

21st century VACCINES *a development renaissance*

Human beings have benefited from vaccines for more than two centuries. From eradicating some of the deadliest diseases to nearly eliminating a host of others, including polio, measles, mumps and tetanus – vaccines are one of the world's greatest lifesavers. Vaccines represent the single greatest promise of biomedicine: disease prevention, and among all interventions in medical care, vaccines have had by far the greatest impact on population health¹. In fact, only sanitation and hygiene rank above vaccines as successful means of health improvement. However, the path that led to today's vaccines has been neither direct nor without controversy. With its origins in the late 18th century, vaccinology experienced unabated advances well into the mid-20th century. By the late 1960s there was a significant decline in innovation – and nearly 30 years passed before that trend was reversed. In this article we explore key factors that lead to that 30-year hiatus, and illustrate the remarkable dynamics that are rapidly reversing that stagnation.

Edward Jenner, a 19th century physician from the English countryside, is considered the 'Father of Vaccines', and first suggested the prevention of smallpox by a procedure known as 'vaccination'. Jenner was treating milkmaids for cowpox, a mild infection they received from their cows, when he noticed that these milkmaids were resistant to the deadly smallpox virus. He reasoned that this relatively mild cowpox infection provided immunity to smallpox in milkmaids, and thus, vaccinology was born. At that time, one million people died from smallpox every year in Europe, the majority of which were children. This observation led to the develop-

ment of the first vaccine that less than a century later would completely eradicate the disease.

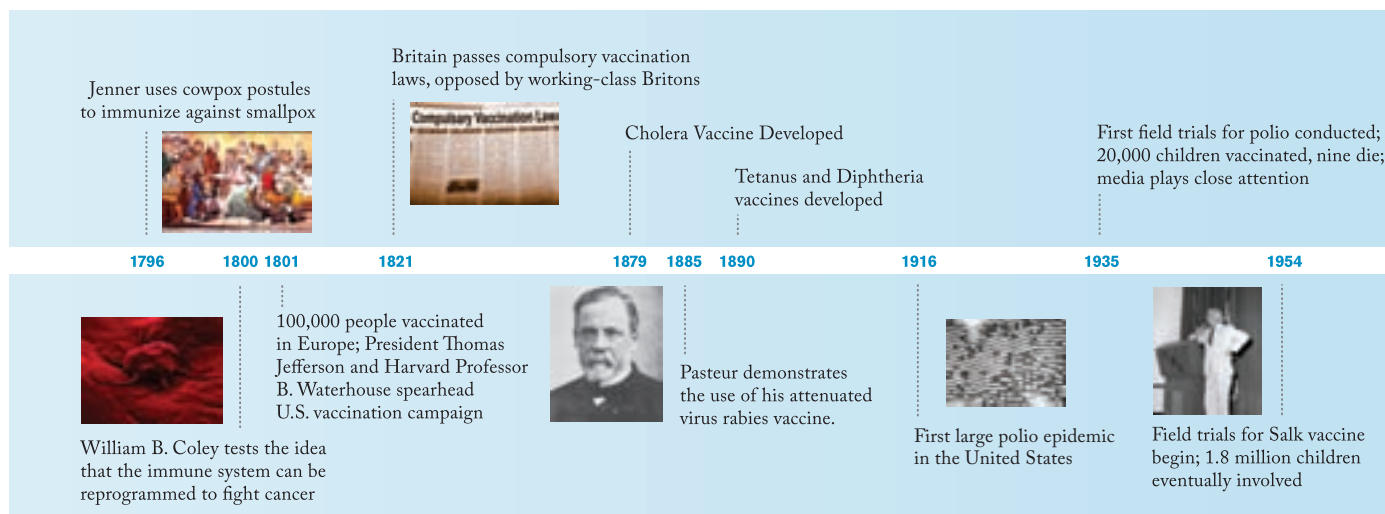
During the 19th century, Jenner became a celebrated figure across Europe. Kings and presidents would seize upon mass-scale vaccination campaigns in an effort to demonstrate their contemporary stance toward science and their commitment to the health of their citizens. By the turn of the 19th century, 100,000 people had been vaccinated in Europe, and vaccination had begun in the United States, spearheaded by Harvard professor Benjamin Waterhouse and President Thomas Jefferson². However, after this initial support for

**By Dr Jeff Stoddard,
Charles Drucker and
Dr Nigel Brown**

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Vaccine Development History

Some of the most significant social, economic, technological and political vaccine development milestones from 1796 – 2007.



vaccination (which resulted in a marked decline of smallpox in the United States), an anti-vaccination movement soon emerged³. Many working-class Britons, for example, viewed compulsory vaccination laws, passed in 1821, as a direct government assault on their communities by the ruling class⁴.

By the turn of the 20th century, the anti-vaccination movement had subsided and the vaccine market entered a Golden Age of innovation. During this time, scientists such as Jonas Salk, Albert Sabin and others developed inoculations for polio, flu, mumps and measles. Vaccinations were widely accepted by the public, as a new spirit of compliance emerged, partly the result of militarisation and a heightened public trust in medicine, especially among the Baby Boom generation. Before mass media, it was hard to shake the controversy surrounding vaccines that began in the 19th century when compulsory vaccination laws were thought to be an invasion of personal privacy. The military, it appeared, was the one institution that could coerce society into believing that vaccines were beneficial – immunisation of soldiers was a necessity for any nation that wished to protect its fighting force and its population. Indeed, the US defence establishment was the innovator of inactivated influenza vaccine and helped to instill – through mandates and coercion – broad and deep acceptance of vaccines as a public good.

Despite the significant progress made during the Golden Age of innovation, from 1949-1960 development slowed and only a handful of vaccines were developed for more than 30 years, beginning

in the late 1960s. Due in part to price commoditisation, narrow profit margins, reduced research funding and the high cost of production facilities, more than 90% of all vaccine manufacturers dropped out of the market by the late 1970s. Vaccine risks – always a part of the landscape for vaccines – became relatively more visible as the very diseases the vaccines prevented declined in incidence. In 1967, there were 26 companies making vaccines in the United States⁵. By the early 1970s, public perception problems increased as many parents came to believe that childhood vaccines were unnecessary and dangerous, attributing them to brain damage and chronic illness. Adverse reactions experienced by small numbers of patients became progressively less acceptable, notwithstanding the substantial, albeit invisible, benefits conferred by mass vaccination. By 2006, only five major firms remained in the market including Merck, sanofi-aventis, GlaxoSmithKline, Wyeth and Novartis.

21st century vaccine development renaissance

By the turn of the 21st century a combination of technological, economic, social and political forces would come together to give rise to a vaccine development renaissance. Prevnar, a vaccine used to prevent invasive pneumococcal infection gained marketing approval in the United States in 2000, and soon began generating more than \$1 billion in annual sales. Prevnar demonstrated that there could be significant profit in vaccine development.

Sabin vaccine licensed (through 1962); Kennedy makes vaccinations a key issue of his administration



1961 1962 1967

90%

More than 90% of vaccine manufacturers drop out of the marketplace in the late 1970's

1974 1977-1979

Prevnar becomes the first vaccine to generate more than \$1 billion in sales



2000 2002 2003

5

Number of major U.S. firms in vaccine market

Three new vaccines launched – Gardasil, RotaTeq, Zostavax – the most ever recorded in a single year



2006 2007

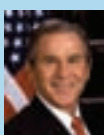


Oral polio vaccine developed

26

Number of vaccine manufacturers in the U.S

MMR vaccine causes controversy in U.K. - linked to autism in children - vaccination rates decline



President George W. Bush receives smallpox vaccination as part of public health campaign

BILL & MELINDA GATES foundation

Bill & Melinda Gates launch Grand Challenges in Global Health Initiative, focusing on the creation and improvement of vaccines



Merck records revenue of \$2 billion in the first half of 2007 from vaccine sales

By 2006, the launch of three new vaccines – a vaccine for the human papillomavirus, one for rotavirus and another that prevents shingles in the elderly – were the most vaccine launches ever recorded in a single year, and became the shot in the arm that caught the attention of the industry as a whole. These new vaccines brought with them significantly higher profit margins, new optimism and increased investment.

This new potential for increased profit motivated some of the largest pharmaceutical companies to re-enter the field of vaccinology through organic growth or high-priced acquisitions. Pfizer, which left the vaccine market in the 1970s, acquired PowderMed in 2006, attracted to its novel method for administering vaccines without the use of a needle. In addition, Novartis paid \$5.7 billion to finalise its acquisition of Chiron in 2006, and AstraZeneca bought MedImmune for \$15.2 billion in May 2007.

Technological influences

According to market research firm Wood Mackenzie, the global vaccines market generated sales of \$13.5 billion in 2006, and could nearly double in size over the next six years, reaching \$24.8 billion by 2013⁶. Much of this success is due to technological, manufacturing and scientific advances, including genomics and proteomics. The mapping of the human genome increased the number of targets available to vaccine developers and led directly to the development of Novartis' meningitis-B vaccine⁷. The remarkable speed with which biologists could

read the entire genomes of microbes has given vaccine makers a wealth of new information about pathogens and a host of new molecules around which to design vaccines⁸. Some experts believe this new information may also open the door to vaccines for extremely complex viruses such as HIV, and for non-viral afflictions like allergies.

From prophylactic to therapeutic vaccines, the new technologies of reverse vaccinology, genomics and proteomics have significantly advanced vaccine development. These new technologies have the potential to improve the process of vaccine development through genome sequencing that can identify genetic patterns related to the virulence of a disease, as well as genetic factors that contribute to immunity or a successful vaccine response. Molecular biology, genomics and proteomics reveal a great deal about antigens and can foster the development of vaccines through cellular and molecular manipulation rather than extensive *in vivo* experimentation or other traditional research approaches.

Cancer vaccines, which are being used to prolong and dramatically improve the quality of life in oncology patients, have benefited greatly from recent technological advances. The idea that the immune system could be reprogrammed to fight cancer was first tested in the late 1800s by Dr William B. Coley, a New York surgeon, who infected patients with a vaccine made from benign bacteria in an attempt to set off an anti-tumour response. Some patients experienced complete remissions, but the results were too inconsistent to gain traction.

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Some oncologists now believe that vaccines will work best at stopping cancer recurrences after initial surgery by preventing metastases, a common cause of mortality⁹. Oncophage, a cancer vaccine developed by Antigenics Inc, was found to produce a strong immune reaction in glioblastoma patients, prolonging life by three months on average. Similarly, Cell Genesys Inc reported that patients taking its prostate cancer vaccine, GVAX, lived a median of 35 months after treatment, compared with 19 months on standard therapy.

Improved manufacturing techniques and invention of new adjuvants have greatly advanced the development of influenza vaccines, the fastest growing segment in the adult vaccine area, which is expected to generate \$4 billion in sales by 2012. Influenza vaccines were traditionally manufactured in a lengthy process that involved inactivation of viruses grown in embryonated chicken eggs, but newer technologies now increasingly rely on 'recombinant' approaches using reverse genetics. In 2007, Novartis announced plans to invest up to \$2 billion over a five-year period to turn its vaccines business into one of the world's top three operators. At the heart of this plan was a strategic partnership between Novartis and Intercell, a biotechnology company that focuses on vaccine design and innovation, making possible an improved influenza vaccine through Intercell's adjuvant IC31[®] technology by reducing antigen content in the vaccine or antigen sparing. The new technology is currently being used to grow the influenza virus in animal cells (for example, Madin-Darby Canine Kidney (MDCK) cells) rather than chicken eggs. In June 2007, Novartis received European approval for its flu vaccine Optaflu[®], which claims to be the first vaccine that uses the company's proprietary cell culture technology.

Economic influences

Issues of funding have been central to the steady development, distribution and uptake of vaccines. However, as vaccines became more commonplace, they have lost some of their allure, particularly to public funding agencies, partly because the diseases they prevent are no longer visible threats. Initially considered a matter of national pride and prestige, vaccines soon became integral to utilitarian and public health notions of societal security, productivity and protection. The scientific success of vaccines has paradoxically contributed to many of the current problems related to adequate funding mechanisms; ironically, they have become victims of their own success.

In the 20th century, vaccine production migrated away from governmental entities and into commercial hands, resulting in the positive benefits of competition, superior production and lower cost¹⁰. Unfortunately, this was not constant, and soon the lack of potential profits and increased regulatory pressures prevented many drug companies from developing vaccines to treat the diseases that most demanded vaccinations. In 1998, Warner Lambert (now part of Pfizer) stopped making Fluogen vaccine for influenza because of regulatory obstacles and financial losses. Fluogen soon sold its factory to King Pharmaceuticals which exited the market after realising that bringing its new plant into federal compliance was too costly. Clearly, this pattern greatly contributed to the United States vaccine shortage in the fall of 2004¹¹. Five companies currently control 80% of vaccine productions, but just one company manufactures the 10 basic childhood vaccines, including measles-mumps-rubella (MMR) and chickenpox vaccines¹². To avoid a potential childhood vaccine shortage, the US National Vaccine Advisory Board listed an increase in funds for vaccine stockpiles at the top of its list of recommendations back in 2003¹³.

Increased government funding, financial incentives, and greater potential for higher profits has reignited vaccine development innovation. The high-profile successes of Gardasil and Prevnar demonstrated that vaccines can generate significant returns as compared to vaccine profitability just five years ago. Merck, in the first six months of 2007 recorded revenue of nearly \$2 billion from vaccine products alone, more than the company's vaccine sales for all of 2006. These sales account for three new vaccines that were approved; Gardasil, a breakthrough preventative treatment for cervical cancer, a vaccine against rotavirus and another for shingles. Intracel's OncoVAX, used to prevent recurrence in colon cancer patients following surgical tumour resection is expected to generate approximately \$1.2 billion by 2012. Claimed by some to become the most lucrative vaccine ever developed, GlaxoSmithKline's inoculation against the human papillomavirus (HPV), Cervarix, was submitted for FDA approval in March 2007. Some analysts estimate that Cervarix will generate \$2.4 billion in sales by 2012¹⁴.

Social Influences

Today, controversy continues around the vaccine against the human papillomavirus, or HPV; an oncogenic virus that is spread through sexual intercourse. As such, mandated vaccination against such a pathogen is actively opposed by

some social groups. While opposition to vaccines may never cease to exist, most anti-vaccinationists in rich nations do not realise how difficult it is to survive childhood in many parts of the world due to inadequate funding of vaccine programmes and subsequent vaccine shortages. About 1.4 million children die every year from diseases that existing vaccines can prevent, and another 1.1 million die from diseases for which we will soon have vaccines¹⁵. In the 1970s and 1980s, the world made dramatic progress in expanding access to basic vaccines, due to the leadership of the World Health Organization and UNICEF, but unfortunately, this progress slowed substantially in the 1990s.

In November 1998, American philanthropists Bill and Melinda Gates challenged a dozen leading scientists to develop a breakthrough solution that would overcome the barriers that prevented nearly 30 million children from receiving basic vaccines every year. This challenge resulted in the blueprint for the Global Alliance for Vaccines and Immunizations (GAVI), and the seeds of an idea for a sister entity that would raise money to support GAVI's work. The goal was to radically improve access to established and underused vaccines and to accelerate the development and introduction of new ones.

The result of this effort includes various research grants available through the Bill & Melinda Gates Foundation as part of the Grand Challenges in Global Health initiative, which grants funds for research in 14 different categories, some of which are dedicated to improving childhood vaccines and creating new vaccines. The goals for improving childhood vaccines include the development of single-dose vaccines that can be used soon after birth, preparing vaccines that do not require refrigeration, vaccines that induce faster immune responses, developing needle-free delivery systems for vaccines, and the development of multivalent vaccines. In terms of creating new vaccines, the foundation is looking for the creation of reliable biomarker tests in model systems to evaluate live attenuated vaccines; ways to design antigens for safe, effective and immunogenic vaccines; and learning which immunological responses provide protective immunity.

Political influences

Politics and war have historically had an impact on vaccine acceptance. In 1961, President John F. Kennedy made vaccinations a key issue of his administration, and his interest in the immunisation programme established a pattern so that every

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time a Democratic administration took office over the next 32 years, public sector support for vaccination got a boost.

The influences of war, or in the example that follows terrorism, can be seen by examining the changes to vaccine development following the attacks of September 11, 2001. In December 2002, President George W. Bush received a smallpox vaccination as part of a public health campaign to immunise 10 million police and health workers against the disease by the fall of 2003, preparing the nation for a terrorist germ warfare attack. History has shown that fear motivates increases in vaccination of a population. With political influence, the CDC recommended the vaccination of 500,000 hospital workers, police officers, and firefighters in the first month of 2003, and 10 million others by the end of summer. Despite CDC and presidential encouragement, the smallpox vaccination campaign lost momentum less than a year after its start, due largely to safety concerns about smallpox vaccine. However, since the 9/11 attacks, the US federal government has dramatically increased funding for biodefence in large part via Project Bioshield, signed into law in 2004, which set aside \$5.6 billion over a period of 10 years for the purchase of next generation countermeasures against anthrax and smallpox as well as other CBRN agents.

Conclusion

As this article has illustrated, vaccine innovation has been at the mercy of a myriad of sociological, economic, political and technological factors, many of which have shown cyclical trends over the last two centuries. Just as history illustrates the causes underlying the decline in vaccine innovation in the latter part of the 20th century, it also affords insight into the factors that will need to be carefully tended as we enter this 21st century vaccine development renaissance. Indeed, the promise of this new era is as great as those early achievements in vaccine technology. But as governments, charities and biopharmaceutical companies expand investment into this sector, contract research organisations (who support these organisations) must ready themselves for increased call on their expert staff, integrated service capabilities and operational capacity. Failure to anticipate and adequately invest in the requisite skills and technologies to support this renaissance will leave this important market segment under-served, and delay the delivery of important healthcare innovations. **DDW**

Dr Jeffrey Stoddard is Vice-President of Medical and Scientific Affairs at Covance, Inc and provides medical and scientific leadership to post-approval research and risk management programmes at Covance. Dr Stoddard has more than 16 years of industry experience, which includes work with influenza vaccine research programmes (Phase II-IV), including immunogenicity studies, effectiveness studies, community intervention trials, and indirect protection ('herd immunity') studies.

Charles Drucker, MBA, is Director of Strategic Initiatives for Covance Inc. He has worked for life sciences companies including Pharmacia Biotech, Amersham Biosciences, AAI Pharma and Covance. His experience includes developing, launching and selling products and services aimed at improving vaccine and biologics. Currently he is leading a Covance initiative to develop integrated solutions for vaccine development.

Dr Nigel Brown is Corporate Vice-President of Business Development and Strategy at Covance Inc, the world's largest publicly-traded Contract Research Organisation (CRO). Dr Brown joined the CRO industry in 1997, having spent the first half of his career with heritage Pfizer and GlaxoSmithKline companies. He heads-up Covance's M&A and strategic planning activities, and is an executive sponsor for Covance's expansion in the vaccine field.