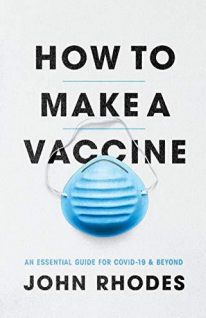

AS NOTAS DO KINDLE PARA:

How to Make a Vaccine: An Essential Guide for COVID-19 and Beyond (English Edition)

de John Rhodes

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124 destaques | 1 nota

Destaque (Amarelo) | Posição 166

> Early in 2003, with worldwide cases running at 3,400 and deaths standing at 143, Canada became the Western nation most severely impacted by the SARS epidemic. In response, scientists at the British Columbia Cancer Agency Genome Sciences Centre in Vancouver switched from their normal task, studying genetic changes in cancer, to sequencing the virus's genome. It took just six days to sequence the 30,000 "letters" of the virus's genetic code, and the data placed the new virus firmly in the coronavirus family—a group of viruses known for causing mild infections of the upper respiratory system. From this, the deadly new virus received its name: SARS coronavirus, conveniently shortened to SARS-CoV. It would be one of several deadly epidemics caused by zoonotic viruses to emerge early in the 21st century. The scale of these outbreaks, however, would be dwarfed by the events that unfolded in 2020.

Destaque (Amarelo) | Posição 193

> The cause of our illness was a guinea pig coxsackievirus targeting the heart. Ted and I had each contracted the virus directly from the infected guinea pigs. Thankfully for us, and those we love, this virus cannot be transmitted person to person.

Destaque (Amarelo) | Posição 215

> At this time, the study of viruses was in its infancy. The observations were largely inferential and the virus itself, unlike bacteria, which could readily be studied under a microscope, remained an invisible and intangible entity. The mystery of viruses began in 1892 when Russian biologist Dimitri Ivanovsky, working at the University of St. Petersburg, discovered that the agent causing a certain disease in tobacco plants could pass through unglazed porcelain filters (which had the smallest pores then available to science) to be collected in the culture vessel below. This was a great surprise. At the time, all living things were thought to be too large to pass through such pores. Even bacteria, the smallest known living things, were too big to pass through that filter. And unlike bacteria, this mysterious substance was not capable of growing independently on nutrient broth in a test tube. In 1898, the Dutch microbiologist Martinus Beijerinck repeated Ivanovsky's experiment and became convinced that the filtered solution contained a new form of infectious agent that could thrive only in growing plants. He called the liquid living thing a virus, a term from the Latin word for poison, originally referring to snake venom. An Italian microbiologist, Adelchi Negri, later showed that the smallpox germ was also a filterable agent, pronouncing it a virus in 1906. But it wasn't until 1935 that viruses were first seen as objects under an electron

microscope. This feat was achieved by Wendell Stanley, a young chemist working in the Rockefeller Institute's laboratories in Princeton, New Jersey. He succeeded in purifying the tobacco plant virus in the form of needle-shaped crystals, which possessed the chemical properties of a protein. It was again a startling discovery. How could a virus, with its ability to infect and multiply, also be an inanimate chemical? An inert molecule? Stanley's finding prompted fundamental philosophical questions about what constitutes life. Further research soon confirmed that the infectious substance, what we now call tobacco mosaic virus, was a combination of protein and nucleic acid. We now know that all genetic material consists of nucleic acid. At the time of Stanley's breakthrough, however, the discovery of the genetic blueprint for all living organisms, by James Watson and Francis Crick, still lay eight years in the future. For his achievements, Stanley shared the 1946 Nobel Prize in Chemistry.

Destaque (Amarelo) | Posição 237

But when would researchers actually succeed in laying eyes on this virus? The novel cold virus was first seen under an electron microscope by Scottish virologist June Almeida working at St. Thomas Hospital in London in 1967. The daughter of a Glasgow bus driver, Almeida left school at 16. But this didn't stop her becoming a pioneering electron microscopist with a gift for photographing viruses. It was Almeida, together with David Tyrrell, who named the germ coronavirus because of its appearance. Her new name first appeared in the journal Nature in 1968. "[The viral] particles are more or less rounded in profile . . . there is also a characteristic fringe of projections 200 angstroms long, which are rounded or petal shaped, rather than sharp or pointed. This appearance, recalling the solar corona, is shared by mouse hepatitis virus and several viruses recently recovered from man." I was lucky to meet Almeida late in her career, toward the end of the 1980s. By then she had returned to work at the Wellcome Research Laboratories in the leafy suburbs of south London to advise on the best way to photograph a novel pathogen recently given its new and final name: HIV.

Destaque (Amarelo) | Posição 254

"angiotensin-converting enzyme 2" or ACE2,

Destaque (Amarelo) | Posição 254

The viral target, ACE2, is not just a passive protein on the surface of cells. When blood pressure is too high, ACE2's job is to reverse a chemical message instructing blood vessels to contract, causing vessels to dilate instead. ACE2 appears on cells in the lungs, arteries, heart, kidneys, and intestines, so the virus can in principle affect these organs.

Destaque (Amarelo) | Posição 260

Once the spike protein gets a grip on ACE2 at the surface of lung cells, the spike changes its shape to expose what's called a "membrane fusion element," rather like unsheathing a weapon. This change is effected by enzymes produced by the target cell. The exposed element then fuses with the membrane of the human cell it's attacking, allowing the virus inside. Once inside, the viral RNA directs the production of copies of the original virus attacker. Viral proteins self-assemble into particles, the new RNA is packaged, and the progeny leave the cell through the normal secretory pathway used in the export of proteins, picking up a lipid coat on the way out.

> Infected cells continue to export virus in this way until their own integrity becomes exhausted or they're picked off by the immune system.

Destaque (Amarelo) | Posição 272

> By January 7, Chinese scientists had isolated a novel virus from patients in Wuhan and analyzed the genetic material. The sequence they obtained revealed it as a novel coronavirus, distinct from SARS-CoV, the cause of the outbreak 18 years before. In consequence, SARS-CoV was renamed SARS-CoV-1 and the new corona virus dubbed SARS-CoV-2. Using this sequence (the order in which the four chemical building blocks of RNA are arranged), scientists constructed diagnostic tests for detecting the virus. The scientists provided full genome sequence information to the WHO and shared their data on the Global Initiative for Sharing All Influenza Data platform. Of the initial 41 people hospitalized with pneumonia and officially identified as having SARS-CoV-2 infection, two-thirds were exposed in the Huanan Seafood Wholesale Market.

Destaque (Amarelo) | Posição 311

> In modern China, the martial arts are, at their best, elegant, intricate, precise, beautiful in their complexity, surprising in their depth, and as much about restraint, inhibition, and forbearance as about striking down an enemy. The image reminds me of the human immune system.

Destaque (Amarelo) | Posição 339

> They named this miraculous substance antitoxin. Each antitoxin appeared to inactivate only the toxin used to produce it. Antitoxin B failed to combat toxin A, while antitoxin A had no effect on toxin B. Mixed with the "wrong" antitoxin, the bacterial poisons retained all their deadly potency. Antitoxins could not only tell the difference between germs and normal tissues, they could discriminate between toxins. This, one of the greatest moments in the history of biomedicine, was the discovery of what would later be called an antibody—the protein actively produced by the body to neutralize, eliminate, or kill invading germs. Kitasato was destined to return to his native land, but Behring went on to use antibodies to save the lives of children with diphtheria. In 1901 he was awarded the first ever Nobel Prize in Physiology or Medicine for having "placed in the hands of the physician a victorious weapon against illness and deaths."

Destaque (Amarelo) | Posição 346

> In line with the new picture of immunity, the fragments of germs (pathogens) stimulating the production of antibodies soon became known as antigens.

Destaque (Amarelo) | Posição 363

> Burnet proposed, in the late 1950s, that receptors (locks) fitting all shapes (keys) in the universe of microbes are present on immune cells but that each cell has only one receptor shape. An invading pathogen will "unlock" a cell with a receptor of the corresponding shape. This unlocking spurs the rapid multiplication of that cell, the progeny of which produce antibodies of the same shape. Think of the receptors on the individual immune cells as a cell-bound version of an antibody. Antibodies of precisely the same shape or "specificity" as the parent

receptor are released by the daughters of that particular cell into bodily fluids. The antibodies then neutralize the pathogens matching the type that unlocked the parent cell. This theory of immunity, which Burnet dubbed "clonal selection," would later be refined but has essentially stood the test of time.

Destaque (Amarelo) | Posição 379

Frederick Sanger, one of only four people to win the Nobel Prize twice.

Destaque (Amarelo) | Posição 414

This gradually emerging picture was a source of great satisfaction to both Porter and Edelman. In 1972, the two scientists jointly received the Nobel Prize in Physiology or Medicine for their achievements.

Destaque (Amarelo) | Posição 425

This implied that there were two different types of lymphocyte working through very different mechanisms. Later, the special class of lymphocyte that rejected the skin grafts would be named T-cells, to distinguish them from B-cells, lymphocytes that produce antibodies. At the same time, James Gowans, an Oxford researcher, was studying the behavior of lymphocytes, showing how these cells endlessly circulate between the vessels and nodes of the lymphatic system and the blood. It was to be the dawn of a new age—an understanding of what we now know as cellular, or cell-mediated, immunity.

Destaque (Amarelo) | Posição 434

These surveillance cells quickly engulf and digest any invading pathogens. They then transport pathogen fragments to their surface and at the same time release signaling molecules called cytokines to attract T-cells. A key molecule mobilizing immune defenses at this stage is a cytokine called interferon, and some pathogens seek to evade immunity by dampening its production.

Destaque (Amarelo) | Posição 437

Immune Cell Tasks

Destaque (Amarelo) | Posição 468

It's important to remember a crucial difference between how antibodies function and how cell-mediated immunity works. Antibodies can bind to viruses directly (in the same sort of way as the spike protein of coronavirus binds to ACE2). This means they can recognize the native shapes of viruses. But in cell-mediated immunity, T-cells see only small fragments of viruses—remnants of the viruses that were digested by surveillance cells. But T-cells can then identify the same tell-tale fragments on the surfaces of virus-infected cells, after which they kill the host cell and, consequently, the virus.

Destaque (Amarelo) | Posição 491

> Although the structure of the T-cell receptor was not known in the 1970s, the great mystery of T-cell recognition (and the biological reason behind surgical graft rejection) had been solved in the suburbs of Canberra, Australia. Twenty-two years later, in 1996, Zinkernagel and Doherty were awarded the Nobel Prize in Physiology or Medicine for their discovery.

Destaque (Amarelo) | Posição 497

> Initially, the idea of joining these scientists was daunting, but I felt blessed with a new self-confidence acquired, somehow, mid-Atlantic. Stateside I felt brash, warm, eager to engage. My host was Charles Kirkpatrick, an immunologist who stood astride the academic and clinical arenas. My sponsor was Alan Rosenthal, a man right in the middle of a seminal discovery. The clinical head of the whole thing was Sheldon Wolff. Among the charming, fresh-faced company were Charles Dinarello and Anthony “Tony” Fauci. Dinarello, with his mentor Sheldon Wolff, would go on to discover the prime mediator of clinical fever. Fauci would take the helm of the institute, guiding it through major storms and remaining in the thick of it for 36 years and counting.

Destaque (Amarelo) | Posição 546

> In this way Miller was the last person in history to discover the function of a major organ. His pioneering work showed that the thymus populates the body with T-cells, while B-cells are produced in the bone marrow. But the extraordinary details of just how the thymus works emerged only gradually in the years ahead.

Destaque (Amarelo) | Posição 567

> Still more diversity is generated when the microbe-binding bits of antibody molecules (antibody receptors) are randomly assembled from different component parts. Some estimates suggest these processes generate more than 10 billion (1010) configurations. In other words, DNA mutations and recombinations, occurring during fetal development, generate the huge diversity of antibodies.

Destaque (Amarelo) | Posição 573

> Tonegawa became, in 1987, the first Japanese scientist to receive the Nobel Prize for Physiology or Medicine (though perhaps Kitasato ought to have been honored in this way 80 years before).

Destaque (Amarelo) | Posição 576

> We can now return to Jacques Miller and the role of the thymus. This organ populates the body with T-cells, but is there some kind of filter for that huge array of specificities that randomly shuffled genes produce? Remember that the starting population of immature T-cells in the fetal thymus possesses a vast range of randomly generated receptors which may or may not bind to pathogens, and which may or may not recognize MHC molecules. What happens is this. During early development, the vast, new random family of receptors in the thymus is screened to weed out those that recognize the self—the natural healthy profiles of the body. In other words, immune cells that could attack the normal tissues and organs of the body are eliminated at this early stage. Among these are

> cells that bind too readily to MHC molecules. Cells that bind too weakly to MHC molecules are also useless, and these too are eliminated. It's a case of the Goldilocks principle. Some developing T-cells bind too strongly to MHC. Others bind too weakly. Only the ones in between are "just right." And these are the only cells that survive the rigorous thymic selection process in the developing fetus. All the rest are killed by a mechanism called programmed cell death. The result is a tailor-made population of mature T-cells ready to recognize pathogens (in fragmented form) when they are bound in the groove of MHC molecules on the surface of antigen-presenting surveillance cells.

Destaque (Amarelo) | Posição 715

> The cowpox virus entered ordinary tissue cells around the injection site and hijacked the normal cellular machinery to reproduce itself. In the course of this, viral fragments ended up in MHC molecules, flagging the cells as infected. At the same time, specialized surveillance cells of the immune system took up the cowpox virus, digested it, and presented fragments, bound to MHC, to the small proportion of immune lymphocytes whose receptors could recognize them. The surveillance cells, stimulated by danger signals on the proliferating virus, also sent the crucial second message: an alarm signal, kicking the virus-specific T-cells into action. The T-cells multiplied; some of their progeny became killer T-cells, directly eliminating virus-infected cells. Others recruited B-cells, which also multiplied and produced antibodies to neutralize the virus. In this way the growth of cowpox was limited to the local site of injection, though James felt feverish because of circulating cytokines—the chemical messengers regulating the immune response. Regulatory T-cells closed down the response when all the cowpox virus was cleared.

Destaque (Amarelo) | Posição 825

> The advent of genetic engineering allowed scientists to create new versions of adenovirus. These lacked a gene essential for replication and therefore provided safe, nonreplicating viral vectors for delivering new vaccines. Because they can't multiply in the body, such vectors are entirely harmless, but because they remain as whole pathogens with all components intact, they still infect cells and look dangerous to the immune system—leading to stronger, more sustained immune responses.

Destaque (Amarelo) | Posição 847

> Jenner Institute,

Destaque (Amarelo) | Posição 861

> 1990, in a laboratory in Madison, Wisconsin, something very surprising took place. Working in the Department of Pediatrics at the University of Wisconsin, Jon A. Wolff and his colleagues took the bold step of injecting engineered RNA and DNA plasmids directly into the muscle tissue of mice. This was the first step in the effort to produce nucleic acid (or genetic) vaccines.

Destaque (Amarelo) | Posição 866

> This opened the door to the development of both DNA and RNA vaccines.

Destaque (Amarelo) | Posição 867

> Two years later, Stephen Johnston at the Department of Medicine, University of Texas, Dallas, repeated the observations but with an impressive addition—researchers placed plasmid DNA onto tiny particles of gold delivered by a futuristic-sounding “gene gun.” This produced an immune response: the mice made antibodies to human growth hormone—the protein coded in the DNA. Just one year after that, Jeffery Ulmer and his colleagues, again studying mice, demonstrated protection against flu infection by a naked DNA vaccine encoding a key flu protein. This simple vaccine produced killer T-cell–mediated immune responses. And within five years the first DNA immunization study in humans succeeded in stimulating a good killer T-cell response to a protein from the malarial parasite. Stephen L. Hoffman and his colleagues at the US Navy Research Facility in Bethesda, Maryland, conducted this research and published it in 1998.

Destaque (Amarelo) | Posição 878

> Human nucleic acid vaccines failed to make it to the clinic. What was needed for nucleic acid vaccines to complete the journey? The answer was a global challenge beginning in 2020—an imperative need not seen before in the modern world.

Destaque (Amarelo) | Posição 933

> Stage Three: Phase I Trials In phase I trials, researchers administer the candidate vaccine to a small group (fewer than 150 people) with the goal of determining whether the candidate vaccine is safe. This constitutes the primary endpoint of the study. But at this early stage, researchers also use every opportunity to determine potential efficacy. For example, for an early COVID-19 front-runner called Ad5-nCov2, the phase I study in China measured the amount of antibody to SARS-CoV-2 spike protein, the ability of these antibodies to neutralize or disable the virus, and the strength of killer T-cell–mediated immunity.

Destaque (Amarelo) | Posição 939

> Stage Four: Phase II Trials Phase II trials, which include hundreds of human test subjects, aim to establish efficacy and also deliver more information about safety, the quality of the immune response that the vaccine induces, the immunization schedule, and the optimal dose. The number of dosing occasions, the interval between them, and the dose level may well be different for each vaccine, while different populations may require particular dosing schedules and formulations. Flu vaccination in the elderly is an example, where a stronger adjuvant is needed.

Destaque (Amarelo) | Posição 948

> The ultimate test of vaccine effectiveness depends on the incidence of infections (acquired by chance) in the vaccinated population compared with unvaccinated individuals. To achieve this, vaccine trials are best conducted in regions where infection rates are high.

Destaque (Amarelo) | Posição 959

> the Cutter Incident, took place in the manufacturing phase.

Destaque (Amarelo) | Posição 959

> Early on Sunday, April 24, 1955, in the midst of the historic first wave of immunization with the Salk polio vaccine, a little girl in Idaho came down with symptoms resembling polio. Remember that the Salk vaccine used dead viruses to immunize recipients, so the appearance of these symptoms was especially surprising. She had received the Salk vaccine six days earlier. Officials assumed that, as with many tragic cases in the great field trial, she had received the vaccine too late, or it hadn't sufficiently protected her. She died three days later. In the days and weeks that followed, the death toll of newly vaccinated children and the number of cases of paralysis mounted. As officials and health-care experts scrambled to get a grip on the catastrophe, it suddenly became clear that the problem vaccine came from a single manufacturer—Cutter Laboratories in Berkeley, California. Even as this information came to light, all polio vaccinations throughout the United States were suspended. Investigations would ultimately show that the problem lay in the fermentation tanks holding the virus undergoing chemical inactivation. Inadequate mixing had allowed clumps to form, and the chemical used to kill the virus could not penetrate these clumps. Filters used to remove such clumps had also performed inadequately. Estimates indicate that at least 10 children died and more than 200 were paralyzed by the defective vaccine.

Destaque (Amarelo) | Posição 973

> Stakeholders must put in place procedures that allow them to track whether a vaccine is performing as expected. Activities include phase IV trials, which are optional studies that researchers can conduct following the release of a vaccine. Such trials establish a wider picture of safety and side effects in particular subpopulations (diabetics, for example). Other post-licensing systems include the Vaccine Adverse Event Reporting System and the Vaccine Safety Datalink. These systems allow administrative and approval bodies to monitor the performance, safety, and effectiveness of an approved vaccine in large populations. These steps require the skills and input of numerous stakeholders, from lab researchers to policymakers to medical professionals.

Destaque (Amarelo) | Posição 993

> But what I most love is the boundary between mystery and discovery, as described in the previous chapters: Kitasato and Behring seeing deadly toxins made harmless; Macfarlane Burnet imagining lymphocyte clones; Porter glimpsing the true shape of antibody; Doherty and Zinkernagel identifying what the T-cell sees; Miller removing the thymus and pondering the resulting loss of immunity; Tonegawa conceiving of shuffled genes; and Janeway intuiting the importance of danger.

Destaque (Amarelo) | Posição 1035

> To make large quantities of DNA, you have to grow it as plasmids, which, as we saw in chapter 3, are autonomous units of genetic material containing all the necessary elements to make the protein they encode. These plasmids are grown in bacteria. The usual choice for growing plasmids is Escherichia coli (E. coli), a type of bacteria common in human and animal intestines and necessary for normal health. E. coli can grow easily in large-scale fermentation vessels, and researchers can then harvest the DNA of interest.

Destaque (Amarelo) | Posição 1038

> the safety of nucleic acid vaccines is crucial, the FDA, EMA, and WHO have released a new set of regulatory guidelines to encompass nucleic acid vaccine production.

Destaque (Amarelo) | Posição 1070

> Let's rerun, for a moment, the alarming calendar of events at the start of the COVID-19 pandemic. On December 30, 2019, Chinese health officials report a cluster of pneumonia cases in the city of Wuhan in Central China to the National Health Commission. Chinese authorities set in motion an investigation to understand and contain the disease. By January 7, Chinese scientists have isolated a mystery virus and analyzed the genetic material, naming the deadly pathogen SARS-CoV-2. On January 11, we learn of the first recorded death, and on January 23, the local government in Wuhan locks down the city. By January 24, China reports 835 cases, while in Korea and Japan, cases are on the rise. A little over six weeks later, on March 11, with 116,558 cases worldwide and more than 4,000 dead, the WHO declares the SARS-CoV-2 outbreak a global emergency. The pandemical disease caused by the virus is named COVID-19. By this date, the United States has confirmed more than 1,000 cases across 38 states, the United Kingdom has reported six deaths, and Italy, the worst hit country in Europe, reports 631 people have died of the disease.

Destaque (Amarelo) | Posição 1086

> Inactivated Whole-Virus Vaccines

Destaque (Amarelo) | Posição 1105

> The SARS-CoV-2 virus was then grown in Vero cells in large (50 liter) culture vessels and subjected to further investigations. These showed that the virus, including the gene for the spike protein (the part of the coronavirus that binds ACE2) was stable in this cellular environment, allowing researchers to proceed. The next step was to kill the virus. In the history of vaccines, the conventional way to kill vaccine viruses has been with formaldehyde, which "pickles" the virus, retaining its native shape, helping to ensure that the immune system can identify it. In this case the scientists used a chemical called β-propiolactone, which is more targeted than formaldehyde. It has been used to kill influenza viruses, and although scientists do not completely understand how it kills viruses, they believe it poisons the proteins whose function is to get the virus inside human cells. After killing the virus, the researchers checked to make sure its shape wasn't damaged. Happily, using an electron microscope, the team of scientists saw discrete, intact, oval shapes "embellished with crown-like spikes," confirming that the virus's shape was unaltered.

Destaque (Amarelo) | Posição 1129

> Protein Subunit Vaccines

Destaque (Amarelo) | Posição 1156

> In the early 20th century, Gaston Ramon, the French veterinarian who pioneered the chemical inactivation of bacterial toxins, was trying to improve the yield of horse antibodies used to treat children with diphtheria. He

> noticed that if an abscess happened to develop at an injection site, the horse produced a lot more antibodies. This prompted him to inject the horses with toxin combined with starch, breadcrumbs, and tapioca. This ingenious use of these otherwise innocuous agents produced sufficient irritation to provoke sterile abscesses, which increased the antibody yield.

Destaque (Amarelo) | Posição 1209

> Live Attenuated Vaccines

Destaque (Amarelo) | Posição 1221

> Nonreplicating Viral Vector Vaccines

Destaque (Amarelo) | Posição 1222

> these vaccines consist of a harmless carrier virus containing an inserted gene encoding a key antigen from the pathogenic virus.

Destaque (Amarelo) | Posição 1223

> Nonreplicating vectors do not grow in the body, but they do infect cells, and the pathogenic antigens they carry present the full range of their danger signals to the innate immune system. This is key to the success of these vaccines.

Destaque (Amarelo) | Posição 1228

> This vaccine was one of the very first to reach clinical trials, just 10 short weeks after the sequencing of the SARS-CoV-2 virus. By the end of March 2020, the live vaccine was in phase I clinical trials in two approved hospitals in Wuhan—the Wuhan Rest Center of the Chinese People's Armed Police Force and Tongji Hospital, part of Tongji Medical College at the Huazhong University of Science and Technology. The trial included 180 healthy people between 18 and 60 years of age. Like all phase I trials, no placebo or mock vaccine was included for comparison, and the trial was not "blinded"—both doctors and recipients knew what was being administered. The study began by giving the lowest vaccine dose to 36 individuals. Once this was shown to be safe (seven days later), a second group of 36 volunteers received a higher dose. Researchers then repeated the process with the third group, who received the highest dose of all—this being the dose predicted to be effective with similar vaccines in previous studies. Not surprisingly, the volunteers had to pass certain tests. They had to be negative for antibodies to coronavirus, meaning they hadn't already been exposed to the disease and developed an immunity. They had to have no previous exposure to the related virus, SARS-CoV-1. And they needed healthy lungs. The primary purpose of this study was to establish safety, but the exciting part for the scientists running the trial was measuring neutralizing antibodies made against the virus. They made this measurement 14 days, 28 days, 3 months, and 6 months after the injection.

Destaque (Amarelo) | Posição 1256

> The Tianjin adenovirus used in the COVID-19 vaccine race is adenovirus serotype 5 (Ad5).

Destaque (Amarelo) | Posição 1265

> the gene encoded the SARS-CoV-2 spike protein was incorporated into the Oxford vector known as ChAdOx1. These studies were led by Sarah Gilbert, whom we met in chapter 3—a vaccinologist well used to challenging diseases such as malaria and, more recently, influenza. Preclinical studies with the Oxford candidate in mice showed good antibody and T-cell responses to the vaccine, known as ChAdOx1 nCoV-19. And in a protection study in rhesus macaques, ChAdOx1 nCoV-19 successfully prevented pneumonia in animals challenged with SARS-CoV-2.

Destaque (Amarelo) | Posição 1315

> On August 11, 2020, Russia announced that it had successfully developed a COVID-19 vaccine at the Gamaleya Research Institute of Epidemiology and Microbiology in Moscow. A surprise aspect of this news was that Russian authorities had already approved the vaccine for general use, an aspect provoking international criticism because no one had yet conducted large-scale phase III safety and efficacy testing. Commentators suggested that vaccinated human subjects were deliberately exposed to virus in a clinical setting in order to demonstrate the vaccine's effectiveness. Reports indicated that the vaccine employed nonreplicating adenovirus vectors delivering the gene encoding SARS-CoV-2 spike protein—the same approach taken by the Belgian COVID-19 vaccine group and Chinese scientists based in Tianjin.

Destaque (Amarelo) | Posição 1321

> Replicating Viral Vector Vaccines

Destaque (Amarelo) | Posição 1323

> These differ from the previous class in that once they are injected and have entered human cells, they undergo several rounds of replication, infecting more cells and providing sustained stimulation of the immune system.

Destaque (Amarelo) | Posição 1330

> Virus-Like Particle Vaccines

Destaque (Amarelo) | Posição 1335

> One principal example of an established vaccine exploiting this technology is the HPV vaccine protecting against cervical cancer and genital warts.

Destaque (Amarelo) | Posição 1346

> DNA Vaccines

Destaque (Amarelo) | Posição 1347

> Investigators have examined many ingenious delivery techniques for DNA vaccines. A US biotech company in Philadelphia has produced an optimized DNA vaccine encoding the SARS-CoV-2 spike protein designed to be injected into the protective middle layer of the skin known as the dermis. A proprietary handheld electrical device is then used to deliver electrical pulses at the site of injection which briefly open small pores in cell membranes, allowing the plasmids to enter dermal cells before the pores close again. The company initiated their phase I clinical trials in healthy volunteers in Kansas City and Philadelphia in 2020.

Destaque (Amarelo) | Posição 1357

> This is the category delivering vaccines in the form of RNA. On March 16, 2020, the same day that Chinese scientists in Tianjin launched their clinical trial of a COVID-19 viral vector vaccine, scientists based in Boston commenced the first clinical trial of their RNA vaccine.

Destaque (Amarelo) | Posição 1361

> RNA has several theoretical advantages over the live vector and the nonliving protein-based vaccines. The first is safety: mRNA or messenger RNA, is noninfectious, eliminating the risk of unwanted invasiveness, and it does not integrate with the genetic material of the human cell. The second is that mRNA, unlike DNA, interacts directly with the machinery of cells without requiring intermediate steps. The third is that once it has done its job, vaccine mRNA is naturally broken down by “housekeeping” enzymes that maintain the normal functioning of cells.

Destaque (Amarelo) | Posição 1373

> The mother of nucleic acid vaccination is Margaret Liu.

Destaque (Amarelo) | Posição 1381

> Things suddenly began to look brighter for RNA vaccines in 2005 with the publication of a paper by medical researcher Drew Weissman and colleagues at the University of Pennsylvania. This provided a promising way around the difficulties for mRNA vaccines in humans. Success hinged on chemically modifying the building blocks of mRNA in relatively subtle ways.

Destaque (Amarelo) | Posição 1399

> The way around these problems, insightfully suggested in Drew Weissman’s publication in 2005, was to add small chemical groups to the building blocks of vaccine RNA. Without these groups, three kinds of Toll-like receptors could sense the RNA. But with the groups added, no Toll-like sensors could sense the modified RNA, allowing RNA vaccines to be effective. Comparing RNA from infectious pathogens and RNA from the human cellular machinery further explained what was going on: chemical modifications were converting the appearance of vaccine RNA from a pathogen-associated profile to a profile resembling normal human RNA. This put control back in the hands of the vaccine designers. Because vaccine RNA is manufactured from DNA by a cell-

free biochemical procedure, this makes it easy to use modified building blocks in the synthetic process, allowing scientists to avoid unwanted effects on the immune system. The vaccine designers can then choose whether or not to add defined adjuvants to their modified RNA vaccines.

Destaque (Amarelo) | Posição 1414

On July 14, 2020, the company behind this leading RNA vaccine published their phase I results in The New England Journal of Medicine. Given as two doses, 28 days apart, their vaccine, mRNA-1273, produced good neutralizing antibodies to SARS-CoV-2 in all subjects, equivalent to antibody levels seen in patients recovering from natural infection. Helper T-cell responses also occurred. And with no concerns about adverse effects, the vaccine progressed to phase III studies and approval in December 2020.

Destaque (Amarelo) | Posição 1441

Operation Warp Speed, a program to fast-track funding, facilitation, and support for selected COVID-19 vaccines. Among them was the RNA vaccine produced by scientists in Boston. The others included the nonreplicating adenovirus vector vaccine from the University of Oxford, the adenovirus vector vaccine produced in Belgium, the replicating VSV vector vaccine originated in Canada, and the four versions of RNA vaccines produced in Germany. Details of the companies sponsoring these and all other candidates in the COVID-19 vaccine landscape are provided in the appendix.

Destaque (Amarelo) | Posição 1463

According to the WHO, most routine childhood vaccines are effective in 85 to 95 percent of recipients. At the lower end of effectiveness are the seasonal flu vaccines. Recent studies by the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, show that flu vaccination reduces the risk of flu illness by between 40 and 60 percent in the general population during seasons when the flu vaccine is well-matched to circulating flu viruses. This is immensely valuable in terms of serious illness. A 2014 study at centers of excellence across the United States showed that flu vaccination reduced children’s risk of admission to an intensive care unit (ICU) with a flu-related illness by 74 percent during the years 2010 to 2012. A later study showed that between 2012 and 2015, flu vaccination among adults reduced the risk of being admitted to an ICU with flu by 82 percent. And in a highly susceptible group, elderly adults, flu vaccination has recently reduced the risk of flu-associated hospitalizations by around 40 percent. Though imperfect, flu vaccinations are still highly worthwhile. In concert with these vaccination efforts, large-scale immunization of young children with a live attenuated nasal vaccine called FluMist helps protect their family members, especially grandparents.

Destaque (Amarelo) | Posição 1584

The reason dexamethasone is effective in seriously ill COVID-19 patients is that life-threatening symptoms are caused by intense inflammation. A host of intercellular messengers (small proteins) released by immune cells orchestrate and amplify the immune response and promote the attack on the invader. But in some circumstances things go too far, and the response begins to damage cells and organs, a course of escalating events that can prove fatal. The corticosteroid dexamethasone can calm this overreaction and save lives.

Destaque (Amarelo) | Posição 1590

> 19. Many different viruses cause colds and the list is quite long: rhinoviruses are most often to blame, and there are 99 different serotypes of these. Then there are coronaviruses, adenoviruses, influenza viruses, parainfluenza viruses, human respiratory syncytial viruses, human metapneumoviruses . . . In all there are more than 200 viral types associated with colds.

Destaque (Amarelo) | Posição 1633

> For two years, in the remote northeastern corner of the Democratic Republic of the Congo, an epidemic of Ebola continued to rage. Ebola is a deadly pathogen. In this particular outbreak, 3,470 people were infected and 2,280 died. But the outbreak was declared over on June 29, 2020, largely thanks to a new vaccine developed by Merck. The vaccine achieved a protection level of more than 80 percent among the 300,000 people immunized. Those who were vaccinated but nevertheless showed signs of disease experienced a much milder illness.

Destaque (Amarelo) | Posição 1653

> Other fast-track vaccines, including the Oxford-AstraZeneca vaccine, started phase III trials at the same time. Countries such as Brazil, facing a burgeoning epidemic, were included in tests of vaccine effectiveness.

Destaque (Amarelo) e nota | Posição 1695

> In the United States, allegations regarding the same DTP (diphtheria, tetanus, pertussis) vaccine would do much greater damage to vaccine confidence. A 1982 TV program titled DPT: Vaccine Roulette dramatically and graphically blamed the vaccine for catastrophic brain damage in infants. The program led to the formation of a new antivaccine group—Dissatisfied Parents Together—which would campaign successfully for representation on national vaccine safety committees and the introduction of vaccine safety monitoring and reporting systems. When numerous successful lawsuits, brought by personal injury lawyers against vaccine companies, began to threaten the existence of the vaccine manufacturing industry, the US government acted. In 1986 Congress passed the National Childhood Vaccine Injury Act, establishing a federal no-fault system to compensate victims of injury caused by vaccines mandated by law. The majority of claims filed through this system, which gives claimants the benefit of any doubt, have been related to damage allegedly caused by DTP.

Relacionado a contrato da Pfizer com Brasil, não responsabilização

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Destaque (Amarelo) | Posição 1735

> Vaccine Adverse Event Reporting System.

Destaque (Amarelo) | Posição 1746

> In 2011, Paul A. Offit, Chief of the Division of Infectious Diseases at the Children’s Hospital at the University of Pennsylvania School of Medicine published an important and illuminating account of childhood vaccine safety and the antivaccination movement: Deadly Choices: How the Anti-Vaccine Movement Threatens Us All.

Destaque (Amarelo) | Posição 1766

> Sociologist Jennifer Reich, in her book Calling the Shots: Why Parents Reject Vaccines, describes the practice of free-riding: children who are unvaccinated through parental choice getting a “free ride” thanks to the immunity of those whose parents have complied with vaccination policy (accepting the small risk of adverse reactions). Reich’s research reveals that the majority of vaccine-avoiding parents in the United States in the 21st century are well aware of this accusation. They maintain their sense of themselves as good people by arguing that since these other children are vaccinated, they are not at risk from their own unvaccinated children. And they believe that by devoting themselves to carefully nurturing their children, maintaining a healthy diet, good hygiene, and a loving, caring family environment, they as parents can best protect their own offspring from harm.

Destaque (Amarelo) | Posição 1786

> Among the recommendations for improvement that a modern sociological analysis distills is the need to alter perceptions of vaccines as only for individual benefit. Marketing vaccines to the public should also promote their great societal advantages, an aspect well understood for a vaccine like rubella, a disease that can be damaging to fetuses in early pregnancy.

Destaque (Amarelo) | Posição 1789

> Rebalancing perceptions of individual liberty versus collective responsibility and the good of the community is essential in the drive to reduce elective vaccine avoidance.

Destaque (Amarelo) | Posição 1798

> Historian Elena Conis, in her book Vaccine Nation: America’s Changing Relationship with Immunization, describes the social factors that dictate vaccine use and perceptions.

Destaque (Amarelo) | Posição 1880

> In January 2017, the Wellcome Trust together with the Bill and Melinda Gates Foundation inaugurated a new organization: the Coalition for Epidemic Preparedness Innovations (CEPI), a global partnership between public, private, philanthropic, and civic organizations with centers in Oslo, London, and Washington, DC. Its mission is to accelerate the development of vaccines against emerging infectious diseases and enable access to these vaccines for people of all nations during outbreaks. CEPI works closely with another long-established group—the Global Alliance for Vaccines and Immunisation (Gavi). Created with funding from the Gates Foundation in the year 2000, Gavi is a public-private partnership, bringing together United Nations agencies, governments, vaccine companies, charities, and civil society. Its goal is the sustained improvement of childhood immunization in poor countries and accelerated access to new vaccines. In line with these global objectives, pharma giant AstraZeneca has agreed a multimillion-dollar collaboration with CEPI and Gavi to support the manufacture and distribution of its COVID-19 vaccine to low- and middle-income nations on a not-for-profit basis. AstraZeneca is just one of several global pharma companies working with Gavi in this way to deliver vaccines for the developing world.

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kindle

Destaque (Amarelo) | Posição 1890

> Against pandemic infectious disease, nobody wins the race until everyone wins.

Destaque (Amarelo) | Posição 1907

> Nonreplicating viral vector vaccines work by infecting tissue cells and exposing the immune system to all the danger molecules present in a live virus. Replicating viral vector vaccines do the same but also grow in the body and infect new cells. Nonliving subunit protein vaccines powerfully stimulate the immune response to key vaccine antigens through the inclusion of adjuvants, which amplify the body's response. Nonliving whole-virus vaccines do the same but contain all the components of the pathogen. DNA vaccines deliver key antigens to the immune system in the form of proteins encoded in the engineered DNA, and the body's own cells manufacture these proteins. Packaging and special delivery ploys ensure the vaccines reach the right place to stimulate immune defenses. RNA vaccines work in the same way but with fewer intermediate steps in protein production. Some versions of this class of vaccine also reproduce and amplify themselves in the cells of the body.

Destaque (Amarelo) | Posição 2151

> Animal Viruses and Humans, a Narrow Divide: How Lethal Zoonotic Viruses Spill Over and Threaten Us.

Destaque (Amarelo) | Posição 2152

> Deadly Companions: How Microbes Shaped Our History

Destaque (Amarelo) | Posição 2154

> Microbe Hunters.

Destaque (Amarelo) | Posição 2157

> The Pandemic Century: A History of Global Contagion from the Spanish Flu to Covid-19.

Destaque (Amarelo) | Posição 2158

> COVID-19 Catastrophe: What's Gone Wrong and How to Stop It Happening Again. Cambridge:

Destaque (Amarelo) | Posição 2160

> "Structure, Function, and Evolution of Coronavirus Spike Proteins."

Destaque (Amarelo) | Posição 2161

> COVID-19: The Pandemic That Never Should Have Happened, and How to Stop the Next One.

Destaque (Amarelo) | Posição 2165

> Covid-19: What You Need to Know about the Coronavirus and the Race for the Vaccine.

Destaque (Amarelo) | Posição 2167

> Viruses, Plagues, and History: Past, Present and Future.

Destaque (Amarelo) | Posição 2169

> Spillover: Animal Infections and the Next Human Pandemic.

Destaque (Amarelo) | Posição 2171

> Tyrrell, David, and Michael Fielder. Cold Wars.

Destaque (Amarelo) | Posição 2172

> Waltner-Toews, David. Coronavirus.

Destaque (Amarelo) | Posição 2173

> Zheng, Jun. “SARS-CoV-2: An Emerging Coronavirus That Causes a Global Threat.” International Journal of Biological Sciences 16 (2020): 1678–85.

Destaque (Amarelo) | Posição 2224

> Tending Adam’s Garden.

Destaque (Amarelo) | Posição 2226

> The Beautiful Cure: The Revolution in Immunology and What It Means for Your Health.

Destaque (Amarelo) | Posição 2227

> The Compatibility Gene.

Destaque (Amarelo) | Posição 2228

> Roitt’s Essential Immunology.

Destaque (Amarelo) | Posição 2230

> Janeway’s Immunobiology

Destaque (Amarelo) | Posição 2231

> Fundamental Immunology.

Destaque (Amarelo) | Posição 2232

> An Elegant Defense: The Extraordinary New Science of the Immune System.

Destaque (Amarelo) | Posição 2234

> A History of Immunology.

Destaque (Amarelo) | Posição 2235

> How the Immune System Works.

Destaque (Amarelo) | Posição 2287

> Vaccine: The Controversial Story of Medicine’s Greatest Lifesaver.

Destaque (Amarelo) | Posição 2288

> Life of Edward Jenner MD with Illustrations from His Doctrines and Selections from His Correspondence. 2 vols.

Destaque (Amarelo) | Posição 2290

> The Eradication of Smallpox.

Destaque (Amarelo) | Posição 2291

> House on Fire: The Fight to Eradicate Smallpox.

Destaque (Amarelo) | Posição 2293

> The Life and Death of Smallpox.

Destaque (Amarelo) | Posição 2294

> Smallpox: The Death of a Disease.

Destaque (Amarelo) | Posição 2295

> Polio: An American Story.

Destaque (Amarelo) | Posição 2296

> The End of Plagues: The Global Battle against Infectious Disease.

Destaque (Amarelo) | Posição 2298

> Angel of Death: The Story of Smallpox.

Destaque (Amarelo) | Posição 2299

> Paralyzed with Fear: The Story of Polio.

Destaque (Amarelo) | Posição 2355

> Innovation in Vaccinology: From Design, through to Delivery and Testing.

Destaque (Amarelo) | Posição 2357

> The Vaccine Book.

Destaque (Amarelo) | Posição 2358

> History of Vaccine Development.

Destaque (Amarelo) | Posição 2360

> Development of Vaccines: From Discovery to Clinical Testing.

Destaque (Amarelo) | Posição 2361

> Vaccine Design: Methods and Protocols: Volume 1: Vaccines for Human Diseases.

Destaque (Amarelo) | Posição 2363

> Development of Novel Vaccines Skills, Knowledge and Translational Technologies.

Destaque (Amarelo) | Posição 2364

> Vaccine Development and Manufacturing.

Destaque (Amarelo) | Posição 2375

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Destaque (Amarelo) | Posição 2383

> Novel Technologies for Vaccine Development.

Destaque (Amarelo) | Posição 2386

> The Cutter Incident: How America’s First Polio Vaccine Led to the Growing Vaccine Crisis.

Destaque (Amarelo) | Posição 2402

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