

2021
The Claremont Colleges Library
Undergraduate Research Award

Junior Award Winner

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Reflective Essay

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I'm setting out to eradicate measles from our planet. I want to save the lives of children in Africa where wars prevent them from being vaccinated. I want to save refugee children in Haiti, Myanmar, Syria, Somalia, and so many other countries who are not vaccinated because they have left their countries and are migrants. I want to save the lives of American children, the underimmunized Orthodox Jewish people of New York City, Amish of Ohio, and citizens of Vashon Island, Washington--all locations where measles outbreaks have occurred in the United States. My vision is conceivable because of the foundational work that has come before me and its comprehensive characterization in scientific literature and the history of science.

Our library matters. For instance, my engagement with Claremont Colleges library services enabled me to read the primary journal articles detailing the successful campaign to globally eradicate smallpox. I had access to critical supportive manuscripts from the 80's characterizing the safety of aerosolized measles vaccination in almost four million children in Mexico. Claremont Colleges library services provided me the original vision of Albert Sabin who, after helping eradicate polio, set his sights on measles and conducted aerosolized measles vaccination campaigns before his death in 1993.

For the citation format and source selection for this paper, I am grateful for Adam Rosenkranz who shared his valuable time with my integrated biology and chemistry (IBC) class during my freshman year to teach us how to correctly format our citations, ensure that we are citing reliable and appropriate sources, and have the tools necessary to maneuver the omnipotent advanced search option on the library website. Using what Adam Rosenkranz taught me, all sources that I have cited in my research have been peer-reviewed including the national/global databases from the WHO and the CDC.

Before the COVID-19 pandemic, the basement of the library is where I spent my weekends and weeknights, curled up on the green couches at the bottom of the stacks with my roommates reading interesting books we found on the shelves, like Paul Ewald's *Evolution of infectious diseases* found on the first floor of the library. The library enabled me to grow myself as a scholar studying infectious diseases as well as a person. My first date, freshman year, was a study date in the basement of the library by the old map section where we worked on a psychology problem set until the announcement that the library was closing echoed through the halls. On the second floor, in the private rooms to the left of the stacks, my friend from Harvey Mudd and I sketched out the first design of a noninvasive inexpensive diagnostic device for detection of malaria that set me on a track to study infectious diseases. On the top floor of the library, on the blue and black couches by the elevator, I used the focused quiet space to study day and night for my organic chemistry final which reinforced my love of and commitment to science. In the Fall of 2021, I intend to convene an advisory panel I

have named MEST, Measles Eradication Super Team, in which our first meeting will take place in the library--where it all started for me.

As the COVID-19 pandemic hit, overnight, we unpinned our Thelonious Monk posters off the wall, packed our belongings into cardboard boxes and headed to scattered homes, awkwardly disrupting our sophomore college year. Remarkably though, the pandemic afforded me stunning opportunities. On my train ride home from Pitzer College, I read a book about viruses and zoonotic infections titled *Spillover: Animal Infections and the Next Human Pandemic* by David Quammen and was at once transfixed. After that moment, I tried to learn everything I could about viruses and found myself in the laboratory of virologist Dr. Gene Tan of the J. Craig Venter Institute (JCVI).

I believe we underestimate measles. Over 100,000 children continue to die each year from preventable measles. Measles vaccination rates have declined because of the pandemic. Measles is a persistent problem and globally we now have a real opportunity to eradicate it once and for all. Through my personal experience volunteering in a SARS-CoV-2 vaccination supersite as a nationally certified emergency medical technician (EMT), I personally observed the challenges of moving the fragile vaccines from freezers to syringes, and finally to arms. The difficulty rapidly responding to viral outbreaks in developing nations now felt exceptionally real. Moreover, vaccine hesitation was an impactful social movement that we'd need to face with compassion and evidence.

I have come to my measles vaccine interests quite naturally (Figure 1). In 2014 my grandfather, Dr. Robert Sievers, assembled a measles task-force and received a \$20 million grant from the Gates Foundation to develop a dry inhalable measles vaccine and pushed it through a phase I clinical trial. In 2020, my father, Dr. Eric Sievers, is developing a bacteria-vectored SARS-CoV-2 vaccine and is currently in phase I clinical trials. In 2021, I intend to pick up where my grandfather left off and proceed onwards with a phase II clinical trial of the measles inhalable vaccine and work towards the implementation of flash-bang vaccination and ultimately the global eradication of measles.

We have a remarkable opportunity to make a difference with measles right now. With the culmination of technological advancements in surveillance and rapid vaccination that have been primed and perfect over hundreds of years paired with a world hungry to stomp out SARS-CoV-2, measles eradication is an achievable goal. I look forward to the time when I get to sit and read by the towering windows behind the stacks about measles and draft an eradication plan. Measles has overstayed its welcome, it's time to end it once and for all.

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Research Project

Measles Eradication:
Let's Root Out Measles, Ring-vaccinate
Hotspots, and Eradicate this Deadly Scourge
Forever



Figure 1. My 11-year-old self, Benjamin Sievers, demonstrating inhalation of a mock dry powder measles vaccine delivered by my grandfather, Robert Sievers. Image taken from the article “The Man Fighting Measles One Breath at a Time” published by the University of Colorado Boulder Alumni Magazine in 2011.

Measles Eradication: Let's Root Out Measles, Ring-vaccinate Hotspots, and Eradicate this Deadly Scourge Forever

Abstract

Amidst an unremitting pandemic, we have become amateur virologists. Let's now summon our collective spirit and wipe **measles** from our planet. Why measles? Well, it is a dreadful and deeply impactful infection. First, it kills over 200,000 children every year. Those who survive infection often subsequently experience profound "immune amnesia" that puts them at increased risk from other infections. All of this can be prevented through safe and effective measles vaccination. It is unconscionable that more children worldwide are now dying from measles than in nearly a quarter century. Second, thanks to our current pandemic, shared interest in virology and vaccine awareness is robust. Many of us now view vaccines as our collective salvation for both individual health and our global economy. What an exceptional opportunity! So let's vaccinate for measles while we all care about viruses. Third, global cooperation is improved, we are better able to rapidly detect measles outbreaks, and inhaled measles vaccines have been shown to be safe. A global eradication campaign based upon these elements has the potential to eradicate measles once and for all. Finally, a persistent, humanitarian call to action over decades has helped surface the pitfalls and illuminate the road to success, as demonstrated through the thoughtful and strategic eradication of smallpox that culminated in 1979. During those heady, optimistic years the US Center for Disease Control set a four-year goal to eradicate measles in the United States by 1982. We collectively came close: the measles incidence in the United States fell to nearly zero. Since that time, the global incidence of measles has rebounded vigorously. Worldwide, there were more cases of measles in the first six months of 2019 alone than in any full year since 2006. We now need to arrest our backward slide by using novel, highly sensitive technology to track regional outbreaks and innovative inhaled vaccine delivery approaches to more easily and rapidly increase herd immunity. Let's step up, act decisively, and eradicate measles forever to save millions of lives over the coming decades.

2.1 A Global Education Regarding Viruses and the Power of Vaccination

Rarely in history has there existed a shared conversation that spans all religions, languages, and borders. The dialogue regarding the SARS-CoV-2 virus has generally inspired deeper respect for vaccines. The momentum is tangible and we are on track for global mass vaccination to prevent death and severe morbidity from COVID-19. In 2020, nearly 4% of the world's research output was dedicated to SARS-CoV-2 with over 200,000 publications about COVID-19 and more than 30,000 COVID-19 preprints, many

of them related to vaccinology and combating the virus [1]. Compared with pre-pandemic levels of interest, a large proportion of global populations has indicated a willingness to vaccinate.

Sometimes we forget that measles is a ferocious virus. Although the majority of infected individuals have fever and moderate misery they often recover without chronic complications. However, predominantly in developing countries, devastating complications arise leading to serious illness, hospitalization, and in some cases death. For every 10,000 measles infected individuals, 2,500 people will be hospitalized and 1,000-2,000 people will die [2]. In almost all cases infected individuals suffer abject misery for approximately two weeks.

In tandem with its disease burden, measles is as contagious as it is harmful. Measles is so contagious that for much of human history, infection was practically universal in childhood. Before an available vaccine, the Centers for Disease Control and Prevention (CDC) estimated that children in the United States experienced several million cases yearly, resulting in approximately 500 deaths, 1,000 cases of encephalitis, and 48,000 hospitalizations every year [3]. In epidemiology, the basic reproductive number is the expected number of infections generated by a single case, meaning how many people can a single infected person spread the virus to. Each person infected with measles typically transmits it to another 12 to 18 other people--six times more infectious than SARS-CoV-2 [4, 5].

Vaccination was an unequivocal success. The first measles vaccine, a live-attenuated vaccine known as the Edmonston-B strain, was developed and licensed by John Enders and his colleagues in 1963 [6]. Through intense empirical development, the vaccine was created through attenuation of wild-type measles [7]. The 1963 measles vaccine is the same vaccine we use for measles today. After the creation of the safe vaccine a wave of relief swept over the United States and people buzzed with excitement as a public health victory potentially stood before us, the CDC publishing a document titled *Measles Eradication 1967*, and a measles eradication movement backed by President Lyndon Johnson formed [8, 9].

In 1998, broad celebration regarding the public health value of measles vaccination was placed at risk following the publication of what was later determined to be a falsified study that claimed a causal relationship between receipt of the MMR vaccine (measles, mumps, and rubella) and the development of autism. As a preponderance of studies have since demonstrated, the measles vaccine has been confirmed to be a safe vaccine [10]. Ultimately, the Wakefield manuscript was retracted in 2010 [11]. Multiple followup studies were conducted with large, statistically compelling sample sizes and proved no connection between the MMR vaccine and autism [12].

Despite its terrifyingly high reproductive number and consequential pathogenicity, measles has one defining feature that can be used against the virus - measles has no nonhuman reservoirs. Unlike many viruses that plague humans, measles is not a

zoonotic virus and thus can only propagate in human hosts making eradication of measles feasible through continued widespread use of intramuscular measles vaccines and methodical tracking of new measles outbreaks coupled with immediate ring vaccination responses when they occur. Once measles is eliminated in humans it will be eliminated forever. It will take an inspired, enduring, coordinated, global push to completely eradicate measles from the planet--one akin to the collective efforts deployed to eradicate smallpox. We can do this. We've done it before.

The global eradication campaigns, including the 1967 measles eradication campaign in the United States and the 1985 national immunization program in India, profoundly reduced the incidence of measles worldwide, but unfortunately did not lead to absolute eradication (Figure 1). In 2018 alone, measles cases surged to approximately 10 million cases worldwide with 140,000 deaths, a 58% increase since 2016 [13]. With a safe, inexpensive, highly protective injectable vaccine widely available, why haven't we eliminated measles globally? And how can measles incidence be again on the rise? Wealthy nations, including the United States, have recently experienced scattered measles outbreaks as a result of vaccine hesitancy. In contrast, in developing nations, measles outbreaks have persisted because of a lack of access to vaccination to the people who need it most due to wars, political conflicts, unavailability of healthcare, inadequate medical infrastructure, and ultimately, a failure of will.

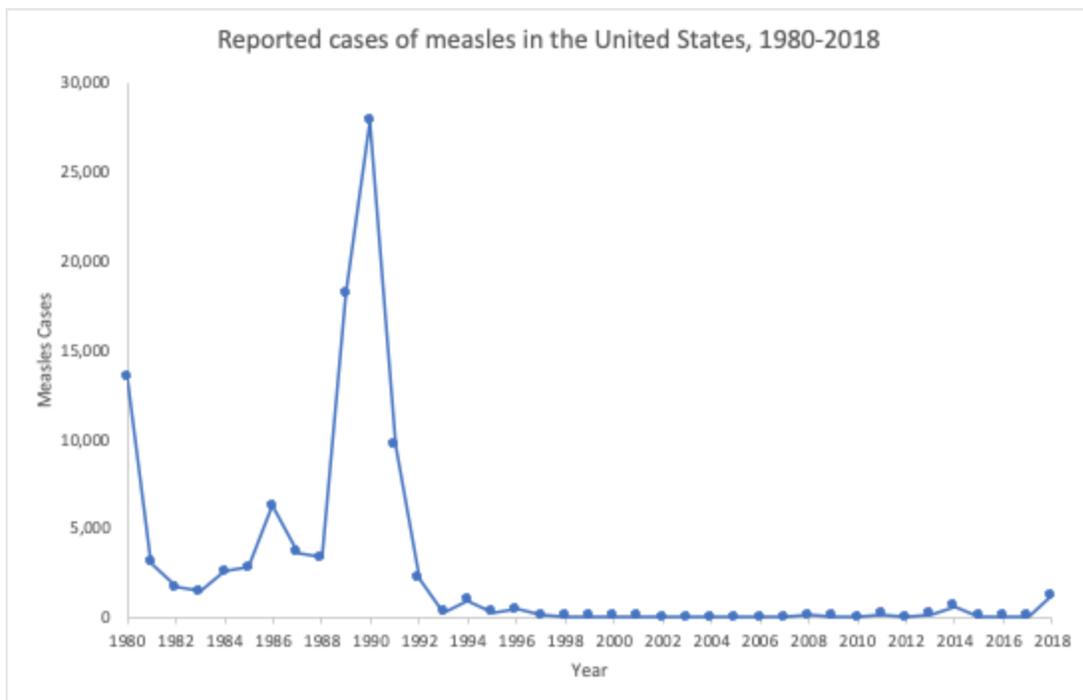


Figure 1. Reported measles cases in the United States by year from 1980 to 2018. Measles cases are defined as epidemiologically linked, clinical and laboratory confirmed cases as reported by the World Health Organization (WHO). Data to create this graph was retrieved from the WHO global measles summary in February 2021.

2.2 Measles can be Deadly; Measles Vaccination is Safe and Effective

Measles is particularly deadly for those living in developing countries. According to the World Health Organization, the death rate of measles in developing nations hovers around 2-15% and has the potential to jump up to 25% in the worst outbreaks, particularly when local health systems are overwhelmed [14]. Measles survivors experience considerable morbidity and can be left with permanent disabilities, including deafness, blindness, and even brain damage [15]. Primarily found in children, measles has the ability to induce a phenomenon known as immune amnesia, where the measles virus erases 11-73% of the patient's capability to produce antibodies against previously-encountered pathogens as the virus targets plasma cells in the bone marrow [16]. This can cause children who are recovering from measles to suffer from another pathogen that they were previously protected from prior to their measles infection.

Two doses of the MMR vaccine is 88% (95% CI: 62-96%) effective in preventing measles [17]. In many poor countries, children are fortunate to even receive a single dose of the vaccine. In the Democratic Republic of the Congo (DRC), in 2018, 57% of children received a single dose of the measles vaccine according to a UNICEF study [18]. In order to prevent outbreaks of measles in a population, it is estimated that 92-95% of the population needs to be fully immunized with two doses to achieve herd immunity [19]. Making matters more challenging, the MMR vaccine must be kept between 2°C and 8°C from the moment vials are pulled from refrigerated storage until the vaccine is injected into the upper arm. Healthcare workers need the necessary training to safely inject the vaccine, a problem we did not face with the oral poliovirus vaccine [20].

Remarkably, even though vaccination costs US\$1.80 per child, eradication campaigns can be prohibitively costly. Moreover, African countries with few additional resources have been required to fund a portion of campaigns [21]. In 2010, the DRC was unable to cover the costs of the vaccination campaign, resulting in an unremitting measles outbreak that lasted 30 months [22]. Taken together, measles eradication campaigns have met limited success for manifold reasons including lack of funding, political instability, a challenged infrastructure for storage and administration of the vaccine, and ultimately, a paucity of trained vaccinators. Although these deficiencies might argue to supplant the standard intramuscular injection of measles vaccine, a counter argument can be made to bolster the standard approach with rapid response to outbreaks with novel inhaled vaccinations. Simply put, we should continue to embrace effective established technology when and where these approaches optimally serve and look to new strategies where conventional vaccination campaigns fall short. For example, cold-chain dependent intramuscular measles vaccines might be well-suited and familiar for urban settings while dry-powder, inhaled measles vaccine might

represent a better fit for rural settings lacking trained vaccinators, refrigeration, and established medical infrastructure. Ultimately, blending established approaches with newer technologies has the best potential to accomplish protective herd immunity levels that can achieve global eradication.

2.2.1 Liquid Aerosolized Measles Vaccine

Recognizing the limitations of intramuscular injection of the measles vaccine, the concept of the aerosolized measles vaccine was originally envisioned by Albert Sabin, and aimed to be a vaccine that was needle-free, simple, safe, inexpensive, and easily deployed in mass vaccination campaigns [23]. A jet nebulizer was used to generate liquid aerosolized vaccine particles for inhalation. Through substantial clinical testing, the liquid aerosolized measles vaccine was shown to be both safe and well-tolerated, producing similar immune responses as the subcutaneous vaccination. Nearly 4 million children were vaccinated against measles in a mass aerosolized measles vaccination program conducted in Mexico between 1982 and 1990. Both primary and booster doses of the inhaled aerosolized Edmonston-Zagreb measles vaccine were delivered by nebulization using an electric air compressor and disposable paper cones.

The aerosolized vaccine program was a remarkable success, leading to containment of the 1980s measles epidemic in Mexico [24]. In a followup confirmatory study, children vaccinated against measles by the aerosol route demonstrated a vaccine effectiveness of 92% that was comparable to the effectiveness of the subcutaneous measles vaccination via intramuscular injection [25]. Over a decade later, in a clinical trial conducted in 2004, 59 children ages 11-13 months, were vaccinated with the aerosolized measles vaccine, in which 77.5% of the children had presence of measles antibodies >120 mIU/ml as read through plaque reduction assays. Among the children in this study, 91% of them vaccinated through the aerosolized measles vaccine had detectable measles PRN antibodies and an SI of ≥ 3.0 [26]. A systematic review of the liquid aerosolized measles vaccine concluded that aerosolized liquid mist vaccine was immunogenic, safe, and well-tolerated [27]. Notably, the aerosolized measles, mumps, and rubella combination vaccine has also been shown to induce immune responses that are similar or in some cases superior to the subcutaneous vaccine [28].

2.2.2 Inhaled Dry Powder, Temperature Stable Measles Vaccine

Although wet mist aerosolized measles vaccination campaigns are feasible, there are considerable additional benefits that can be achieved using dry powder inhalation formulations. Conceivably, some dry powder formulations can be stored at room temperature for prolonged periods and inexpensive single-use inhaled dose devices may be much easier to deploy urgently in outbreak settings. The Bill and Melinda Gates

Foundation supported evaluation of a needle-free, temperature stable dry powder measles vaccine as a part of the Grand Challenges in Global Health initiative in the early 2000s. Exploratory manufacturing and preclinical work ultimately led to a successful phase I clinical study that confirmed safety of an inhalable dry powder measles vaccine in 60 measles-antibody-seropositive adult males of 18-45 years of age. Measles antibody titers were measured 7 days before vaccination and at 21 and 77 days post vaccination by ELISA and plaque reduction neutralization assays. All individuals were seropositive for measles and had a baseline titer of <120 mIU as measured by plaque reduction neutralization test (PRN) on day 7. The dry powder measles vaccine was well tolerated in all subjects and had an immunogenicity profile comparable to the widely used subcutaneous measles vaccine.

Utilizing the plaque reduction neutralization test, the gold standard for assessing measles immunity as PRN titers are directly correlated with measles immunity, a person with a PRN titer of under 120 mIU/ml is of high risk for measles disease if exposed to the virus [29]. On the other hand, persons with PRN titers of 120-1052 mIU/ml are often protected from measles disease but have the potential to acquire subclinical measles infection if exposed to the virus. For persons with PRN titers of greater than 1052 mIU/ml, they are highly unlikely to become infected by measles and/or develop an immune response post vaccination [30]. Approximately half of the cohort of patients with baseline PRN titers of 120-1052 mIU/ml experienced a four-fold increase in titer 28 or 84 days post vaccination [31]. For all of the patients, the dry powder inhaled vaccine increased the measles antibody titers whilst simultaneously maintaining a reassuring safety profile. The dry powder vaccination cost per dose in the developing world was anticipated to be US\$0.17--a tiny fraction of the cost for intramuscular injections.

2.3 Diagnostic Technology

Timing matters in accurate measles diagnostics. From a measles eradication perspective, once infections are identified through reports of the classic skin rash, an outbreak is most certainly in full bloom. Rapid detection of a measles infection is critically important as it enables the initiation of rapid booster vaccination of exposed persons. For exposed, non-immunized people like pre-vaccinated infants, a measles vaccination can be given within 72 hours and can prevent or greatly reduce the severity and time of the illness. And this is where an easily stored, dry powder inhaled vaccine might have the greatest impact. Imagine thousands of self-inhalation doses stored at geographical locations that can be swiftly deployed to outbreaks for rapid ring vaccination. As rapid assembly of trained vaccinators to inject conventional vaccines simply isn't feasible, self-administration of inhaled vaccines provides a key to success.

Measles infections are identified by the appearance of erythematous maculopapular (non-vesicular) rashes developing cephalocaudally and at least one of

the three “C”s: cough, coryza, or conjunctivitis. However it is readily evident that routine surveillance with reverse transcriptase-polymerase chain reaction (RT-PCR) tests that can detect viral RNA from blood, nasal, throat, or urine samples has the potential to identify outbreaks before they infect large communities [32]. There are multiple surveillance systems set forth to track, control, and monitor on both the national and global scale like the National Notifiable Diseases Surveillance System (NNDSS) for the United States and the WHO’s Measles Mortality and Regional Elimination Strategic Plan for global surveillance.

Although in 2000, the United States declared elimination (absence of continuous disease transmission for greater than 12 months) of measles, measles cases worldwide are once again rising. Current measles outbreaks in the United States have become a thorny political issue. Since 2014, 75% of measles infections in the United States have happened within closed religious communities, such as the Orthodox Jewish population in Williamsburg, Brooklyn, the Amish populations in the Midwest, and Somali migrants in Minnesota [33]. Current MMR vaccination rates for children of ages 19-35 months in the United States is approximately 91% but can be as low as 60% in certain close knit communities such as the Orthodox Jewish community in New York [34]. With low vaccination rates and vaccine hesitancy, these communities are at enormous risk for a larger epidemic of measles. In fact, in 2019, the World Health Organization (WHO) named vaccine hesitancy as one of its top ten threats to global health that year [35].

2.4 The Time for the Eradication of Measles is Now

Now is a pivotal time for vaccinology and viral surveillance. New vaccine delivery systems are available with new platforms including mRNA vaccines and an inhaled dry powder, live-attenuated measles vaccine evaluated in humans. In addition to new delivery systems, vaccine willingness is also at an all-time high as nations globally are committed to vaccinate their populations to protect against SARS-CoV-2. For all these reasons, an inexpensive, easily deployed, inhalable vaccine for measles is highly attractive.

The demonstrated evidence showing safety and protective efficacy of aerosolized measles vaccination in almost 4 million recipients coupled with technological advances in dry powder delivery strategies now enable us to envision a more effective, rapid response approach to outbreaks. Imagine the World Health Organization receiving urgent word of a new measles outbreak among Rohingya refugees at a large camp in Cox’s Bazar in Bangladesh. Instead of assembling 132 trained vaccinators, 264 volunteers, 1400 Community Health Workers, and 2000 Majhies as was impressively performed recently as a part of a conventional vaccination campaign, a much smaller group of health workers would distribute single use, biodegradable, vaccine-filled straws; a quick inhale would vaccinate and protect. There

would be no needles, no syringes, no trained vaccinators, and no dangerous sharps requiring specialized disposal. The technology for this approach is readily available. We now require the collective will to embrace a methodical global measles eradication vision [36].

I envision in the next 5 years a phase II safety trial of a simplified dry powder inhaled vaccine, through a streamlined inexpensive whistle/straw shaped device that enables quick and effective measles vaccination. Antibody levels of dry powder inhaled vaccine will be observed and compared with the current subcutaneous MMR vaccine. The device will be easy-to-use, have no additional parts, and safe to receive multiple times. Rapid deployment of these vaccines can be achieved through airdrop using drones, the possibilities are endless. There is no better time than right now to deploy an inhaled vaccine for measles and eradicate measles for good.

2.5 Mandate

When a disease ceases to be circulating in a region, it is considered eliminated for that region. On the global scale, when a disease stops circulating globally it is considered to be eradicated. Smallpox, a disease that killed approximately 35% of its hosts and left many blind or scarred, was eradicated in 1977 [37]. Like measles, smallpox has no non-human hosts meaning its eradication can be guaranteed once it stops circulation in humans. A Somali cook named Ali Maow Maalin was the last person to be infected by wild smallpox, and on October 12th 1977 smallpox was declared eradicated [38].

The successful eradication of smallpox was accomplished through a confluence of continuous surveillance and a key technique known as ring vaccination. The ring vaccination technique is used to quickly identify and isolate exposed individuals and vaccinate them as quickly as possible, stopping the spread of the virus into the community. Unlike smallpox with the fast detectable onset of a highly-visible rash, the rash that forms with measles occurs later in infection with patients becoming contagious before the appearance of the rash, making the ring vaccination technique more difficult but nonetheless likely to succeed with a combination of rapid initiation of easy-to-conduct, self-vaccination using a dry inhalable measles vaccine and dedicated, enduring measles surveillance. As mentioned earlier, rapid deployment of vaccination to exposed individuals to measles within 72 hours can change the entire course of infection, even having the potential to stop the infection. Utilizing a new technique, I have named "flash-bang vaccination," I envision rapidly deployable inhalable measles vaccine kits to quickly flood outbreak hotspots extinguishing the outbreak through mass rapid vaccination, of both recently infected and uninfected people, vaccinated and unvaccinated people, before it can infect any more of the community as well as minimizing the severity of the already infected measles patients.

In two years alone, we can eradicate measles by working hand-in-hand with local clinics, hospitals, health centers, and community centers globally, saturating outbreak hotspots with flash-bang vaccination using dry inhalable measles vaccines before measles can spread any further, upping our measles surveillance and outbreak response time, and increasing vaccine awareness and the importance of vaccination. We've done it before with smallpox virus and rinderpest virus, measles you're next!

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