"Should you find incorrect information, please advise vaccineresearch@who.int".

STATE OF THE ART OF VACCINE RESEARCH AND DEVELOPMENT.

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Preface

Infectious diseases are responsible for one fifth of all deaths worldwide, killing at least 11 million people a year [1]. More than five million of these deaths are recorded every year in children under five years of age, more than a third of which occur during the first three months of life. HIV/AIDS kills more people than any other single infectious disease, accounting for more than 2.1 million deaths per year in the adult population and about 290,000 deaths each year in less than 15-years-old children [2]. Other major killers are acute respiratory infections (ARIs), diarrhoeal diseases, tuberculosis, malaria and other parasitic diseases. Deaths in <5 years-old children are mostly caused by ARIs and diarrhoeal diseases, followed by malaria, measles and HIV/AIDS. Malaria alone is responsible for one child death every 30 seconds in the world.

The most effective way to reduce disease and death from infectious diseases is to vaccinate susceptible populations. The impact of vaccination on the health of the world's population cannot be overstressed. With the exception of water sanitation, no other modality – not even antibiotics – has had such a major effect on mortality reduction and population growth [4]. It has been estimated that vaccines annually prevent about 6 million deaths worldwide, and provide a global direct saving in the order of tens of billions of US dollars [5].

Vaccination has allowed the global eradication of a deadly human scourge, smallpox, allowing discontinuation of routine smallpox immunization globally [6]. The next disease targeted for eradication is poliomyelitis, which is still a global challenge [7]. The campaign for the eradication of poliomyelitis, which involved vaccination of more than 2 billion children, spectacularly reduced the global incidence of polio by 99.9%, from 350,000 cases per year in 125 countries on 5 continents in 1988, to less than 800 cases in 6 countries on 2 continents in 2002 [8]. A sudden decline of community acceptance of polio vaccination in Northern Nigeria in 2002 interrupted the trend towards eradication, leading to a disastrous epidemic polio resurgence that spread from Nigeria to most African countries, Yemen, Saudi Arabia and Indonesia. Following the launching of new vaccination campaigns, mostly based on monovalent type 1 and type 3 oral polio vaccines, the number of confirmed polio cases worldwide started to decline again by the second semester of 2006, reviving the hope to eradicate the disease within the next few years [10].

Short of global eradication of the disease, the systematic use of vaccines can lead to the local elimination of the causative pathogen. This is the case for measles, which has been eliminated in four

of the six WHO regions, where the only remaining cases are imported cases that do not lead to sustained spread of the virus . The global mortality due to measles has dropped in a spectacular fashion from about 750 000 deaths in 2000 to less than 200 000 in 2007, due to the increase in vaccination coverage. This has been particularly true in Africa, which showed a 63% decrease in measles mortality over the past eight years. Recent epidemics of measles in Europe however are a matter of concern. Bacterial diseases caused by *Haemophilus influenzae* type b, *Neisseria meningitidis* serogroup C and *Streptococcus pneumonia*e [13], also appear to have been eliminated from the countries which introduced national vaccination programs based on the use of new conjugate vaccines against these pathogens. In addition to individual protection, these vaccines also provide "herd protection" in unvaccinated persons, which occurs when a sufficient proportion of the group has been made immune by vaccination [15].

Today's technologies can provide adequate tools to detect, control and even prevent emerging infections. Direct engineering of attenuated mutant, reassortant or recombinant viral strains, deletion of virulence genes from pathogenic bacteria and expression of protective antigens through manipulation of DNA, proteins or polysaccharides all allow the development of newer vaccines against infectious diseases. New vaccines have recently been marketed such as, in the field of viral diseases, rotavirus and human papillomavirus (HPV) vaccines. Numerous new vaccines are at an advanced stage of clinical trials and hopefully should be made available within the next five-to-seven years. Considerable progress has also been made in the field of adjuvants, based on advances in basic immunology and a better understanding of innate immunity mechanisms and the way they can shape subsequent adaptive immune responses [17]. In parallel, efforts are being made to increase ease and speed of vaccine delivery, decrease costs and reduce pain associated with vaccination by developing needle-free injection devices, transcutaneous immunization and mucosal immunization [20] .

However, during the last decade, not only did malaria, tuberculosis (TB) and HIV - the three diseases which alone contribute to half the global burden of infectious diseases – thrive, but there actually was a worsening of tuberculosis and malaria in the immunocompromised population infected by HIV. New threats such as hepatitis C and avian influenza challenge vaccine efforts worldwide. Worse, at least two million children still die each year from diseases that could have been prevented by already existing low-cost and effective vaccines. On top of this high death toll, millions more children are suffering disability and illness because they have not been properly immunized.

The global control of infectious diseases requires global and continuous collaboration, coordination of regulatory agencies and development of vaccines to prevent all diseases, as well as a sustainable economic system to support these initiatives [21]. Although highly effective vaccines are available against a number of pathogens, the world's poorest regions are still suffering a heavy toll of premature death and disability from infectious diseases for which vaccines do not exist or else need to be improved. For these diseases, it is of crucial importance that vaccine research and development be considered a priority. The present document represents an extensive analysis of the state of the art of vaccine R&D against infectious diseases of public health importance for which vaccines are still either non-existent or need substantial improvement. The following series of chapters will regroup infectious diseases based on commonality of transmission route and/or major symptoms (see Table of Contents below).