Drawing a research agenda

1) **Measuring parameters of infection and immunesenescence in selected populations (SAGE study)**
2) **Identification of selected studies to address existing gaps/ Identification of selected tools**
3) **Recommendations**

Time	Session/Speaker	Purpose
11.00 - 11.20	Karl-Heinz **Krause** University of Geneva, Switzerland	Which parameters for analysis of immune senescence?
11.20 - 11.40	Pierre-Olivier **Lang** University Hospitals Geneva, Switzerland	Is it possible to trace naïve T-cell pool in older adults?
11.40 - 12.00	Somnath **Chatterji** HIS/WHO	WHO's Study on Global Ageing and Adult Health (SAGE) - description of methods and sample
12.00 - 12.45	**Discussion Session 3**	
12.45 - 14.00	*Lunch Break*	
14.00 - 15.30	**Discussion panel and Recommendations**	
15.30 - 16.00	*Coffee Break*	
16.00 - 17.00	**Discussion panel and Recommendations (Cont.)**	
17.00 - 17.30	John **Beard** ALC/WHO	To link immune discussions with the broader population issues
17.30h	**End of the consultation**	

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List of participants

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The World Health Organization has provided technical support to its Member States in the field of vaccine-preventable diseases since 1975. The office carrying out this function at WHO headquarters is the Department of Immunization,Vaccines and Biologicals (IVB).

IVB's mission is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases. The Department covers a range of activities including research and development, standard-setting, vaccine regulation and quality, vaccine supply and immunization financing, and immunization system strengthening.

These activities are carried out by three technical units: the Initiative for Vaccine Research; the Quality, Safety and Standards team; and the Expanded Programme on Immunization.

The Initiative for Vaccine Research guides, facilitates and provides a vision for worldwide vaccine and immunization technology research and development efforts. It focuses on current and emerging diseases of global public health importance, including pandemic influenza. Its main activities cover: i) research and development of key candidate vaccines; ii) implementation research to promote evidence-based decision-making on the early introduction of new vaccines; and iii) promotion of the development, evaluation and future availability of HIV, tuberculosis and malaria vaccines.

The Quality, Safety and Standards team focuses on supporting the use of vaccines, other biological products and immunization-related equipment that meet current international norms and standards of quality and safety. Activities cover: i) setting norms and standards and establishing reference preparation materials; ii) ensuring the use of quality vaccines and immunization equipment through prequalification activities and strengthening national regulatory authorities; and iii) monitoring, assessing and responding to immunization safety issues of global concern.

The Expanded Programme on Immunization focuses on maximizing access to high quality immunization services, accelerating disease control and linking to other health interventions that can be delivered during immunization contacts. Activities cover: i) immunization systems strengthening, including expansion of immunization services beyond the infant age group; ii) accelerated control of measles and maternal and neonatal tetanus; iii) introduction of new and underutilized vaccines; iv) vaccine supply and immunization financing; and v) disease surveillance and immunization coverage monitoring for tracking global progress.

The Director's Office directs the work of these units through oversight of immunization programme policy, planning, coordination and management. It also mobilizes resources and carries out communication, advocacy and media-related work.

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