Advancing vaccine innovation and public health impact at GSK

AUTHORS
Emmanuel Hanon, head of research and development at GSK Vaccines
Thomas Breuer, chief medical officer of GSK Vaccines
Rino Rappuoli, chief scientist and head of external research and development at GSK Vaccines
ADDRESS
GSK, 20, Avenue Fleming, Building W23, 1300 Wavre, Belgium

According to the World Health Organization (WHO), only access to clean drinking water rivals vaccination in its ability to help save lives (around two to three million each year). For more than 200 years, scientists have been developing vaccines to address devastating diseases and help protect people of all ages worldwide. However, public trust in vaccines is currently being eroded, and vaccine-preventable diseases have made a comeback in countries that had previously managed to eliminate them. Findings from the Wellcome Global Monitor 2018 (wellcome.ac.uk) suggest that an increased understanding of science behind vaccines tends to correlate with increased confidence in vaccines, which in turn impacts decisions about vaccination. Therefore, stakeholders in vaccination are countering vaccine hesitancy through education and by increasing the pool of easy-to-find and easy-to-comprehend, balanced information on immunization. As a leading developer of vaccines, GSK has a part to play in this, with experts who are well positioned to provide insights into the vaccines of today, and those that are to come.

SELECTING FUTURE VACCINES

Disease burden (the public health impact a disease has on a region or population) has the largest influence on which vaccines are pursued. This is often calculated in terms of quality-adjusted life-years (QALYs) and costs; considering factors such as disease frequency (is it common or rare), impact on quality of life (are the symptoms mild, severe or fatal), healthcare resource use, the financial cost to society and ability to pay. This overall burden-cost is then compared between different diseases and populations, and results can vary greatly. For instance, the developed and developing world can have differing priorities due in large part to their healthcare infrastructure, sanitation and socioeconomic circumstances.

Historically, the first vaccines were developed against diseases with high morbidity and mortality rates, such as smallpox (successfully eradicated in 1980), diphtheria and tetanus; diseases which also primarily affected children. Great societal progress was made because of advances in the fight against these diseases. In the early 1900s, families tended to be much larger (often due to the threat of high childhood mortality) and the average life expectancy was around 60 years of age. Nowadays, families tend to be much smaller and life expectancies are around 80+ in industrialized nations. However, as societies experience a growing proportion of older adults, the burden of disease is starting to shift; of the more than 40,000 deaths from vaccine-preventable diseases that occur every year in the United States, now 99% are in adults. Therefore, thinking about vaccination across the whole life course is a key opportunity, making vaccination part of the increasing emphasis on preventative medicine for all.

THE VACCINE DEVELOPMENT PROCESS

Vaccine development is a long, costly and complex process that can often take more than 10–20 years to complete. Moreover, vaccines, unlike other medicines, are not being given to people who are already suffering from a specific illness; vaccines are given to millions of healthy individuals with the aim to help prevent them from contracting the disease. Therefore, it is critically important that vaccine developers and regulators meet the highest standards and demonstrate that the benefit of any new vaccines far outweigh any potential risks.

A scientist working on a Malaria vaccine.

Furthermore, while the very early years of vaccine development focused primarily on assessing the efficacy of vaccines, the emphasis has appropriately shifted to the benefit-risk profile of vaccines. There is the requirement that industry and regulators not only demonstrate a vaccine's efficacy, but equally its safety profile. This requires more investigations throughout the development process, even after vaccines are licensed, along with more comprehensive regulatory and licensing procedures; but all with the aim of ensuring that new vaccines have a positive benefit-risk profile – in other words that the benefits far outweigh any potential risks.

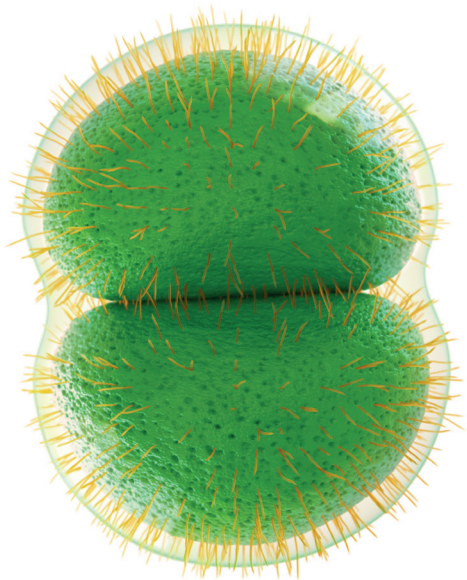

Figure 1. Meningococcal serogroup B bacteria, commonly known as meningitis B.

THE EXPLORATORY AND PRE-CLINICAL STAGES

The first step of vaccine development is the exploratory stage. This takes place in the lab, typically takes two to four years, and aims to identify natural or synthetic antigens that might help prevent or treat a disease. Historically, these antigens have included virus-like particles, weakened viruses or bacteria, weakened bacterial toxins, or other components derived from pathogens; and this stage has involved a lot of time-consuming trial and error. Today, scientific advances, and new technologies such as digitalization and artificial intelligence, are helping reduce the time needed to identify candidate vaccines and are providing solutions for vaccines that were difficult to develop in the past.

For example, in the case of meningococcal meningitis B (MenB), a rare but life-threatening illness, the exploratory stage was especially hard due to the variability of the surface proteins of MenB and the similarity between the MenB capsule and other cells in the human body (**Fig. 1**). To overcome this roadblock, scientists under the lead of Rino Rappuoli invented reverse vaccinology, a process that screens an entire genome and uses bioinformatic tools to identify different genes as antigen candidates (Rappuoli, R. *Vaccine* **19**, 2688–2691; 2001). These are then further filtered for attributes that would potentially make safe and effective vaccine targets.

Once the antigen is identified, the preclinical stage starts. This increasingly involves using cell-culture systems (relying less and less on animal testing) to assess both the safety of the candidate vaccine as well as the immune response it causes before testing in humans is considered. The journey for many candidate vaccines ends at this stage, but those that do show promise are then approved for testing on humans.

CLINICAL TESTING

Phase I vaccine trials involve a small group of healthy volunteers (<100), although if the vaccine is for children, researchers will start with adults and gradually step down to individuals at the target age. The aim of phase I is to test the safety of the vaccine and assess the immune response that it causes on humans. Phase II trials involve a larger group of volunteers (100–1,000), confirms formulations and doses, identifies if there is a need for boosters and determines the best intervals between each dose. This stage again evaluates safety, immune response and, sometimes, initial results on efficacy. It may also include individuals belonging to groups at higher risk of catching the disease. Phase II trials are randomized, controlled and involve a placebo group.

During phase III trials, the vaccine is tested on a much larger group of volunteers (1000s or 10000s of individuals). These tests are randomized, double blind and involve placebos (saline, a vaccine for another disease, or another substance). Phase III is an important step for identifying the less frequent possible adverse events because these might not show up in the much smaller phase I and II trials. Regulatory approval is sought before each phase of the clinical trials, with independent boards assessing the safety and efficacy of the vaccine candidate to help ensure the safety of trial participants throughout the process.

While phase III trials are running, work also begins on setting up the vaccine manufacturing facility because it can take at least six years from the time the building commences to the time that the facility typically gets its first regulatory approval. This is done to ensure a seamless start in the manufacturing and supply of a new vaccine after licensure. The construction work and clinical trials mean that the company is making large investments, at its own financial risk, before the phase III results are published and licensure is granted by external authorities at the regional (for example by the European Medicines Agency in Europe) and/or national level (for example by the Food and Drug Administration in the US).

MANUFACTURING, TESTING AND SAFETY MONITORING

A little known but important fact about vaccines is that manufacturing a single dose of vaccine can take up to 24 months. This is mainly driven by the high number and level of quality checks that are performed on every single batch that is produced. Up to 500+ quality tests are performed on more complicated vaccines, such as multivalent pneumococcal vaccines, before release. In addition, vaccine manufacturers are regularly inspected by regulatory authorities from around the world. At GSK for example, at least one site in its global manufacturing network undergoes a routine inspection by a regulatory authority almost every week, in addition to its own internal inspection processes (GSK Annual Report 2016, p. 33; www.gsk.com).

The vaccine production process itself can be divided into the following steps, with quality checks happening throughout:

1. Generating the antigen; by growing and harvesting the pathogen's proteins, polysaccharide or deoxyribonucleic acid.
2. Releasing and isolating the antigen; by separating it from the media on which they are grown and isolating it from other proteins or growth mediums still present.
3. Purifying the antigen; by using different techniques according to protein size, physico-chemical properties, binding affinity or biological activity.

4. Adding supporting components; i.e. adjuvants (to enhance the vaccine recipient's immune response), stabilizers (to prolong shelf life) or preservatives (to allow for the safe use of multi-dose vials).
5. Filling syringes or vials; and packaging the vaccines before they are labelled and distributed worldwide.

To support post-licensure vaccine safety surveillance and pharmacovigilance, vaccine companies such as GSK employ a dedicated team who, through regular engagement activities with regulatory authorities and/or independent external experts, continually evaluate the benefit-risk profile of GSK vaccines throughout their entire lifecycle. Their work typically includes long-term effectiveness and safety studies, studies on broader populations and ongoing characterization and quantification of potential safety signals. Routine safety oversight processes, established by the authorities for medicinal products, include the independent assessment of available safety data by experts in regulatory authorities and public health institutes and aim to ensure the early detection and assessment of any potential safety signals. Both GSK and independent experts also continue to perform studies on how vaccination benefits individuals and society. This includes, but is not limited to, studies into the downstream effects of vaccines, cross-protection and broader health economic aspects.

DISEASE PREVENTION AND THERAPY

Vaccines are the product of the steady and detailed progress in our understanding of human–pathogen interactions. Scientists today better understand how the human immune system interacts with the diseases that infect them and are using this knowledge, combined with the use of game-changing technologies, to address new disease areas (such as parasites) and populations (such as older adults), with faster response rates and shorter lead times. GSK and its partners are at the forefront of this new wave of science and technology. They are opening new possibilities for global health initiatives that aim to reduce the burden of diseases such as malaria and tuberculosis, and new ways to tackle anti-microbial resistance. These new discoveries are also starting to unleash the potential of therapeutic vaccines for diseases like chronic obstructive pulmonary disease (COPD).

COPD affects around 10% of the population >40 years of age and is the third most common cause of death worldwide, with a global death toll of 3.1 million in 2015. Prevalence of the disease is increasing and millions affected by the disease do not even know that they have it. Therefore, GSK is currently developing a vaccine targeting the bacteria implicated in 30–45% of acute exacerbations of COPD; non-typeable *Haemophilus influenzae* (NTHi) and *Moraxella catarrhalis* (Mcat). The aim of the COPD vaccine will not be to help prevent the disease itself, but rather to reduce exacerbations, slow the disease progress and hopefully improve the quality of life for the growing number of people suffering and dying from COPD worldwide.

A NEW ERA OF VACCINES

New technologies enable the industry to potentially complete tests in less time, streamline production processes, lower costs and develop vaccine against diseases or for patient populations that were previously not possible. All while ensuring that the highest safety and quality standards are maintained. These technologies include GSK's self-amplifying mRNA (SAM), a technology that could allow our own cells to 'manufacture' the antigen in-situ, instead of introducing antigens into the body; bioconjugate technology, which could remove complexity from production of conjugate vaccines; and adjuvants.

Adjuvants are substances designed to enhance our immune response to vaccines. Although adjuvants have been used in vaccines since the 1930s, scientists today have a better understanding of how the human immune system interacts with the pathogens it confronts; including the part played by adjuvants in producing and controlling an immune response. For example, as we age, our immune system reduces its ability to mount an effective response to infection. This also means that our immune system has lower ability to mount an effective response to most vaccinations. Therefore, a new generation of adjuvanted vaccines is being designed to appropriately stimulate the immune system and thereby target diseases that primarily effect older adults, such as shingles, COPD and RSV (respiratory syncytial virus), as well as vaccines for major global health issues including malaria and tuberculosis.

PARTNERING FOR INNOVATION

In addition to technological advances, the key drivers of scientific progress are people – scientists, doctors and other experts – collaborating to find new and innovative ways to solve problems, to work better and faster, and to maintain the highest standards of quality and safety. GSK recognizes that research and development (R&D) solutions may come from many sources and welcomes partnerships, which range from early research to late-stage development, that help to advance the frontiers of disease prevention. More than 90% of GSK's vaccines are developed in partnership and the company has more than 150 active scientific collaborations with pharma and biotech companies, consortia, charities, foundations, government researchers, academic groups and businesses in non-life sciences. GSK also provides opportunities for PhD or postdoctoral researchers to work on cross-disciplinary R&D projects for the discovery and early development of vaccines.

FROM VACCINES TO VACCINATION

The scientific progress being achieved, and solutions developed, will only benefit individuals and society if vaccines are used and turned into vaccination. In addition to developing and manufacturing cutting-edge vaccines, GSK is committed to the role it plays, together with stakeholders worldwide, in helping build understanding of and confidence in vaccination by providing clear answers to the questions being asked. For example, parents want the best for their children and may have questions about the effects of a vaccine on their child. After all, the ultimate aim of the scientific progress being made in the development of vaccines is to realize the outstanding benefits that these vaccines could potentially deliver – for our societies, and for each one of us.