Vaccines: The End of Illness
K. John Morrow, Jr.

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New to Insight Pharma Reports is Vaccines: The End of Illness. This report focuses on the most recent vaccine research, emphasizing their reputation as an unmatched tool of efficient healthcare. Their low cost, extended protection and the impossibility of their circumvention through development of resistance on the part of the target pathogen have been longstanding attributes of vaccines. Today, vaccine technology is undergoing a fundamental revolution, taking advantage of the profound understanding of the immune system and its ability to mount protective antibody production and cell-based responses to foreign antigens. Understanding these properties will not only enable the development of innovative diagnostics but also the advancement of therapeutic applications.

Specific Highlights Include:

• This report profiles some of the major pharma companies involved in vaccine R&D and a number of biotech companies developing new vaccine products and technologies – including 35 small pharma companies and 8 big pharma companies profiled

• The logistics and management of the vaccine industry are increasingly based on partnerships between the private sector (pharma and biotech companies), government agencies (WHO) and large non-profits (such as the Gates Foundation).

• An assessment of the future directions of vaccines as innovative medical therapies for a wide range of diseases.

• Explores conditions not normally thought to be in purview of vaccination, including substance abuse and neurological disorders such as Alzheimer’s disease and Parkinson’s disease.

• Survey of industry experts concerning the political economic and technological future of vaccine technology.
Executive Summary

Vaccines are probably the most effective discovery in the history of medical science. Their low cost, extended protection and the impossibility of their circumvention through development of resistance on the part of the target pathogen render them unmatched as a tool of efficient healthcare.

Vaccines are also one of the oldest medical devices, with a history going back at least a thousand years. Modern vaccine advances date from the 19th century. Today vaccine technology is undergoing a fundamental revolution, taking advantage of the profound understanding of the immune system, and its ability to mount protective antibody production and cell-based responses to foreign antigens.

In the latter part of the 20th century, vaccines endured a rollback in which concern over legal challenges and negative publicity over real and imagined side effects of vaccination. Protective legislation passed by congress in the 1980s combined with improvements in vaccine technology have driven a resurgence in its public acceptance.

This report profiles some of the major pharma companies involved in vaccine R&D and a number of biotech companies developing new vaccine products and technologies.

The logistics and management of the vaccine industry is more and more based on partnerships between the private sector (pharma and biotech companies), government agencies (WHO) and large non-profits (such as the Gates Foundation). This relationship will grow and expand in the foreseeable future.

The report concludes with an assessment of the future directions of vaccines as innovative medical therapies for a wide range of diseases. In addition it explores conditions not normally thought to be in purview of vaccination, including substance abuse and neurological disorders such as Alzheimer's disease and Parkinson's disease.

Since the attacks on the World Trade Center in 2001, the federal government has committed substantial resources to investigating biological warfare agents and treatments for such weapons. However data available in the public sphere suggests that the risk that these agents would be employed in a meaningful way is slight, and may drain resources from much more likely challenges, such as flu pandemics.

The long range outlook for vaccines is bright. Traditional vaccines worked through stimulation of the humoral arm of the immune system, and so were limited in their effectiveness for the treatment of cell-based diseases. New technologies and an expanded understanding of the basic science of cellular immunity are opening innovative pathways to the engineering of more effective vaccines.

A final chapter presents results of a survey of industry experts concerning the political economic and technological future of vaccine technology.
Executive Summary

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CHAPTER 1

Introduction

1.1. The History of Vaccination

There are few unalloyed triumphs in the long history of humanity’s war against illness. The weapons that medical science has mustered over the millennia have in many cases been a mixed blessing, sometimes bringing as much harm as benefit. Think of bleeding, purging, emetics, gold salts, mercury salts, and babies delivered by physicians with unwashed hands straight from the autopsy theater.

Even in recent times, as the scientific underpinnings became more and more solid, we see that therapies fail, that unpredicted side effects of drugs become manifest, and that the actual benefits of new technologies turn out to be much less than initially promised. Indeed, some scholars of the history of medicine have argued that the discoveries of modern medicine have not increased lifespan nearly as much as public health measures, including clean water, uncontaminated food and improved sanitation. These advances, introduced in the late 19th and 20th centuries, long before the era of contemporary medicine, resulted in a precipitous decline in the crude death rate (Figure 1.1).

The inadequacies of modern medicine are widespread. Today there is an impassioned debate over the use and overuse of antibiotics and the rise of antibiotics-resistant strains of bacteria. Yet there is one shining city on the hill of medical science which has yielded amazing health benefits going back hundreds, perhaps thousands of years: vaccination. This procedure is notable for the fact that pathogens do not develop resistance to its effects; adverse reactions and side effects measure in the fraction of a percentage point; the cost is infinitesimal; it can be delivered in the darkest reaches of the jungle by minimally trained medical personnel; and its protection may, under optimal circumstances, last a lifetime.

So this report will orient the reader consider some historical background, based on the assumption that we can’t decide where we are going if we don’t know where we came from; especially given the struggle for research funding support of vaccine technology in the last decade. It is not the purpose of this report to present a comprehensive treatise on this topic, but simply to highlight some of the most important accomplishments on this long road to our present state of knowledge.
**Figure 1.1: Overall Decline in Worldwide Death Rates**

Death-rate in ten European countries during the period 1861-1954. The decline during the period 1861-1910 and 1861-1954 is in percentages of the death-rate of the period 1861-1870.

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<tr>
<td>Belgium</td>
<td>23.7</td>
<td>15.9</td>
<td>32%</td>
<td>11.9</td>
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<tr>
<td>Denmark</td>
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<td>United Kingdom</td>
<td>22.6</td>
<td>14.7</td>
<td>36%</td>
<td>11.2</td>
<td>51%</td>
</tr>
<tr>
<td>Germany</td>
<td>26.9</td>
<td>17.5</td>
<td>35%</td>
<td>10.6*</td>
<td>61%</td>
</tr>
<tr>
<td>Italy</td>
<td>30.3</td>
<td>21.2</td>
<td>27%</td>
<td>9.8</td>
<td>68%</td>
</tr>
<tr>
<td>France</td>
<td>23.6</td>
<td>19.2</td>
<td>18%</td>
<td>12.4</td>
<td>50%</td>
</tr>
<tr>
<td>Netherlands</td>
<td>25.4</td>
<td>14.3</td>
<td>44%</td>
<td>7.4</td>
<td>71%</td>
</tr>
<tr>
<td>Norway</td>
<td>18.0</td>
<td>13.8</td>
<td>23%</td>
<td>8.5</td>
<td>53%</td>
</tr>
<tr>
<td>Spain</td>
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<td>24.3</td>
<td>20%</td>
<td>9.5</td>
<td>69%</td>
</tr>
<tr>
<td>Sweden</td>
<td>20.2</td>
<td>14.3</td>
<td>30%</td>
<td>9.5</td>
<td>53%</td>
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*Concerns in the period 1952-1954 Federal Germany*

We will then examine the strategies for vaccine development, based on the position of basic medical science today. Following is an analysis of large pharma companies that have the resources for extensive clinical trials, and small phamas that are on the forefront of research, with an array of exciting new products and technologies. This report will conclude with a look into the future of vaccine technology.

1.1.1. Ancient

The earliest understanding of immunity to a disease that had already infected an individual came to us through the Greek historian Thucydides, who observed in 500 BC that individuals who had already had the plague and recovered from it were now immune to a subsequent exposure. However these ancient physicians were unable to connect the dots and never proposed the exposure of a person at risk to infected material from a disease victim until variolation probably started in the
Adjuvants can elicit severe side effects and for this reason the regulatory bar is extremely high. This may explain why there is not more investigation going on in this lucrative area. Petrosky et al recommended the avoidance of adjuvants that work through toll-like receptors as these can produce unacceptable side effects. According to these authors, there is an urgent need for a wider range of products which can only be addressed by national and international funding agencies.

### 2.5. Nanoparticle-Based Vaccines

Nanoparticles are artificially or naturally occurring entities in the size range of 1-100 nm (Figure 2.5). Because of their size they have the potential to enter easily into cells and serve as transfer vessels for a variety of materials. Gathered under this tent are virus-like particles, liposomes, polymeric nanoparticles, and non-degradable nanospheres. They can act as adjuvants, carrying antigens into antigen-presenting cells and other cell types. Because the uptake of antigen by dendritic cells is typically so meager, nanoparticles have been explored as a method for driving cell uptake, thereby expediting induction of an immune response.

Nanoparticles can be modified by the addition of ligands, thus allowing them to target specific cell types. These include peptides, antibodies, proteins, polysaccharides, glycolipids, glycoproteins and lectins. The binding to the cell receptors may also induce dendritic cell maturation. Other molecules such as lipopolysaccharides and pathogen-derived lipopeptides interact with immune cell-surface receptors. This brings on the production of type 1 IFN and proinflammatory cytokines, as well as the surface expression of co-stimulatory molecules.

Novavax (see below) is one of the leading companies in the development of nanoparticle-based vaccines.

### 2.6. DNA Vaccines

DNA-based immunization has been around for about two decades, growing from observations that injection of plasmids containing specific DNA sequences for the Influenza A nucleoprotein generated a protective nucleoprotein cytotoxic T lymphocyte response. The plasmids are easy and cheap to synthesize and they are quite stable, so they would be a good choice for treating diseases in third world countries. Because DNA is much easier to manipulate than proteins, it would be a viable option choice for treatment of rapidly emerging diseases, and diseases that are rapidly
Figure 6.2: Development of Anti-cancer Vaccine Products and the Regulatory Guidance Throughout the Process

- **Pre-clinical and Phase I study**
  - Determine the pre- and clinical significance of the immune response against the tumor (using literature, previous models and own experimental studies)
  - Determine clinically feasible ways of assessing the immune response to tumor and propose the strategy for implementing validated immunological assays throughout the whole global clinical program or in a representative subset of patients
  - Develop methods to stimulate the antitumor immune response as a strategy for immunotherapy and link it with selected immune read-out

- **Global Phase III program**
  - Design well-powered observational studies to assess the prognostic role of immune response, controlling for various clinical, pathological and molecular parameters
  - Design clinical trials to assess the efficacy of immunotherapy as well as the predictive role of immune cell evaluation
  - Evaluate clinical utility of selected biomarker

- **Development of companion diagnostic test**
  - Regulatory approval of the product and companion diagnostic
  - Qualification of biomarker

- **Approval of the product with payers**
  - Implement immune response evaluation in routine clinical practice
  - Perform cost analysis for various clinical management schemes
  - Monitor efficacy of immunotherapies in both oncology and pathology practices. Risk minimisation in by excluding biomarker-negative population and enhance clinical benefits and outcomes. Monitor assay use penetration and maintain education amongst oncologists on appropriate use of biomarker

- **Life cycle management and development of additional indications**
  - Perform cost analysis for various clinical management schemes