



Caring Begins with Prevention

Our Company, Our Mission, Our Heritage

The only thing better than finding a cure for a disease is preventing illness in the first place. Novartis Vaccines—the world’s fifth largest manufacturer of vaccines and the second largest producer of influenza vaccine—is committed to the fulfillment of this highest of medical ideals. By our very function, we play a key role in the Novartis core mission: keeping healthy people healthy by alleviating suffering and enhancing quality of life. At Novartis Vaccines, *caring begins with prevention.*



Vaccines protect not only the people who have received the immunization, but others as well.



Nothing prevents viral or bacterial infections quite as well as a vaccine, which trains the human immune system to attack invading microbes before they can establish themselves in the body and cause diseases that can lead to death or a lifetime of disability. Vaccines can be composed of dead or inactivated pathogens, but are increasingly made from purified antigens—proteins or other biomolecules found on the pathogen being targeted. Once the immune system is exposed to these antigens, it learns to recognize and attack the pathogen that bears them before the infectious agent has a chance to cause disease. But the protective power of a vaccine can reach beyond those who have received it. Vaccinating even one person in a community against an infectious disease can impede the transmission of that disease to other people. In this way, vaccines protect not only the people who have received the immunization, but others as well.

This is one of the reasons the World Health Organization (WHO) considers vaccines the most cost-effective healthcare intervention available today¹; the only measure



“If you work on vaccines, you have the opportunity to develop products that can protect the majority of people against important infectious diseases. You can really make a difference. And, for me, that’s what it’s all about.”

– Derek O’Hagan, Head of Vaccine Delivery Research, Novartis Vaccines

that has done more to improve global health in the past century is access to clean drinking water.² In the US, according to a recent study by the Centers for Disease Control and Prevention (CDC), a dozen often deadly diseases targeted by childhood vaccinations—from polio to diphtheria—have been either eliminated or have declined in incidence by more than 90 percent over the past century.³ The WHO estimates that vaccines saved the lives of more than two million people in 2003 alone by preventing the onset of a host of preventable diseases.⁴

While vaccines have eradicated devastating diseases such as smallpox, the battle against infectious disease is far from over. Novartis continues to strive to develop and deliver innovative vaccines against pathogens that have long proved intractable, as well as those that are only now emerging as threats to global health; one such threat is the H5N1 avian influenza virus, thought most likely to cause the next influenza pandemic.

¹ WHO Fact Sheet. No 288. <http://www.who.int/mediacentre/events/2006/g8summit/vaccines/en>

² http://www.cdc.gov/ncidod/dpd/healthywater/features/drinking_water_week_07.htm

³ <http://www.cdc.gov/od/oc/media/pressrel/r990923.htm>

⁴ <http://www.who.int/mediacentre/news/releases/2005/pr48/en/index.html>

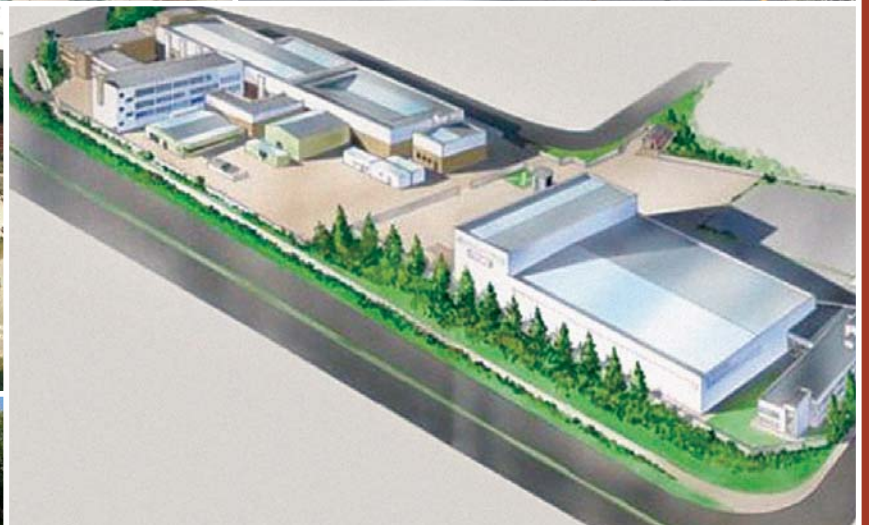
A History of Firsts

- 1890 Emil von Behring discovers diphtheria and tetanus antitoxins
- 1895 Achille Sclavo develops a serum against anthrax
- 1970 Sclavo Institute begins collaborating with the WHO on supply of smallpox vaccine
- 1984 RABIPUR® PCEC rabies vaccine, the world's first second generation cell culture vaccine against rabies
- 1989 First recombinant bacterial vaccine against pertussis
- 1997 FLUAD® adjuvanted influenza vaccine, the world's first influenza vaccine launched with a novel adjuvant (MF59®)
- 2000 First use of genomics to develop new vaccine candidates against meningococcus B
- 2003 Mapping of the SARS virus
- 2004 Novartis scientists develop and manufacture its first MeNZB™ vaccine to combat an epidemic caused by a specific strain of meningococcal B disease that gripped New Zealand for more than a decade
- 2006 Novartis announces plans to build the first US-based cell culture-derived manufacturing facility, pioneering next-generation vaccines manufacturing technology
- 2007 Optaflu®, the first cell culture-derived influenza vaccine, is approved by the EMEA
- 2008 Novartis Vaccines Institute for Global Health (NVGH), a not-for-profit foundation dedicated to developing affordable vaccines for neglected infectious diseases in developing countries, opens in Siena, Italy
- 2008 MENVEO® shown in clinical trials to be superior leading quadrivalent meningitis vaccine to protect adults and children as young as two months of age from infection from the meningococcal A, C, W-135 and Y strains
- 2008 First meningitis B vaccine to potentially provide broad coverage against majority of meningococcal B strains enters Phase 3 clinical trials

Our Heritage—A Century of Vaccines Innovation

A solid emphasis on research and a never-ending commitment to preventing disease have been the driving forces at Novartis Vaccines and our heritage companies. Established in April 2006, following the Novartis acquisition of Chiron, our history includes such legends of twentieth-century vaccinology as Emil von Behring, who won the 1901 Nobel Prize for his development of serum therapies against diphtheria and tetanus, and founded the German vaccines firm Behringwerke; and Achille Sclavo, the Italian scientist who developed anthrax serum and established the eponymous vaccine manufacturer that long led the field in Italy. Sclavo amassed a rich inventory of accomplishments in the sphere of global health, not least his participation in the effort to eradicate smallpox.

Today, Novartis Vaccines has a strong global presence, most notably in Europe, with its centers of excellence in Germany, Italy and the UK—where we are among the leading suppliers of several crucial vaccines. In 2007, Novartis won regulatory approval from the European Medicines Agency (EMA) for an influenza vaccine derived from cultured cells instead of chicken eggs. Novartis Vaccines is also expanding in the US, building a large influenza cell culture plant in Holly Springs, North Carolina, and having established its global headquarters and a virology research center in Cambridge, Massachusetts, to mine the high concentration of scientific and industry expertise in the area. The century-old culture of innovation seeded by Sclavo and von Behring infuses everything we do at Novartis Vaccines, as does our mission to alleviate suffering through the prevention of disease.



(Clockwise from top left) Rosia; Siena; Liverpool; Holly Springs; Emeryville; Marburg



Fighting Influenza

Every year, an estimated 3 million to 5 million people worldwide become seriously ill from influenza, and as many as 500,000—primarily children and the elderly—die from the ensuing complications.⁵ The disease, caused by the ever-mutating influenza virus, also takes a severe toll on the global economy. A recent study conducted by researchers at the CDC concluded that, in the US alone, the total economic burden (including direct medical costs, lost wages and impacts on productivity) imposed by such epidemics averages somewhere in the neighborhood of \$87 billion every year.⁶

The best way to cut such losses is to ensure that as many people as possible are vaccinated against influenza every year. In fact, the WHO recommends that anyone considered at high risk for severe illness be vaccinated as soon as the



Novartis is among the world's largest producers of influenza vaccines.

inoculation is available.⁷ This includes young children and people who are more susceptible to developing influenza complications because of underlying disease or old age.

Several governments support annual influenza-vaccination campaigns and, given the toll influenza takes on productivity, corporations too are increasingly joining the battle. Novartis Vaccines is a major player in every one of these efforts. Novartis is among the world's largest producers of influenza vaccines, and a major supplier to the UK, Italy, Germany and the US. Influenza vaccines in the Novartis portfolio are tailored to the needs of particular populations.

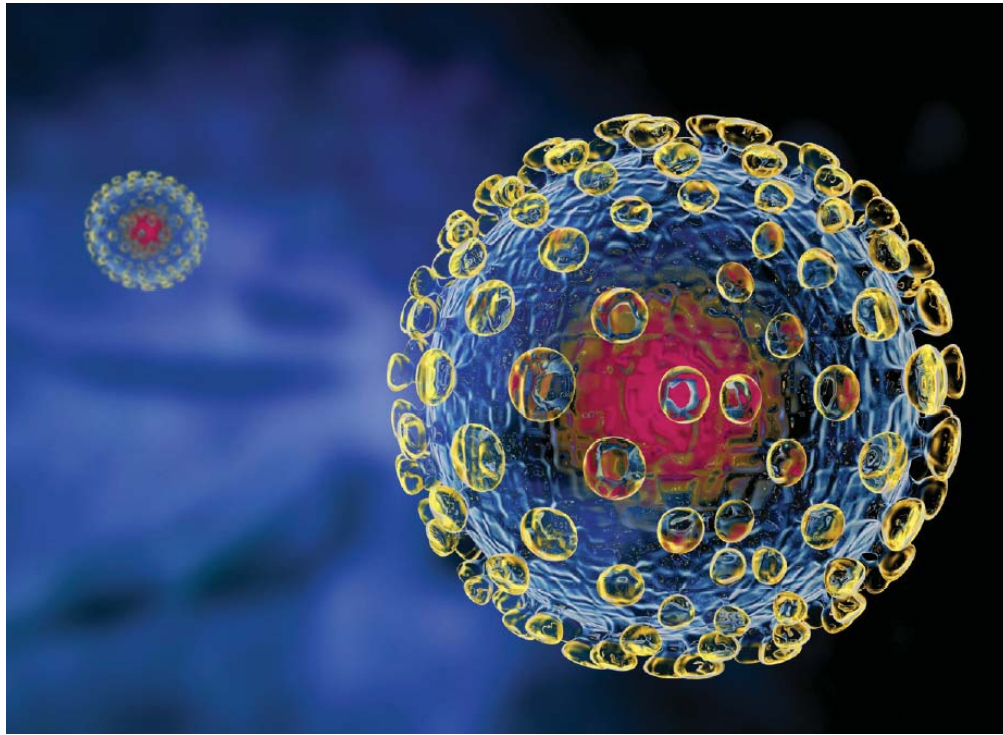
“Influenza, particularly in our population, can be devastating. The elderly often have underlying chronic diseases, making them much more susceptible to influenza and to much worse cases of it as well.”

– Roseanne Searles, Director of Nursing Services, DeWitt Rehabilitation Nursing Center, New York City

⁵ WHO Fact Sheet No. 211. March 2003.

⁶ Molinari, A., et al. *Vaccine*. 28 June 2007; 25 (27): 5086-5096

⁷ WHO Weekly Epidemiological record 2002; 77 (28): 229-240



Viral flu (Influenza)

Adjuvants are used to boost a vaccine's effectiveness by increasing the body's immune response.

Boosting the Shot

Novartis was the first vaccines company to enhance the efficacy of an influenza vaccine through the use of an adjuvant. Adjuvants are used to boost a vaccine's effectiveness by increasing the body's immune response. This adjuvant effect is particularly important in elderly subjects and those already suffering from chronic illness. Both groups run a high risk of developing the most severe influenza-related complications. More than 90 percent of influenza-related deaths occur in people aged 65 and older.⁸ Influenza vaccines, however, have shown to significantly protect the elderly population against severe complications, including hospitalizations and death. The Novartis FLUAD[®] vaccine is adjuvanted with MF59[®], which has been proven to provide superior antibody response, as compared to conventional vaccines, by offering varying degrees of cross-protection.^{9,10,11,12} The MF59[®] adjuvant has shown to augment the antibody response to the influenza vaccine and to circulating influenza strains that were not included in the vaccine (drifted strains). No other adjuvanted influenza vaccine is currently available. Prior to MF59[®], the only other adjuvant approved for use in vaccines was alum (salts of aluminum). While dozens of promising new adjuvants have been tested since aluminum salts were first used in vaccines seven decades ago, the only one that has proved both safe and effective is the Novartis adjuvant MF59[®].

⁸ CDC, <http://www.cdc.gov/mmwr/PDF/rr/rr5103.PDF>

⁹ Flud Fact Sheet

¹⁰ Stephenson, I., et al. *The Journal of Infectious Diseases* 2005; 191 (8): 1210-5

¹¹ Nicholson, K., et al. *Lancet* 2001; 358:1937-1943

¹² Stephenson, I., et al. *Vaccine* 2003; 21:1687-1693.f



Innovating Vaccine Manufacturing

Novartis is revolutionizing the way influenza vaccines are made through a next-generation vaccines technology known as cell culture-derived production. This innovative production method has the potential to bring greater reliability and flexibility to the manufacturing process to enhance our ability to meet the growing need for seasonal influenza vaccines and to quickly respond to a potential pandemic influenza threat.

This new technology offers many advantages over the traditional methods of production, in which the influenza virus is grown in eggs to mass-produce the three antigens used to make the vaccine. It is devoid of the antibiotics used to keep egg-based influenza vaccines free of bacterial infection, as well as the egg proteins that can cause allergic reactions in some people. Further, while every egg used to grow the influenza virus must be handled individually and manually, the cell culture-derived vaccine is produced in a contained, automated and highly standardized system¹³; this system ensures greater consistency and reliability of the product.

Beyond that, while vaccines manufacturers today need lead time of up to a year to order and organize the egg supply required to make seasonal influenza vaccine, starting up the cell culture-derived system simply involves thawing a vial of cells stored in liquid nitrogen and seeding an eminently expandable cell culture. Thus, it would be far easier using the cell culture to scale up vaccine production to meet

¹³<http://focosi.altervista.org/preventionprimaryimmunovaccine.html>



“Currently influenza vaccines are produced using eggs, which means for production of these vaccines, you need millions and millions of eggs. Novartis is now introducing a new cell culture-derived production process where the eggs are replaced by cell culture. This provides us with more flexibility, a more reliable process and also many advantages in case of a pandemic.”

- Ulrich Valley, Site Head of Novartis Vaccines Cell Culture Manufacturing Facility (currently under construction), Holly Springs, North Carolina

sudden surges in demand. These surges could occur should the circulating influenza strain not match the strain originally produced for the season or, in a worst case scenario, in the event of an influenza pandemic.

Novartis made this technology a reality in Germany when it became the first vaccines company to launch a cell culture-derived influenza vaccine. Optaflu®, the Novartis subunit cell culture influenza vaccine, is currently being manufactured in Marburg, Germany, at our first commercial-scale cell culture-derived vaccine facility.

Novartis is also constructing a cell culture vaccine-manufacturing site in Holly Springs, North Carolina. When licensed by the Food and Drug Administration (FDA) and fully operational, it will have the capacity to produce up to 50 million doses of seasonal influenza vaccine. It will also be capable of churning out, within just six months, up to 150 million doses of vaccine against a potential pandemic influenza strain. The cell culture-derived system is particularly attractive for this purpose because the avian influenza virus is currently considered the most likely source of the next pandemic—and is lethal to both chickens and their eggs. Without eggs, traditional influenza manufacturing techniques cannot produce vaccines.

Production in the Novartis cell culture-derived vaccine system is independent of the availability of eggs. So any vaccine produced using cell culture would have greater fidelity to the virus causing the pandemic and would, in theory, be more effective.



Facility for vaccine production.



Preparing for a Pandemic

There's ample reason to worry about avian influenza. The Spanish influenza pandemic of 1918 traversed the globe within four months and took more lives—well over 50 million¹⁴—than did the First World War. The world is a much smaller place now, with 500 million people traveling internationally every year, and a population six times larger and considerably more economically interlinked than it was then. A virulent strain of influenza could cross the globe today in the epidemiological blink of an eye. Many experts now believe that the source of the next global pandemic may be found in the form of the virulent H5N1 avian influenza virus. This threat, combined with the speed and ease of travel today, creates serious implications for pandemic preparation. Since current vaccine production cannot respond quickly enough to deal with condensed time frames, the ideal preparedness approach is to ensure that everyone is adequately protected in advance of the emergence of the pandemic. Unfortunately, that is impossible because we cannot predict the exact next pandemic virus; an alternative is to provide a vaccine that protects the immune system against a potential pandemic virus.

“At Cisco Systems, we are taking the threat of a pandemic very seriously because we do run much of the infrastructure for the Internet. We want to make sure that our employees are available and healthy in case of a pandemic. For that reason, we have a business continuity plan which includes a pandemic preparedness program.”

– Dr. Pamela Hymel, Global Medical Director, Cisco Systems

¹⁴<http://www.pandemicflu.gov/general/historicaloverview.html>



“I understand that any one destination is potentially only 36 hours away from another. Someone who becomes ill in Southeast Asia can easily be at my front door in New York City a day and a half later, ill and potentially spreading disease.”

– Dr. Louis Morledge, Internist
(specializing in travel medicine),
New York City

When the first signs of avian flu appeared in Hong Kong back in 1997, a team led by vaccines vanguard Rino Rappuoli from the Novartis Global Research Center in Siena immediately began developing a vaccine against the H5N1 virus. Two years later, Chiron launched a clinical trial in the UK. Initially, the test was conducted without the use of the new MF59[®] adjuvant. It was soon discovered that the vaccine was ineffective without the adjuvant, but with it only half the dose of the antigen was required. This discovery was demonstrated by a study published in the journal *Lancet* in 2001¹⁵, which showed that Novartis MF59[®]-adjuvanted vaccines require twelve times less antigen to induce antibodies against the H5N1 virus than vaccines lacking the Novartis adjuvant. MF59[®] could go a long way toward easing the expected burden on manufacturing capacity when a pandemic strikes, ensuring that there is enough vaccine to go around.

Novartis is committed to the development and supply of vaccines to protect against the potentially devastating consequences of a pandemic influenza outbreak. Since the exact influenza strain causing disease will only be known once the pandemic starts, any such vaccine would best be devised to provide the broadest protection possible against viral strains thought most likely to seed a pandemic. A study published in *The Journal of Infectious Diseases* suggests that MF59[®] makes vaccines against one strain of H5 avian influenza more reactive against genetic variants of that strain.¹⁶ In other words, it potentially offers broader protection against the avian influenza. Novartis is actively working to develop both a pandemic vaccine, which can be tailored to a specific strain of the virus, as well as a pre-pandemic vaccine, which can provide broader protection against multiple pandemic strains.

With the threat of a global influenza pandemic pending, Novartis Vaccines' top priority is to ensure a supply of much-needed safe and effective vaccines.



¹⁵Nicholson, K., et al. *Lancet* 2001; 357:1937-1943.

¹⁶Stephenson, I., et al. *The Journal of Infectious Diseases* 2005; 191 (8):1210-5.

Mastering Meningococcal Disease

An estimated 500,000 cases of meningococcal disease arise every year around the world, leading to some 50,000 premature deaths.¹⁷ The illness is caused by *Neisseria meningitidis*—an ordinarily harmless denizen of many a nasal passage that, for reasons not entirely clear to scientists, sometimes enters the bloodstream, proliferates wildly and turns into one of the deadliest foes of the human body. Symptoms of the disease include high fever, confusion, vomiting and pain with exposure to bright lights. With breathtaking speed, runaway meningococcal infection can lead to sepsis, organ damage, and a severe inflammation of the membranes that surrounds the brain. As many as 10 to 15 percent of those who survive meningococcal infection emerge from their battle with the bacterium with amputated limbs, brain damage or any of a host of other scars and disabilities.¹⁸ It is, by any measure, a devastating disease.

The Story of Morgan Leyland

One Wednesday morning in 2002, Robert Leyland, a heat engineer from Bolton Manchester, UK, set out like countless other working parents to drop off his daughter, pretty three-year-old Morgan, at her nursery. “The only thing wrong with her,” he recalls, “was a runny nose, which all kids get.” That runny nose, it turned out, was harbinger of the worst day of Leyland’s life. Morgan grew progressively sicker over the course of the day. But a doctor who saw her in the evening dismissed the possibility that Morgan might have bacterial meningitis, despite Leyland’s suspicions. By the middle of that night Morgan was on a trolley in the intensive care unit of a children’s hospital, hooked up to a thicket of tubes and surrounded by a swarm of worried emergency room staff. The physicians told Leyland that sedating Morgan might help her battle her illness better. “So as they sedate her,” recalls Leyland, “my wife is talking to her, and she said, ‘I love you all the world, mommy’.” Those were Morgan’s last words. The girl who had just a runny nose that morning fell asleep, suffered three heart attacks, and was dead by the middle of the night. “One day I’m taking her to the nursery,” says Leyland, “and the next morning I’m picking her up, wrapped in a blanket, from the morgue. That’s how quick the disease moves.”



Robert Leyland, father of Morgan Leyland

¹⁷ WHO Weekly Epidemiological Record. Meningococcal Vaccines: Polysaccharide and Polysaccharide Conjugate Vaccines. 40 (77); 329-340: 2002.

¹⁸ WHO Fact Sheet No 141. May 2003



“Meningitis is probably the only infectious disease that we have in the UK in which, within hours of the onset of symptoms, a previously perfectly fit, healthy child could be dead. It’s that quick.”

– Julia Warren,
Head of Communications for the
Meningitis Research Foundation, UK



Meningococci C

Globally, five subgroups of *N. meningitidis*—A, C, W, Y and B—are responsible for the majority of such infections.¹⁹ This disease can be misdiagnosed in young children because they are often not able to explain what’s happening to them. To make matters worse, since the disease initially induces influenza-like symptoms, it’s often mistaken as a viral illness. Though we have very successful therapies, often treatment comes too late. Clearly, the best thing to do to avert tragedy is to vaccinate children against all groups of *N. meningitidis* that cause meningococcal disease. Indeed, the WHO estimates that a mass vaccination campaign could reduce meningococcal infections by 70 percent.²⁰ A vaccine Novartis developed to help the UK battle meningococcal C disease has contributed to an 87 percent decline in infections caused by that subtype, and has cut the death rate associated with it by 92.5 percent.^{21, 22}

¹⁹ www.who.int/vaccine_research/documents/GVRF04_Report.pdf

²⁰ World Health Organization. Meningococcal meningitis Fact Sheet. May 2003.

Available at: <http://www.who.int/mediacentre/factsheets/fs141/en/>

²¹ <http://www.novartisvaccines.com/products/index.shtml> (Novartis Vaccines website)

²² Balmer, et al. 2002. Impact of meningococcal C conjugate vaccine in the UK. *Journal of Med. Microbiol.* Vol. 51, 717-722.



This disease can be misdiagnosed in young children because they are often not able to explain what's happening to them.

Leading the Charge

Novartis Vaccines' current products to prevent meningococcal disease include Menjugate® meningococcal C conjugate vaccine, which played a key role in reducing the toll of meningococcal C disease in the UK in the past decade, and MeNZB™ meningococcal B vaccine, developed for the specific B strain that caused an epidemic in New Zealand. Novartis Vaccines' development programs target disease caused by the five primary serogroups of meningococcus with a multivalent ACWY meningococcal vaccine candidate and a broad coverage recombinant meningococcal B vaccine candidate. Meningococcal vaccines are typically made from the capsules that encase the *N. meningitidis* bacterium, with complex sugar-chains on their surface serving as antigens for the immune response. The complex sugars on the Men B subtype, however, closely resemble several of those found on the surface of human cells. So any vaccine derived from them would, at best, incite no attack from the immune system, which ignores such molecules to avoid destroying the body it has evolved to protect. This is why the only vaccines against Men B that have proved successful are those that have been tailor-made to attack the proteins, rather than the complex sugars, of specific strains of the Men B subtype.

One such vaccine was devised by Novartis to help New Zealand extinguish an epidemic of meningococcal disease that began in the 1990s. The WHO considers meningococcal meningitis to have reached epidemic proportions when the number



of infections reaches 10 cases per 100,000 people²³; New Zealand was seeing in some areas 2.5 times as many people sick with meningococcal disease at the height of its epidemic. The epidemic itself was unique because it was largely caused by just one strain of the Men B subtype, while many epidemics feature several sub-strains of the predominant subtype. This opened a window to controlling New Zealand's epidemic—a single vaccine, it was clear, would probably suffice. It was equally unusual that a commercial manufacturer had agreed to develop what amounted to an orphan vaccine, one that could only be used on the particular Men B sub-strain endemic to the small population of New Zealand.

The vaccine had to be developed quickly as well; this was, after all, an epidemic. This could only be achieved with an excellent partnership with the public sector. The partnership with New Zealand's Ministry of Health produced a vaccine ready for human use within three years, which was in itself a remarkable accomplishment; most vaccines take north of a decade to make it that far. The vaccine approved by New Zealand's regulators was deployed across New Zealand in a highly effective vaccination campaign that began in 2004. Recent data suggest that beyond ending the epidemic, it has finally brought the incidence of Men B disease back to near-normal levels, at an 80 percent reduction.²⁴

Still, Novartis' contribution to the war on Men B extends well beyond the conquest of a single epidemic. We are also well along the path to developing a universal vaccine against this elusive pathogen, thanks to a novel technology based on genomics that was developed at our research center in Siena in the late 1990s.

²³ Epidemiology of meningococcal meningitis: meningococcal meningitis occurs sporadically in small clusters throughout the world with seasonal variations and accounts for a variable proportion of endemic bacterial meningitis. In temperate regions the number of cases increases in winter and spring. Serogroups B and C together account for a large majority of cases in Europe and the Americas. Several local outbreaks due to *N. meningitidis* serogroup C have been reported in Canada and the US (1992-93) and in Spain (1995-97). For 10 years, the meningococcal meningitis activity has particularly increased in New Zealand, where an average of 500 cases occurs every year. Most of these cases are now due to serogroup B. Major African epidemics are associated with *N. meningitidis* serogroups A and C, and serogroup A is usually the cause of meningococcal disease in Asia. There is increasing evidence of serogroup W135 being associated with outbreaks of considerable size. In 2000 and 2001, several hundred pilgrims attending the Hajj in Saudi Arabia were infected with *N. meningitidis* W135. Then in 2002, W135 emerged in Burkina Faso, striking 13,000 people and killing 1,500. (World Health Organization. Meningococcal meningitis Fact Sheet. May 2003.

Available at: <http://www.who.int/mediacentre/factsheets/fs141/en/>
²⁴ "Novartis MeNZB vaccine campaign data show 80 percent efficacy rate during epidemic meningococcal B disease outbreak in New Zealand" (Press release on NVS website: <http://www.novartisvaccines.com/press-room/news/20060808-MenZB.shtml>)



Revolutionizing Vaccinology

Novartis has pioneered a new strategy for discovering novel vaccines using the power of technology made available by the sequencing of the genome of microbial pathogens. This process, known as reverse vaccinology, is changing how vaccines are designed and developed. The approach essentially turns the traditional method of vaccine discovery on its head, and in the process dramatically accelerates the pace and efficiency of vaccine development.

In the past, in order to design a vaccine one had to study the pathogen in great detail to identify virulence factors that could be used as vaccine candidates. To discover candidate antigens, vaccinologists typically had to first identify antigens unique to the pathogen—or those responsible for causing disease—isolate these molecules, and discover their biological functions. At times, they would even need to find the genes that encode the molecules and clone them to produce proteins. They would then analyze the biochemistry of the complex and often delicate biomolecules they had isolated and elucidate the roles those molecules played in a pathogen's biology. The whole enterprise often took years, if not decades.

The strategy developed by Novartis Vaccines eliminates this delay by exploiting the power of genomics. Instead of focusing on the biology of a pathogen, reverse vaccinology begins with the sequencing of entire genomes and the deployment

Reverse vaccinology is changing how vaccines are designed and developed.



“The easy vaccines have all been made. Now we’re up against the difficult ones. Reverse vaccinology has allowed us to tackle the more difficult problems out there.”

– John Telford, Research Director and Project Leader, Novartis Vaccines

of sophisticated computer algorithms to isolate genes that might encode candidate antigens. This analysis eliminates innocuous proteins, like those involved in common metabolic pathways, and targets those that are either secreted or expressed on the outer surface of the microbe, where they can be “seen” by the immune system. That usually results in the identification of a few hundred genes of interest.

The genes are then rapidly cloned to produce the proteins they encode, and the proteins are in turn screened for their ability to provoke an immune response. This typically results in the isolation of more than a dozen antigens candidate for

Reverse vaccinology should also generate more effective vaccines.

further study and, potentially, vaccine development. While traditional methods of discovery can take close to a decade to find appropriate antigens for a vaccine using reverse vaccinology, that process can be completed in less than a third the time with the new strategy.

Novartis first devised this strategy to find a vaccine against *N. meningitidis* serogroup B. Before Novartis applied itself to the problem, scientists had identified only about a dozen protein antigens on the surface of the Men B subtype, and none of them proved useful for a vaccine. In contrast, within 18 months of beginning a genomic search, Novartis had in hand roughly 90 antigens to assess for a Men B vaccine. While many researchers around the world had been studying meningococcal group B meningitis for more than four decades without having produced an effective vaccine, starting from the genome sequence, Novartis had a candidate in clinical trials within four years. This broad coverage Men B vaccine is currently in late-stage development.

Reverse vaccinology should also generate more effective vaccines. Many proteins on the outer surfaces of pathogens are hypervariable—an adaptation that, like a molecular disguise, allows microbes to escape notice by the immune system. This is, in fact, why it has been so difficult to develop protein-based vaccines against meningococcal pathogens. Genomic analysis can help vaccinologists focus on those antigens that vary the least from strain to strain, and so develop vaccines that target the broadest spectrum of the pathogenic strains.

The technique has indeed proved powerful in the hands of Novartis researchers. It is being used in Novartis labs to explore vaccines against such pathogens as Chlamydia and gonococcus, which causes gonorrhea. Plus a possible vaccine against *H. pylori*, the leading cause of neonatal sepsis and meningitis in industrialized countries, has been prepared using the approach. This vaccine is slated to enter clinical trials in 2008.

Our Products, Our Promise

At Novartis Vaccines, we feel privileged to be working in a field where we can truly make a difference in protecting the lives of so many people from infection and disease. We are keenly aware of the responsibility that comes with this privilege. Every 25 seconds, someone in the world takes a vaccine that has been created by us.²⁵ The 800 million doses of vaccine we produce annually are shipped to 85 countries, where their use helps protect entire societies from some of the most horrible diseases in the world. We give the highest priority to ensuring that our customers—who are, ultimately, our friends and neighbors—are always assured access to the highest-quality vaccines. Our portfolio includes several vaccines devised to protect people who live in or travel to areas where a variety of infectious diseases are common. Diseases prevented by our vaccines include rabies, tick-borne encephalitis (TBE), typhoid, cholera, and hepatitis A.

We also work closely with agencies like UNICEF and the WHO to deliver hundreds of millions of vaccine doses to help protect children from diphtheria, tetanus, pertussis (which causes whooping cough) and polio. We make vaccines against Haemophilus influenzae Type B (Hib), which is one of the leading causes of pediatric meningitis.



And our product Quinvaxem is the first internationally available liquid vaccine that combines five inoculations that are crucial to child health, including diphtheria, tetanus, pertussis, hepatitis B and Hib.

Novartis has also played a key role in the global campaign to eradicate polio. This highly virulent disease of the nervous system, which can cause total paralysis in a matter of hours, kills as many as one in ten of the people who contract it. Of those who survive, one in 200 is left permanently paralyzed.²⁶ Thanks to the global effort to eradicate this disease, the number of polio cases worldwide has declined



“Today the world is facing challenges in terms of global health. There are new diseases that are appearing. There are old diseases that are reemerging and there is a tremendous need of novel vaccines which would be able to prevent the diffusion of these diseases.”

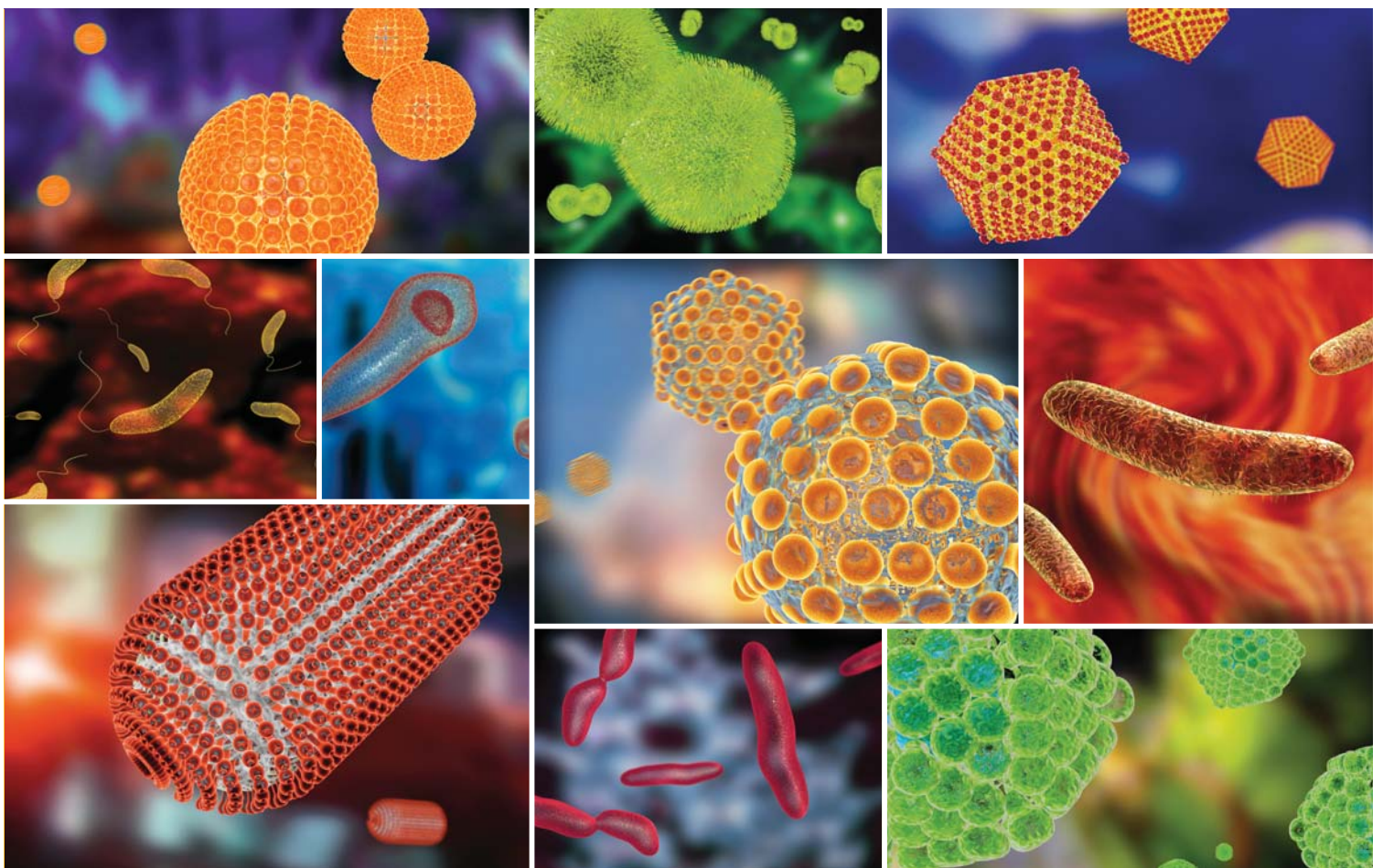
– Giuseppe Del Giudice,
Head of Translational Medicine,
Novartis Vaccines

²⁵ Chiron Vaccines – Pioneering Protection Brochure, p.3

²⁶ Chiron Vaccines – Pioneering Protection Brochure, p.7

steeply, from more than 350,000 reported infections in 1988 to just 1,469 in 2005.²⁷ To date, Novartis has manufactured an average of 350 million doses of the polio vaccine Polioral®.

We take pride in the enormous impact our products have on the quality of our customers' lives. It drives us to take up some of the most pressing and intellectually challenging problems of disease prevention today. To meet these challenges we actively apply ourselves to advancing the science and technology of vaccinology, conducting research on new vaccines, adjuvants and methods of vaccine delivery. We are swiftly advancing the field of influenza vaccinology beyond cell culture-derived vaccines, working with public health agencies to test whether this technology can be used to improve the influenza vaccine itself. And these are just some of our efforts toward improving the world's health. As demonstrated by our work on meningitis and influenza, and our participation in global efforts to combat epidemics, Novartis Vaccines has long invested its intellectual and material resources in the alleviation of human suffering. We will continue to dedicate ourselves to this mission, because at Novartis Vaccines—Caring Begins with Prevention.



(Top row) Hepatitis A (Traveler's Jaundice); Pneumococci; TBE (Tick-Borne Encephalitis)
 (Middle row) Cholera; Tetanus; Polio; Typhus
 (Bottom row) Rabies; Diphtheria; Yellow fever

²⁷ Pan American Health Organization. Scientific and Technical Publication No. 607. 2006
 Available at: http://whqlibdoc.who.int/paho/2006/9275116075_eng.pdf

Caring Begins with Prevention



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