CLINICAL AND EXPERIMENTAL VACCINE RESEARCH

Vaccines today, vaccines tomorrow: a perspective

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Vaccines are considered as one of the major contributions of the 20th century and one of the most cost effective public health interventions. The International Vaccine Institute has as a mission to discover, develop and deliver new and improved vaccines against infectious diseases that affects developing nations. If Louis Pasteur is known across the globe, vaccinologists like Maurice Hilleman, Jonas Salk and Charles Mérieux are known among experts only despite their contribution to global health. Thanks to a vaccine, smallpox has been eradicated, polio has nearly disappeared, *Haemophilus influenzae B*, measles and more recently meningitis A are controlled in many countries. While a malaria vaccine is undergoing phase 3, International Vaccine Institute, in collaboration with an Indian manufacturer has brought an oral inactivated cholera vaccine to pre-qualification. The field of vaccinology has undergone major changes thanks to philanthropists such as Bill and Melinda Gates, initiatives like the Decade of Vaccines and public private partnerships. Current researches on vaccines have more challenging targets like the dengue viruses, malaria, human immunodeficiency virus, the respiratory syncytial virus and nosocomial diseases. Exciting research is taking place on new adjuvants, nanoparticles, virus like particles and new route of administration. An overcrowded infant immunization program, anti-vaccine groups, immunizing a growing number of elderlies and delivering vaccines to difficult places are among challenges faced by vaccinologists and global health experts.

Keywords: Vaccinology, International Vaccine Institute, Impact of vaccines, Vaccines of the future, Inactivated oral cholera vaccine

Introduction

Vaccinology is a growing field. The establishment of the Korean Society is a strong indication that it is acknowledged as an important new discipline in Korea as well. The International Vaccine Institute (IVI) is dedicated to vaccines and vaccinology for developing countries. Since the discoveries of Louis Pasteur, vaccines made major contribution to global heath. Despite many successes, vaccines are facing important challenges. Research is targeting more complex problems including delivery.

The International Vaccine Institute

Created 15 years ago, IVI mission is to combat infectious diseases through innovations

in vaccine design, development and introduction, addressing the needs of people in developing countries. IVI is the first international organization that was established in Korea. Based on a concept of the Children Vaccine Initiative, it became a project driven by the United Nation Development Programme. It is a research organization working on enteric and diarrheal diseases as well as dengue. It is a global health organization committed to reducing the burden of neglected diseases and to building capacity in vaccine sciences in developing countries. IVI is working in more than thirty countries and has made major contribution in epidemiologic research on neglected diseases. It has pioneered a "lab to community approach" and established strong laboratory research programs in vaccine design, development, production and technology transfer [1].

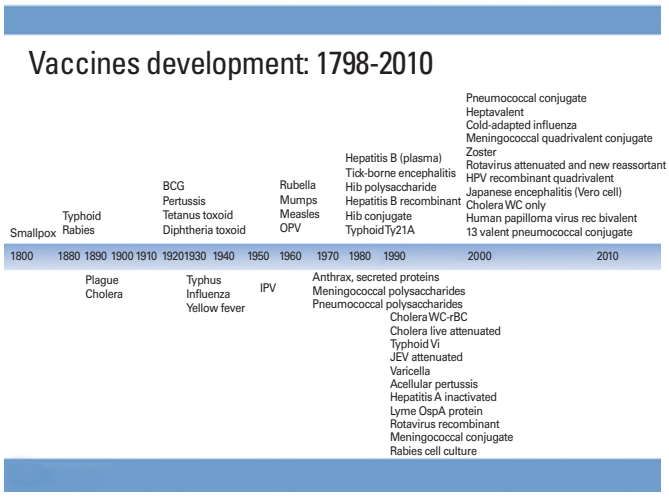

Fig. 1. Vaccines developed since 1798, an exponential growth [3]. BCG, bacillus Calmette-Guérin; IPV, inactivated polio vaccine; OPV, oral polio vaccine; Hib, *Haemophilus influenzae* type b; JEV, Japanese encephalitis virus; OspA, outer surface protein A; HPV, human papillomavirus; WC, whole-cell.

Historical Aspects of Vaccine Discovery and Development

At the end the 19th century Louis Pasteur established the foundations of bacteriology and vaccinology. Chemist by training, he is best known for the discovery of the first rabies vaccine, for his work on cattle and poultry infectious diseases as well as his work on fermentation of beer and wine [2]. Thanks to vaccines, the opisthotonos due to tetanus and iron lungs are image of the past relegated to medical books. During the 20th century, vaccinologists like Jonas Salk, Maurice Hilleman, and Charles Mérieux have discovered, developed and manufactured more than forty vaccines. Unfortunately they seem to have been forgotten. The smallpox vaccine is considered by many as the first vaccine to be used. It was followed during the end of the 18th century and the first half of the 20th century by the discovery, development and introduction of a little bit more than 10 vaccines. The last five decades have seen a nearly exponential growth of the number of new vaccines as shown on Fig. 1 [3].

Impact of Vaccines and New Developments

Vaccines are considered as one of the most important contributions of the 20th century. Their introduction has led to the control or near elimination of diseases such as diphtheria, measles, pertussis, polio and tetanus. While the world population was increasing by 54% between 1980 and 2009, the clinical cases due to these diseases were reducing respectively by 99%, 95%, 95%, 97%, and 91% [3]. When the Global Polio Eradication Initiative was launched in 1988, 125 countries were endemic and more than 350,000 children were paralyzed every year. In February 2012, India was declared free from polio while three countries remain endemic: Pakistan, Nigeria, and Afghanistan [4]. Introduction of *Haemophilus influenzae* type b (Hib) vaccination in Kenya in 2001 has witnessed an 88% reduction of meningitis due to Hib [5]. The conjugated meningitis A vaccine was introduced in Burkina Faso in December 2010. Nineteen million people were immunized in 15 days. Subsequent surveillance has evidenced a control if not an elimination of the disease in the following years [6].

In September 2011, an inactivated oral cholera vaccine (developed by IVI and Shanta Biotechnics in collaboration with VaBiotech in Vietnam and the University of Gothenburg in Sweden) was successfully pre-qualified by the World Health Organization (WHO). Pre-qualification is the end of a process that sees WHO qualify a vaccine for purchase by United Nation agencies such as the United Nations Children's Fund (UNICEF) and by extension the Global Alliance for Vaccines and Immunization (GAVI). The vaccine was licensed in India and pre-qualified thanks to a successful phase 3 trial in Kolkata, India. Results of one and three years follow-up have shown a protective efficacy of 67% (one tailed 99% confidence interval [CI], lower bound 35%) [7].

In October 2011, the first results of a malaria vaccine phase 3 trial conducted in Africa were published. RTS,S is most clin-

ically advanced malaria vaccine made of fusion protein comprising of the repeat ANAP region of the circumsporozoite protein of the sporozoite (*Plasmodium falciparum*) and the hepatitis B surface antigen expressed in *Escherichia coli* mixed hepatitis B surface antigen and used with a proprietary adjuvant of GlaxoSmithKline Biologicals. The phase 3 trial is conducted in two cohorts of 5 to 17 months of age and of infants of 6 to 12 weeks. In the 5 to 17 month cohort and after one year of follow-up, the vaccine reached an efficacy of 55.8% (95% CI, 50.6 to 60.4%) against the risk of clinical malaria and 47.3% (95% CI, 22.4 to 64.2%) against severe malaria [8]. In the 6 to 12 weeks cohort, after one year of follow the risk of getting clinical malaria was reduced by 31.3% (95% CI, 23.6 to 38.3%). Vaccine efficacy against severe malaria was 36.6% (95% CI, 4.6 to 57.7%) [9].

Both oral cholera vaccine and malaria vaccine candidates were found safe [7-9]. They are part of a new generation of vaccines that will be introduced first in developing countries opening a new challenge that is the understanding of their safety when given to large population in countries where pharmacovigilance systems are still weak [10].

The past two decades have seen major developments in the environment of new and existing vaccines development and introduction. The Bill and Melinda Gates Foundation (BMGF) has been a game changer. GAVI has been able to reduce considerably the time between introduction of vaccines such as rotavirus and pneumococcal vaccines in developed and developing countries. The decade of vaccines collaboration, an initiative led by the BMGF, WHO, UNICEF, and National Institutes of Health (NIH), has developed a Global Vaccine Action Plan in consultation with a large number of experts [11]. It has been endorsed by the last World Health Assembly (resolution EB130.R12). Collaborations between for profit and not for profit have helped resolving the economic challenges of vaccines made for developing countries only [12].

Vaccines of the Future

Among the vaccines candidates that are in research and development, one could highlight a vaccine against dengue; several vaccine candidates are under development. They are either live attenuated or subunit vaccine candidates and target the four different serotypes of the virus [13]. Malaria vaccine candidates aiming at blocking transmission between mosquitoes and human beings will introduce the new challenge of vaccines that will not directly protect their recipient but the community [14]. Influenza is another part of vaccinology where a lot of progresses are done in terms of preparedness for a potential pandemic or development of "universal flu" vaccine based of the M2 protein [15]. A universal flu vaccine would be interesting clinical development case as the hypothesis of a protection against new strains would always remain to be demonstrated. Nosocomial infections are an important problem of modern hospitals and aging populations, a promising *Clostridium difficile* vaccine candidate is under development [16].

Besides new target, a considerable amount of work is looking into enhancing immunogenicity of vaccines thanks to new adjuvants as it was done already with the pandemic flu vaccine, the malaria vaccine (RTS,S), and the human papillomavirus vaccine. A better understanding of the immune response has led to interesting work on presenting platforms such as nanoparticules and virus like particles [17]. Most of vaccines used today are inoculated by intramuscular or subcutaneous route with syringes and needles. One of the focuses of IVI research is the possibility to give vaccines orally (under the tongue) [18].

New Challenges for Vaccines

With the development of many new vaccines, infants' immunization programs have to deliver a large number of inoculations, a burden for them and for the mothers. Combining antigens is one of the solutions despite their technical, clinical, and regulatory difficulties.

Several publications and campaigns have recently had a very negative impact on vaccine programs. One of the most dramatic consequences has been the resurgence of measles in Europe following a drop in measles, mumps, and rubella (MMR) vaccination coverage due to a fabricated perception of a link between MMR and autism [19].

An aging population requires preventions such as influenza, pneumococcal, shingles, and regular booster. An aging immune system will require new approaches [20].

Conclusion

Thanks to vaccines, diseases have or are on the verge of being eliminated and eradicated. The last two to three decades have seen major development take place. A large number of vaccines have been brought to market. From a trial and error period, vaccinology is moving into a new era where research

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will guide the design of new vaccines that prove more difficult to develop.

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