Vaccines: Proven Safe and Effective, Though Not Without Risks

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"One of the basic rules of the universe is that nothing is perfect. Perfection simply doesn't exist... Without imperfection, neither you nor I would exist."
- Stephen Hawking

"*The impact of vaccination on the health of the world's people is hard to exaggerate. With the exception of safe water, no other modality, not even antibiotics, has had such a major effect on mortality reduction and population growth.*" - was said by Stanley A. Plotkin, one of the most influential figures in modern vaccinology. Nevertheless, the historical use of vaccines has not been devoid of failures or adverse events.

Epidemiological evidence consistently demonstrates that, from a public health standpoint, the benefits of vaccination overwhelmingly surpass the associated risks. The remarkable success of vaccination programs, particularly in developing regions, has led to a significant decline in public awareness regarding the high mortality and morbidity historically associated with endemic infectious diseases—now largely preventable through immunization.

Despite these achievements, serious vaccine safety incidents have been recorded over the years. Although such events do not diminish the profound contribution of vaccines to global health, it remains imperative to critically analyze these occurrences, identify their underlying causes, situate them within their proper scientific and historical context, and acknowledge that biomedical knowledge is inherently incomplete and that medicine is not an exact science.

The Mulkowal Incident, India – 1902

On October 30, 1902, a fatal outbreak occurred in Mulkowal, India, where 19 of 107 individuals vaccinated with an inactivated *Yersinia pestis* (bubonic plague) vaccine died due to contamination with *Clostridium tetani*. The vaccine was produced by the Haffkine Laboratory in Bombay (established in 1899), under the direction of Dr. Mordecai Waldemar Haffkine[1], who also developed the vaccine.

[1] **Waldemar Mordecai Haffkine**
(Haffkine) – was born in Odessa in 1860 to a Jewish merchant family. He studied physics, mathematics, and zoology at the University of Odessa under Elie Metchnikoff, who later won a Nobel Prize for discovering phagocytes. Haffkine earned his Doctor of Science degree in 1884, then moved to Switzerland and Paris. With Metchnikoff's support, he joined the Pasteur Institute, where he developed a live cholera vaccine using Pasteur's methods. In 1893, he traveled to India, where his vaccine was administered to over 42,000 people. The Haffkine Institute in Mumbai is named in his honor.

An investigative commission determined that Haffkine had deviated from the originally approved production protocol (validated in 1898–1899), and that the vaccine bottle marked "N53" was contaminated in the Bombay facility (Simpson, 1907). The modified method, which introduced 0.5% phenol for inactivation—a technique adopted from the Pasteur Institute—had been in general use since 1900. Although the commission viewed the deviation as a serious breach and required Haffkine's resignation, he argued that contamination had occurred at the vaccination site.
After prolonged advocacy by prominent scientists, Haffkine was exonerated, and his production method was officially adopted in December 1904. He was subsequently invited to resume his work in India.

Diphtheria: Toxin–Antitoxin Batch 86 Incident, Australia – 1928

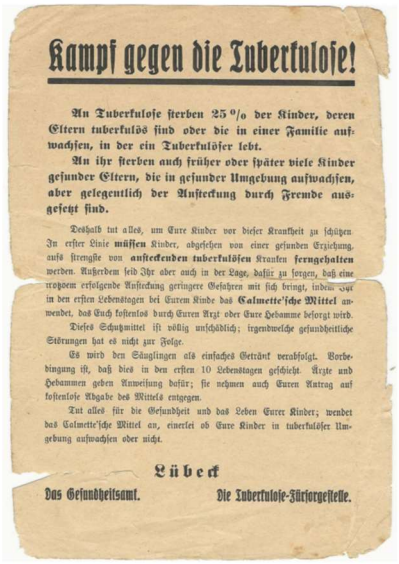
In 1928, a fatal incident occurred in Bundaberg, Queensland, Australia, resulting in the deaths of twelve children aged between 23 months and 7 years following administration of a diphtheria vaccine found to be contaminated (Kellaway et al., 1928). An additional five children developed severe illness but eventually recovered. At that time, the diphtheria immunization practice involved the use of a toxin–antitoxin mixture, in which diphtheria toxin was combined with specific antitoxin antibodies—a method first introduced in 1914 (Park, 1914). The vaccine was distributed in multi-dose vials, a common practice that later emerged as a risk factor for contamination events.
The official investigation concluded that the vaccine preparation had been contaminated with *Staphylococcus aureus* (Akers and Porter, 2008), leading to severe septicemia among the affected recipients. This tragedy contributed significantly to later reforms in vaccine production protocols, particularly emphasizing sterility assurance and the risks associated with multi-dose containers.

The Lübeck Disaster, Germany – 1930

In 1882, Robert Koch identified the causative agent of tuberculosis (reporting his findings on March 24, 1882, at the Institute for Physiology in Berlin during a lecture titled "The Etiology of Tuberculosis"). In 1905, he was awarded the Nobel Prize in Medicine for this discovery.
In 1921, two French researchers, Calmette and Guérin, developed a vaccine against tuberculosis (Calmette et al., 1927). The vaccine was a live attenuated preparation based on *Mycobacterium bovis*, the etiologic agent of bovine tuberculosis. The vaccine was administered orally during the first weeks of life. This method of vaccination became widespread in France, and the vaccine was produced by the Pasteur Institute in Paris. From France, the use of the vaccine expanded to additional countries; however, in Germany, opinions regarding its use were divided.
In 1929, two physicians in the city of Lübeck, Germany—Dr. Deycke, director of the

local hospital, and Dr. Altstädt—decided to promote vaccination against tuberculosis. A culture of the BCG vaccine strain was sent by Calmette to Dr. Altstädt, who then transferred it to Dr. Deycke. Dr. Deycke cultivated the strain in the hospital's laboratory. At that time, tuberculosis outbreaks were occurring in the region, and clinical isolates were processed in the same laboratory and incubated in the same incubator used for the vaccine strain.
The vaccine was produced in small vials, each vial constituting a vaccination dose. The protocol indicated that three doses should be administered within the first ten days of life, with at least one day separating each administration. An explanatory leaflet for parents accompanied the vaccine (Fig. 1).

Fig. 1 The information leaflet accompanying the tuberculosis vaccine responsible for the Lübeck disaster (Jonas, 2017)



Kampf gegen die Tuberkulose!

An Tuberkulose sterben 25 % der Kinder, deren Eltern tuberkulös sind oder die in einer Familie aufwachsen, in der ein Tuberkulöser lebt.

An ihr sterben auch früher oder später viele Kinder gesunder Eltern, die in gesunder Umgebung aufwachsen, aber gelegentlich der Ansteckung durch Fremde ausgesetzt sind.

Deshalb tut alles, um Eure Kinder vor dieser Krankheit zu schützen. In erster Linie **müssen** Kinder, abgesehen von einer gesunden Erziehung, aufs strengste von **ansteckenden tuberkulösen** Kranken **ferngehalten** werden. Außerdem seid Ihr aber auch in der Lage, dafür zu sorgen, daß eine trotzdem erfolgende Ansteckung geringere Gefahren mit sich bringt, indem Ihr in den ersten Lebenstagen bei Eurem Kinde das **Calmette'sche Mittel** anwendet, das Euch kostenlos durch Euren Arzt oder Eure Hebamme besorgt wird.

Dieses Schutzmittel ist völlig unschädlich; irgendwelche gesundheitliche Störungen hat es nicht zur Folge.

Es wird den Säuglingen als einfaches Getränk verabfolgt. Vorbedingung ist, daß dies in den ersten 10 Lebenstagen geschieht. Ärzte und Hebammen geben Anweisung dafür; sie nehmen auch Euren Antrag auf kostenlose Abgabe des Mittels entgegen.

Tut alles für die Gesundheit und das Leben Eurer Kinder; wendet das Calmette'sche Mittel an, einerlei ob Eure Kinder in tuberkulöser Umgebung aufwachsen oder nicht.

Lübeck

Das Gesundheitsamt. **Die Tuberkulose-Fürsorgestelle.**

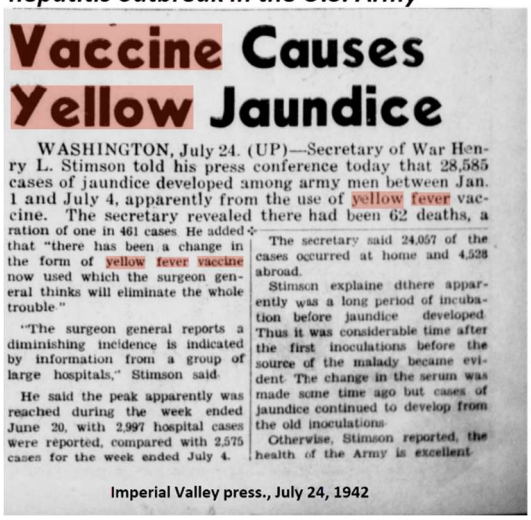
Between February 24 and April 25, 1930, a total of 249 newborns (out of 412 born) in the Lübeck region were vaccinated with three doses of the BCG vaccine. As a preliminary trial, two infants had been vaccinated in December 1929, and one additional infant on February 10, 1930.
The first newborn had been separated from his mother, who suffered from tuberculosis, at birth. After being diagnosed with cervical lymphadenitis, it was initially concluded that the child had been infected by his mother. The second child did not become ill but tested positive in the tuberculin skin test. The third child developed mild signs of tuberculosis.
On April 22, 1930, the first death was reported. Although clinical signs of illness had appeared earlier, the association between the vaccine and the clinical manifestations was not initially recognized.
Among the vaccinated cohort, 72 infants died. An additional 135 developed clinical

tuberculosis but survived, while 44 became tuberculin-positive without developing clinical disease. In contrast, 161 unvaccinated newborns remained unaffected and did not develop tuberculosis during the first three years of life.
The investigation of the disaster concluded that the vaccine produced in the Lübeck hospital laboratory had been contaminated, due to a laboratory error, with a virulent strain of *Mycobacterium tuberculosis*—the Kiel strain (Lange, 1931).
In the trial that followed the incident, Dr. Deycke was sentenced to two years' imprisonment, and Dr. Altstädt to one year and three months (Jonas, 2017).

Hepatitis B Outbreak in the U.S. Army – 1942

During World War II, a widespread outbreak of hepatitis B was reported among U.S. soldiers. The event began in March 1942 and prompted an intensive investigation (Sawyer et al., 1944), which determined that the source of infection was a live yellow fever vaccine contaminated with the hepatitis B virus. The contamination originated from infected serum used as a stabilizer in the vaccine (Fig. 2)
On July 24, 1942, it was reported that 28,585 cases of jaundice had been diagnosed between January 1 and July 4 following vaccination with the live yellow fever vaccine. Sixty-two of those infected died.
On April 14, 1942, the use of the contaminated vaccine was discontinued and replaced with another formulation that did not utilize human serum.

Fig. 2 The news report following the hepatitis outbreak in the U.S. Army



Vaccine Causes Yellow Jaundice

WASHINGTON, July 24. (UP)—Secretary of War Henry L. Stimson told his press conference today that 28,585 cases of jaundice developed among army men between Jan. 1 and July 4, apparently from the use of yellow fever vaccine. The secretary revealed there had been 62 deaths, a ration of one in 461 cases. He added that "there has been a change in the form of yellow fever vaccine now used which the surgeon general thinks will eliminate the whole trouble."

"The surgeon general reports a diminishing incidence is indicated by information from a group of large hospitals," Stimson said.

He said the peak apparently was reached during the week ended June 20, with 2,997 hospital cases were reported, compared with 2,575 cases for the week ended July 4.

The secretary said 24,057 of the cases occurred at home and 4,528 abroad.

Stimson explaine dthere apparently was a long period of incubation before jaundice developed. Thus it was considerable time after the first inoculations before the source of the malady became evident. The change in the serum was made some time ago but cases of jaundice continued to develop from the old inoculations.

Otherwise, Stimson reported, the health of the Army is excellent.

Imperial Valley press., July 24, 1942

Kyoto Disaster, Japan – 1948

In November 1948, a total of 15,561 infants and children, ranging in age from a few months to 13 years, were vaccinated in Kyoto, Japan, with a second dose of diphtheria toxoid adsorbed onto aluminum hydroxide (APT – Alum-Precipitated Toxoid). The first dose had been administered two weeks earlier without incident. One to two days following administration of the second dose, 606 infants and children developed symptoms of illness, and 68 subsequently died.
A comprehensive investigation identified the presence of active diphtheria toxin in the vaccine vials used for the second immunization. This contamination was attributed to incomplete neutralization of the toxin during vaccine production (Kurokawa and Murata, 1961).

Cutter Laboratories, United States – 1955

Immediately following the successful conclusion of the large-scale clinical trial of Dr. Jonas Salk's inactivated polio vaccine, the encouraging results signaled the initiation of mass vaccination of the general population.

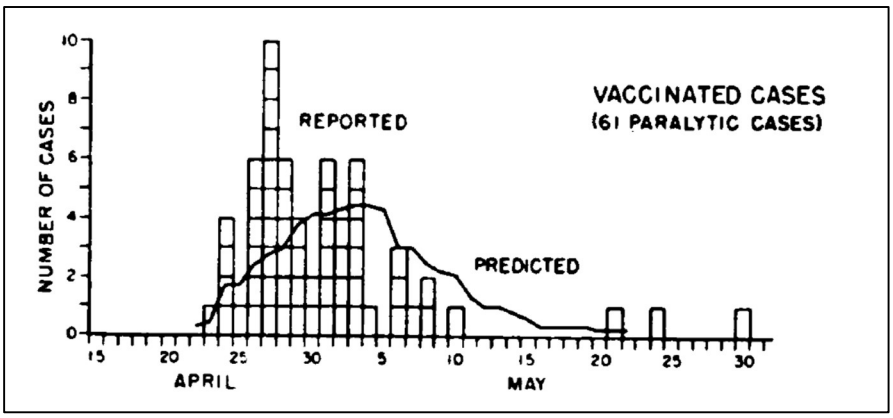
On April 24, 1955, a wave of polio cases was reported among vaccinated children and their families. Two vaccine lots (6039 and 6058) produced by Cutter Laboratories of Berkeley, California, were implicated. A comprehensive investigation revealed that the virus in these two lots had not been properly inactivated.

By the time the defect was detected, approximately 200,000 children had already been vaccinated with these lots.

The outcome: 204 individuals were affected—79 vaccinated children, 105 family members who had contact with vaccinated individuals, and 20 others in the community. Eleven deaths were recorded (Langmuir et al., 1955).

The disease in the "vaccinated" individuals was more severe than in naturally infected patients. The outbreak was associated with the Mahoney strain of poliovirus, a highly virulent strain (Fig. 3).

Fig. 3 Polio cases among vaccinated individuals compared to the expected outcome of such an infection, based on studies involving the injection of the virulent Mahoney strain virus into the drum-muscle of monkeys (Langmuir et al., 1955; Bodian, 1954).



Polio, East Germany – 1960

In May 1960, approximately 290,000 individuals in East Germany were vaccinated with the Lederle-Cox live attenuated polio vaccine. Forty-eight suspected cases of vaccine-associated poliomyelitis were reported. Of these, 25 cases occurred within four weeks of vaccination (17 in vaccinated individuals and 6 in their contacts; Raetting, 1962).

Rabies, Brazil – 1960

Between November 11 and 24, 1960, 18 cases of human rabies were reported in Fortaleza, Ceará, Brazil. All affected individuals had been bitten by stray dogs and subsequently vaccinated with a locally produced inactivated rabies vaccine.
Fourteen of the victims had received three or more doses of vaccine.
Of 66 individuals vaccinated, 18 developed encephalomyelitis and died.
The vaccine, produced from sheep brain tissue and inactivated with 0.5% phenol (following the method of Fermi, 1908), was found to be inadequately inactivated (Pará et al., 1964; Pará, 1965).

Inactivated Measles and RSV Vaccines – 1960s

In the 1960s, an inactivated measles vaccine was developed based on whole virus inactivation using formaldehyde, with aluminum hydroxide as an adjuvant.
Following widespread use, it became evident that vaccinated individuals experienced more severe disease upon exposure to wild-type virus, a phenomenon termed "atypical measles" (Fulginiti et al., 1967).
This phenomenon was likely due to the induction of a primary immune response producing non-protective antibodies directed at nonspecific epitopes.
Formaldehyde inactivation was presumed to damage critical protective epitopes.
A similar phenomenon occurred during clinical trials of a formalin-inactivated Respiratory Syncytial Virus (RSV) vaccine.
Among vaccinated children, 80% required hospitalization, and two children died, leading to the cessation of the use of inactivated vaccines for measles and RSV (Kapikian et al., 1969; Kim et al., 1969; Castilow et al., 2007).
Studies suggested that this adverse phenomenon might be characteristic of viruses within the Paramyxoviridae family (De Swart et al., 2002; 2007).

Swine Influenza, United States – 1976 (Neustadt and Fineberg, 1978)

In January 1976, an outbreak of respiratory illness occurred among soldiers at Fort Dix, with one soldier, David Lewis, dying from infection with an H1N1 influenza virus.
In March 1976, serological testing revealed that approximately 500 soldiers had been exposed to the virus (serological evidence of infection).
With support from the CDC and political advocacy by President Gerald Ford, a decision was made to vaccinate the entire U.S. population (approximately 220 million people).
Initial testing was conducted on 3,000 volunteers. Based on the reported results, a decision was made on June 21, 1976, to approve adult vaccination.
Two vaccine formulations were produced:

1. A monovalent vaccine containing inactivated H1N1 influenza virus.
2. A bivalent vaccine containing inactivated H1N1 virus and the seasonal Victoria/A strain, intended for high-risk groups and adults over 65 years of

age.

Manufacturers (Wyeth, Parke-Davis, Merrell, and Merck) demanded and received indemnity from the government against liability for adverse effects.

The vaccination campaign commenced on October 1, 1976. Children were initially excluded, as an appropriate pediatric dose had not yet been established.

On October 11, three elderly individuals in Pittsburgh died shortly after receiving the vaccine.

Following the start of vaccination, additional deaths and adverse events were reported.

On December 16, after approximately 40 million people had been vaccinated, the campaign was halted.

The vaccination effort ultimately resulted in 532 reported cases of Guillain-Barré syndrome and 32 deaths.

Rotavirus Vaccine, United States – 1999

The first rotavirus vaccine approved for use was the live attenuated *Rotashield* vaccine, developed by Albert Kapikian of the National Institutes of Health (NIH) and subsequently transferred to Wyeth Laboratories for further development and clinical research. The vaccine was introduced into use in the United States in August 1998.

By March 18, 1999, a total of 62 reports of adverse events following vaccination had been submitted to the Vaccine Adverse Event Reporting System (VAERS), including 3 cases of intussusception (Wharton, 2000). By June 17, an additional 9 reports of intussusception were received.

On June 13, the Director of the Centers for Disease Control and Prevention (CDC), Jeffrey Koplan, decided to suspend the use of the vaccine pending completion of an investigation into the matter (Schwartz, 2012). The official announcement regarding the suspension of vaccine use was made on July 16, 1999 (CDC, 1999).

During the approximately nine months in which the vaccine was in use, approximately 600,000 infants were vaccinated (Smith et al., 2016; Khare et al., 2003).

Vaccination recommendations included three doses administered at 2, 4, and 6 months of age. The adverse event of intussusception was observed predominantly following the first vaccine dose, and it was found that the risk of developing intussusception was increased by a factor of 21.7–29.4 among vaccinated infants compared to unvaccinated individuals (Murphy et al., 2001).

Swine Influenza, Narcolepsy, and the *Pandemrix* Vaccine – 2009

In the first half of 2009, a respiratory syndrome was observed in Mexico, later identified as influenza caused by the H1N1 virus. Although there is no consensus regarding the virus's origin, it is estimated that the initial appearance occurred in Mexico (Mena et al., 2016), and it is attributed to a 5-year-old child named Edgar Fernandez.

On April 12, the Mexican authorities reported outbreaks of an influenza-like respiratory illness to the World Health Organization (WHO). Soon thereafter, reports of virus identification emerged from the United States as well, and on April 15 and 17, the Centers for Disease Control and Prevention (CDC) diagnosed cases in humans in California, which were confirmed on April 23 as H1N1 cases (Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team, 2009). Additional cases were subsequently diagnosed in various countries, raising concerns about a potential pandemic influenza outbreak.

Since 2003, there had been fears of a pandemic influenza outbreak, particularly centered on the H5N1 avian influenza virus (Robertson and Inglis, 2011). The low immunogenicity of the H5N1 strain in humans led to the decision to include an adjuvant in the vaccine formulation. The WHO regarded the addition of an adjuvant not only as a means to enhance the immune response but also as a strategy to conserve antigen and expand vaccine coverage for the global population (WHO, 2005).

As part of the race to develop a vaccine, the European Union approved an accelerated registration process known as "mock-up vaccine" registration (EMA, 2008), based on research and development efforts for a pandemic influenza vaccine. These studies were based on the H5N1 avian influenza virus strain. In May 2008, the EMA (within the pandemic preparedness framework) approved a vaccine named *Prepandrix*, developed by GlaxoSmithKline (GlaxoSmithKline, 2008). In September 2009, the EMA approved the manufacture and marketing by GSK of a vaccine based on the A(H1N1)pdm09 strain, derived from the "pre-pandemic" H5N1 vaccine development (the vaccine was not approved for use in the United States). The new vaccine by GSK was named *Pandemrix* (EMA, 2009a).

In the manufacturing process of the vaccine containing the A(H1N1)pdm09 strain, GSK utilized a novel adjuvant, AS03. This adjuvant had not been previously used in any commercial vaccine, except in clinical trials conducted with the H5N1 strain (Rümke et al., 2008; Chu et al., 2009). *Pandemrix* was used in two dosage forms: 0.5 mL for individuals aged 10 years and above, and 0.25 mL for children aged 6 months to 9 years (EMA, 2009b).

The rapid registration of *Pandemrix* under the mock-up framework implied that at the time of its approval, it had been administered to fewer than 200 children aged 3–9 years, and to no children under the age of 3 (Baker and Snape, 2014).

During 2010, concerns arose in Finland and Sweden following an increase in cases of narcolepsy among children and adolescents who had been vaccinated with *Pandemrix*. As narcolepsy is uncommon in children under 10 years of age (Stores, 1999), these events generated significant concern.

The first report suggesting a possible association between *Pandemrix* vaccination and narcolepsy was made on August 18, 2010, when the Swedish Medical Products Agency reported a cluster of six cases of narcolepsy in adolescents aged 12–16 years, occurring approximately two months post-vaccination (MPA, 2010a). Simultaneously, in Finland, in May 2010, a narcolepsy expert named Partinen reported concerns to health authorities regarding a potential link between *Pandemrix* and narcolepsy cases.

On August 24, 2010, the Finnish National Institute for Health and Welfare (THL) announced the suspension of *Pandemrix* vaccination pending a comprehensive investigation into the matter (THL, 2010; EMA, 2010b).

Investigations conducted by the EMA (2010a) and other national regulatory agencies confirmed the association between the use of the *Pandemrix* vaccine and the occurrence of narcolepsy.

The incidence of narcolepsy is estimated at approximately 0.74–1.37 cases per 100,000 persons per year (ECDC, 2012), and manifestation below the age of 10 years is considered quite rare. A study examining the incidence of narcolepsy in Finland between January 1, 2009, and August 16, 2010, found that vaccination with *Pandemrix* was associated with a 12.7-fold increase in narcolepsy cases among children and adolescents aged 4–19 years (THL, 2011; Fig. 4).

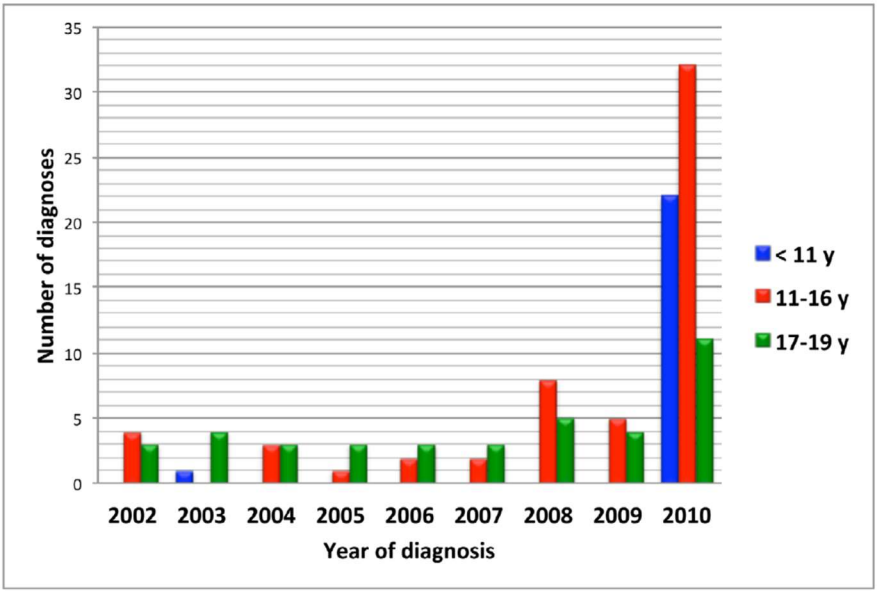
A study conducted in Sweden demonstrated a fourfold increase in narcolepsy cases among vaccinated children. Data collected in Sweden between October 2009 and December 2010 indicated an incidence rate of 4.2 cases per 100,000 vaccinated individuals compared to 0.64 cases per 100,000 unvaccinated individuals (MPA, 2010b). According to a Swedish report dated June 2, 2010, a total of 769 neurological adverse events were reported following vaccination, of which 187 were classified as severe, including 27 deaths. Investigation into these deaths concluded that in four cases, a causal link to *Pandemrix* vaccination could not be excluded (Lakemedelsverket, 2010).

In Ireland, the incidence of narcolepsy between April 2009 and December 2010 was found to be 5.8 cases per 100,000 among vaccinated children, compared to 0.5 per 100,000 among unvaccinated children (DOHC.IE, 2010).

The ECDC VAESCO report confirmed the association between *Pandemrix* vaccination and narcolepsy among children aged 5–19 years in Finland and Sweden, consistent with national reports from these countries (ECDC, 2012).

The strong association observed in countries such as Ireland, Finland, and Sweden was likely due to national vaccination policies that overwhelmingly recommended vaccination of the entire population from 6 months of age almost exclusively with *Pandemrix*, alongside high vaccine uptake rates (Finland: 75%; Sweden: 67%; Ireland: 39–47%). Additionally, narcolepsy is known to have a strong genetic predisposition, particularly in Northern European populations (Partinen et al., 2012).

Fig. 4: Narcolepsy in individuals under 20 years of age in Finland following vaccination with the Pandemrix vaccine (Partinen et al., 2012).



Manufacturer Liability:

Due to the urgency of pandemic response and the need to rapidly deploy vaccines to the public, vaccine manufacturers demanded, primarily from governments of developed countries, indemnity from liability for potential safety events occurring after vaccine administration (WHO, 2012).

In Germany, concerns were expressed regarding the use of *Pandemrix*. Michael Kochen, President of the German College of General Practitioners and Family Physicians, argued—even before the vaccine's deployment—that *Pandemrix* had not been sufficiently tested to guarantee its safety for millions of people, particularly young children and pregnant women. His primary concern related to the adjuvant component (Stafford, 2009).

It is estimated that more than 1,300 young individuals developed narcolepsy following *Pandemrix* vaccination (Vogel, 2015). Some countries accepted responsibility and established compensation funds for affected individuals (e.g., Sweden, Finland, the United Kingdom). In contrast, other countries, such as Ireland, along with GSK, denied responsibility, forcing injured citizens to pursue lengthy and costly legal proceedings against the state and GSK's legal teams (Lintern, 2018).

One notable case involved Aoife Bennett, an Irish woman who developed narcolepsy at age 16 following vaccination. In a protracted and expensive legal battle, she sued the Minister for Health, the Department of Health, the Medicines Registration Authority, and GSK. As the case progressed and trends suggested that she was likely to win, the defendants opted to settle the case out of court (Irish Times, 2019; TheJournal.ie, 2019).

Further revelations indicated that as early as December 2009, GSK possessed data showing a higher incidence of adverse events associated with *Pandemrix* compared to a similar vaccine marketed in Canada. However, no one within the company analyzed these data at the time (Doshi, 2018).

Measles Vaccine and Incorrect Diluent, Syria – 2014

Fifteen children, aged 6–18 months, died in Idlib, northwestern Syria, following the administration of a measles vaccine. The incident occurred after an error led to the use of a muscle relaxant, *Atracurium*, instead of the required vaccine diluent. This substance is typically used during anesthesia prior to surgical procedures. Investigation of the incident revealed that vials of the substance had been mistakenly included in the vaccine shipment at the distribution center (WHO, 2014; Cousins, 2014).

Dengue – Sanofi Vaccine, 2017

In April 2016, the World Health Organization (WHO) approved the use of *Dengvaxia*, Sanofi's dengue vaccine, and recommended its use in regions with high disease prevalence. Following this recommendation, and after intensive efforts by Sanofi to persuade the Philippine health authorities, a mass vaccination campaign began in April 2016 with the aim of vaccinating approximately 800,000 children.

Despite clear warnings published by one of the leading experts in the field, Dr. B. Scott Halstead, the WHO did not deem it necessary to halt the widespread vaccination campaign with this vaccine among children in the Philippines.

In 2015, the vaccine's data were published in the *New England Journal of Medicine* (Hadinegoro et al., 2015). The data presentation was structured in a way that suggested the vaccine was safe for use. However, Halstead and another researcher decided to reanalyze the data and published their findings in the scientific journal *Vaccine* (Halstead and Russell, 2016).

After analyzing the data, the researchers concluded that there was a significant safety concern associated with the vaccine. This issue was not overlooked by WHO experts, who, in their Strategic Advisory Group of Experts (SAGE, 2016) recommendations, stated that the decision to use the vaccine in any given country required careful evaluation of the local epidemiological situation. Although not explicitly stated, their guidance implied that vaccination should target children previously exposed to the virus.

According to Halstead, this was precisely the problem: he asserted that the WHO's position was not sufficiently decisive. He strongly contended that the vaccine should not be used without first confirming the serological status of the recipient. Nevertheless, the vaccine continued to be administered.

By late 2017, accumulating safety data associated with the vaccine revealed the phenomenon known as *antibody-dependent enhancement* (ADE)[2]. On November 29, 2017, Sanofi Pasteur halted the vaccination campaign, and an investigation was launched in the Philippines against both the company and involved government officials.

Contaminants in Vaccines

By definition, vaccines are intended to be "sterile," meaning free from contaminating agents, even if these agents are non-pathogenic. Over the years, several reports have documented instances where vaccines were found to be contaminated.

[2] Dengue is a viral disease (caused by a Flavivirus) transmitted by mosquitoes, with four distinct serotypes (DENV-1 to DENV-4). While it often causes fever alone, it can progress to severe illness or death. Epidemiological studies show that children with maternal antibodies experience severe disease upon first exposure, and secondary infections with a different serotype, especially after a long interval, also lead to more severe outcomes. This is because initial infection generates neutralizing and non-neutralizing antibodies. Over time, heterologous neutralizing antibodies wane, while non-neutralizing antibodies persist, facilitating viral entry into host cells during subsequent infections. This immune-mediated worsening is known as Antibody-Dependent Enhancement (ADE).

SV40 Virus

Contamination of Poliovirus Vaccines:

In the early years of using the live oral poliovirus vaccine (OPV), cell cultures utilized for vaccine production were found to be contaminated with the simian virus 40 (SV40). The virus was identified by researchers during the production of poliovirus vaccines (Sweet and Hilleman, 1960) and was later found to be oncogenic in hamsters (Eddy et al., 1961).

However, no increased incidence of cancer was demonstrated among individuals vaccinated with the contaminated poliovirus vaccines (Lewis and Egan, 1997). Nevertheless, the debate regarding the carcinogenic potential of SV40 persists (Butel and Lednicky, 1999; Butel, 2000).

SV40 is highly prevalent in its natural hosts, where it can establish persistent infections without pathological manifestations. Asian Rhesus Macaques, which served as the source for kidney cell cultures used to propagate the poliovirus, are natural hosts of SV40, and the virus does not induce cytopathic effects in these kidney cells. In contrast, when cultured in African green monkey kidney cells, the virus produces cytopathic effects, and it was through transfers to these cultures that SV40 contamination was detected.

Adenovirus Vaccine Contamination:

In the 1950s, new viruses causing respiratory disease were identified and named *adenoviruses*. Maurice Hilleman, one of the leading researchers and vaccine developers, created the first vaccine against this disease—a formaldehyde-inactivated whole virus vaccine based on adenovirus serotypes 4 and 7 (Gaydos and Gaydos, 1995).

The vaccine was produced in monkey kidney cells and was intended exclusively for the vaccination of military personnel. In the early 1960s, the seed material for vaccine production was found to be contaminated with SV40. After unsuccessful attempts to eliminate the virus from the seed material, the use of the vaccine was discontinued in 1963 (Top, 1975).

Porcine Circovirus

In 2010, a study conducted at the University of California, San Francisco, identified that the *Rotarix* vaccine (a live attenuated rotavirus vaccine developed by GSK) was contaminated with porcine circovirus (Victoria et al., 2010). A thorough investigation conducted by the FDA, GSK, and Merck confirmed the presence of porcine circovirus contamination in the vaccine (GSK, 2010; Merck, 2010; McClenahan et al., 2011).

Although the presence of the virus was not associated with any identified safety concerns, its detection indicated a breach of vaccine purity standards. Consequently,

manufacturers were required to ensure the removal of porcine circovirus from these vaccines in subsequent production.

Contamination with Endogenous Viruses

Avian leukosis virus and endogenous avian retroviruses have been reported as contaminants in live vaccines (such as measles and rubella vaccines) produced in chicken fibroblast cultures (Tsang et al., 1999; Hussain et al., 2001). However, no evidence of safety concerns among vaccinated individuals has been identified (Hussain et al., 2001).

SRV (Simian Retrovirus): SRV is a simian retrovirus. During testing of *RotaTeq* (Merck's rotavirus vaccine), a genomic fragment with high sequence similarity to SRV was detected. The source of the contamination was traced back to the cell lines (VERO) used for vaccine production (Victoria et al., 2010).

The Veterinary Field

The use of vaccines in veterinary medicine, similarly to human medicine, is extensive, essential, and central to the management and control of various diseases.

Scotland – 1930s: One of the earliest reported incidents involving contaminated veterinary vaccines occurred in the 1930s (Cuille, 1939). An inactivated vaccine (formaldehyde-treated) against "Louping ill," produced from sheep brain tissue (Gordon, 1946), resulted in the infection of over 1,000 sheep with scrapie.

Foot-and-Mouth Disease, Italy: Outbreaks of foot-and-mouth disease in Italy during 1985 and 1989 are believed to have been caused by the use of a vaccine that had not been properly inactivated with formaldehyde. Subsequently, formaldehyde was replaced by binary ethyleneimine (BEI) as the inactivating agent for the production of this vaccine (Valarcher et al., 2008).

Adenoviruses: In China, live Newcastle disease vaccines contaminated with adenovirus and infectious anemia virus were found responsible for widespread outbreaks of viral hepatitis with inclusion bodies (IBH) (Su et al., 2018a,b).

Egg Drop Syndrome ’76: Egg Drop Syndrome '76 is considered a disease that was, among other factors, disseminated via contaminated vaccines. This hypothesis was proposed in a study published in 1977, although it was not definitively confirmed by subsequent research (McFerran et al., 1977; McFerran, 1979).

Retroviruses

Retroviruses are classified as either exogenous or endogenous, depending on their mode of transmission (Gifford and Tristem, 2003). Endogenous retroviruses are viruses integrated into the host genome (proviruses) and are transmitted vertically

from the host to its offspring. Most endogenous viruses are nonfunctional due to mutations or genetic degradation. However, some retain their infectivity, become exogenous, and can infect the host and other animals.

Leukosis and Vaccines

Marek's disease vaccines were found to be contaminated with exogenous leukosis virus, identified in four different vaccine batches. According to reports, the limited use of these batches was not associated with any clinical manifestation (Zavala and Cheng, 2006). The presence of endogenous leukosis viruses has also been reported in Marek's disease vaccines (Barbosa et al., 2008).

In China, leukosis virus was identified as a contaminant in live Newcastle disease vaccines (Zhao et al., 2014). A retrospective study in China examined 918 batches of live poultry vaccines manufactured before 2010. Three types of vaccines (Newcastle disease, fowlpox, and infectious bursal disease) were found to be contaminated with leukosis virus, with the strains corresponding to field viruses involved in severe poultry outbreaks and substantial economic losses between 2006 and 2009 (Mao et al., 2020).

Reticuloendotheliosis Virus (REV) as a Vaccine Contaminant

REV and Fowlpox Vaccines: Fadly and Witter demonstrated through laboratory and field studies that reticuloendotheliosis virus (REV) was a contaminant in fowlpox vaccines (Fadly and Witter, 1997). Other studies investigating fowlpox vaccines similarly identified contamination with REV (Awad et al., 2010). A fowlpox vaccine contaminated with REV was reported to cause neoplastic disease in a heavy breeder flock (Fadly et al., 1996).

REV and Marek's Disease Vaccines: Marek's disease vaccines have also been found contaminated with REV (Bagust et al., 1979). In Israel, Dr. Bendheim reported in 1973 neoplastic disease following the vaccination of turkeys with a fowlpox vaccine contaminated with REV. This investigation was initiated following reports of severe outbreaks of neoplastic disease in turkeys in Israel between 1966 and 1969; however, the specific type of neoplastic disease was not identified (Bendheim, 1973).

During the 1970s, reports from Japan and Australia indicated that contaminated Marek's disease vaccines carrying REV caused growth retardation, immunosuppression, and poor feathering (Kawamura et al., 1976; Yuasa et al., 1976; Taniguchi et al., 1977; Jackson et al., 1977).

REV can integrate into the DNA genome of viruses such as Marek's disease virus (as a provirus) or contaminate other vaccines like fowlpox vaccines (Hertig et al., 1997; Cui et al., 2010; Biswas et al., 2011; Moore et al., 2000).

REV and Other Poultry Vaccines: Following cases of visceral lymphomas in a breeder farm in China, all vaccines used in the affected flock were examined. The investigation revealed contamination in the *Rispens CVI988* Marek's disease vaccine and in a combined live Newcastle disease + infectious bronchitis vaccine (Wei et al., 2012).

Chicken Infectious Anemia Virus (CIA)

Chicken Infectious Anemia Virus (CIA) was first identified as a contaminant in Marek's disease vaccines in Japan in 1979 (Yuasa et al., 1979). In a study examining vaccines marketed in Brazil, the virus was detected as a contaminant in vaccines for Marek's disease, infectious bronchitis, fowlpox, Newcastle disease, and Egg Drop Syndrome (Varela et al., 2014).

Pestiviruses as Vaccine Contaminants

On March 9, 1999, the Netherlands issued an alert to all European Union member states following the emergence of a disease resembling bovine viral diarrhea (BVD), accompanied by high mortality, after vaccination with a live IBR vaccine produced by Bayer, *Bayovac IBR Marker Vivum*, which in some countries was licensed and marketed by Hoechst under the name *Rhinobovin Marker Live*.

The initial report focused on batch WG4622, the only batch marketed at that time in the Netherlands. Italy subsequently reported a similar outbreak associated with batch 02U056 of *Rhinobovin Marker Vivum*. Both batches originated from the same production batch, 77/V4392.

On February 26, the Dutch Veterinary Institute reported the detection of BVD virus in the vaccine. On March 26, the Italian authorities suspended the use of both vaccines. Laboratory testing in Italy also confirmed contamination with BVD virus. The source of the contamination was identified as bovine fetal serum used in the cell culture production process (Falcone et al., 1999). Additional tested batches were also found to be contaminated.

Border Disease Outbreak in Goats

Five herds comprising a total of 276 female goats experienced a severe outbreak of Border Disease following vaccination with an *orf* (contagious ecthyma) vaccine that was contaminated with *Pestivirus*. Two years after the outbreak, the infected herd transmitted the infection to nearby sheep and cattle herds (Løken et al., 1991).

In 1991–1992, Border Disease virus was identified in Israel as a contaminant in a fowlpox vaccine manufactured by Merial. The company acknowledged responsibility and compensated the affected farmers.

In Tunisia, Sheep Pox vaccines were found to be contaminated with *Pestivirus*, and their use led to outbreaks of Border Disease in the country (Thabti et al., 2002). The implicated vaccine was a locally produced vaccine manufactured in ovine kidney cell cultures. Eleven out of fourteen batches tested were found contaminated with *Pestivirus* (Russo et al., 1999).

Contaminated Swine Vaccine, France – 1984

In January 1984, reports emerged of disease outbreaks among swine herds in northern and western France, characterized by high morbidity and mortality rates, especially among piglets. All the affected herds had been vaccinated against Aujeszky's disease using a single vaccine batch (33DO4). A correlation was found between the severity of symptoms and the timing of vaccination in pregnant sows. Serological testing revealed that the vaccine was contaminated with a virus resembling Border Disease virus (*Pestivirus*) (Vannier et al., 1988).

Contamination of Ovine Pox Vaccine with Pseudorabies Virus, Uzbekistan - 2012

A total of 228,000 doses of ovine pox vaccine, contaminated with swine Aujeszky's disease virus (pseudorabies virus), were smuggled from Kazakhstan into Uzbekistan and used to vaccinate sheep herds. Approximately 2,000 sheep died following vaccination with the contaminated product (Promed, 2013).

Bluetongue Virus (BTV) as a Vaccine Contaminant

United States – 1992: In 1992, a veterinarian observed a series of abortions and occasional deaths among pregnant bitches. A common factor among the cases was vaccination with a multivalent live vaccine 3–4 weeks prior to the events (Evermann et al., 1994). Investigation revealed that both the vaccine and the seed material were contaminated with Bluetongue Virus (BTV) serotype 11 (Levings et al., 1996). The manufacturer subsequently recalled all vaccine batches. A similar event was reported in 1993 (Akita et al., 1994).

Israel: In Israel, ovine pox vaccines and Lumpy Skin Disease vaccines were reported to be contaminated with BTV (Bumbarov et al., 2016).

Vaccines as a Cause of Sarcoma

In 1991, suspicions of fibrosarcoma development following vaccination in cats were first reported (Hendrick and Goldschmidt, 1991). Two vaccines were particularly associated with these reports: rabies vaccines and feline leukemia virus vaccines. Both vaccines contained aluminum hydroxide as an adjuvant. The phenomenon was subsequently demonstrated in ferrets (Munday et al., 2003) and also reported in dogs (Vascellari et al., 2003). Although the exact etiology remains unclear, the prevailing hypothesis is that vaccine-induced inflammatory processes are responsible

for the development of these tumors.

Is Neonatal Bovine Pancytopenia (BNP) Associated with Vaccines?

In 2006, a new and unusual disease in calves was observed in Germany (which reported the highest number of cases) and in other European countries (Friedrich et al., 2009; Bell et al., 2010). The disease was characterized by hemorrhages from various organs and was also referred to as "blood sweating" or "bleeding calf syndrome."

After years of investigation into the origin of the disease, suspicion arose regarding a possible association with an inactivated Bovine Viral Diarrhea (BVD) vaccine manufactured by Pfizer, named *Pregsure® BVD*[3], which had been introduced in Europe in 2004. It was hypothesized that the vaccine contributed to the occurrence of the disease.

On July 15, 2010, the European Medicines Agency (EMA) ordered the recall of the vaccine and its withdrawal from the market. Pfizer cooperated with the process, although the company claimed that there was no causal link between the vaccine and the disease. Pfizer continued to market the vaccine in New Zealand but ceased its distribution there one year later following reports of disease occurrence.

As of February 2011, it was estimated that at least 4,500 calves had died in Europe from this condition (Paul-Ehrlich-Institut, 2011). Cessation of Pregsure® BVD vaccine use led to a decline in the incidence of the disease (Reichmann et al., 2016).

The vaccine was produced in MDBK (Madin-Darby Bovine Kidney) cell lines (Madin and Darby, 1958) and contained the adjuvant Procison A™. Vaccination with Pregsure® BVD stimulated the production of antibodies directed against MHC class I molecules expressed on MDBK cells[4]. Residual bovine cell proteins present in the vaccine triggered a specific alloantibody response against MDBK-derived MHC class I antigens. These antibodies were subsequently transferred to the newborn calf through the colostrum and specifically targeted hematopoietic cells with high MHC class I expression, such as leukocytes, platelets, and bone marrow cells (Bell et al., 2015).

Pathogenesis of Neonatal Bovine Pancytopenia

The Pregsure® BVD vaccine contained MHC class I antigens originating from the bovine cell cultures used for vaccine production.

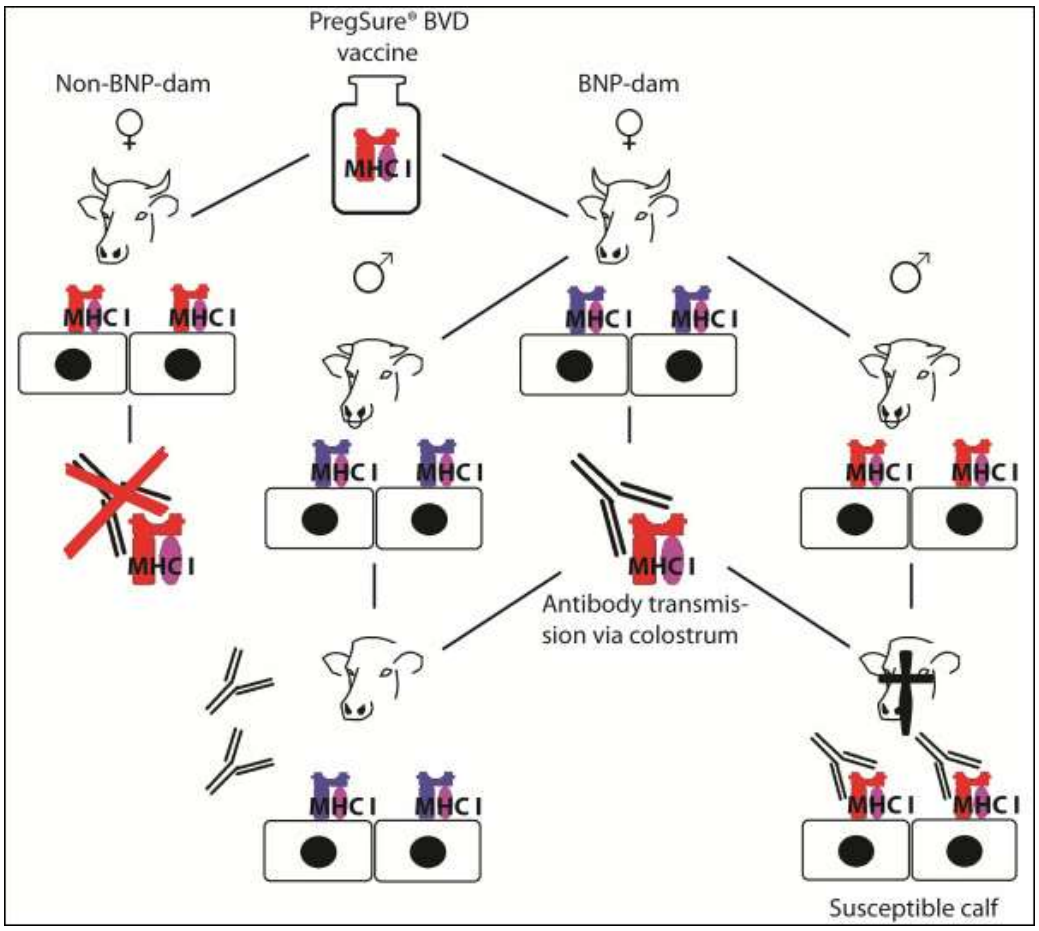
If the vaccinated cows shared identical MHC class I antigens with those present in the vaccine, no adverse effects were expected. However, in cases where there was MHC class I disparity between the vaccinated cows and the vaccine-derived antigens, cows

[3] BVD PregSure is an inactivated vaccine intended for the immunization of cattle against Bovine Viral Diarrhea Virus (BVD) type 1.

[4] Madin-Darby Bovine Kidney Epithelial Cells.

developed alloantibodies against the vaccine MHC class I molecules.
These antibodies were transferred to the newborn calf via colostrum. If the calf expressed MHC class I antigens recognized by these maternal antibodies, the calf would develop the disease.

Fig. 5: Model of the BNP-etiology (Deutskens et al., 2011)



Recombination Between Live Attenuated Vaccines and the Emergence of a Virulent Virus

Australia, 2008: Beginning in early 2008, infectious laryngotracheitis (ILT) viruses belonging to genotypes Class 8 and Class 9 were identified in Australia (Blacker et al., 2011). These strains were diagnosed as virulent and were involved in severe outbreaks of ILT across various regions of Australia. Mortality rates reached up to 17.6% in certain cases (Lee et al., 2012). In Australia, three types of live vaccines against ILT are available: two vaccines manufactured by Zoetis, based on local strains (SA2 and 20A), classified under Class 1 genotype. In 2006, Intervet registered a live vaccine based on the Serva strain. This strain, originally from Europe, had never been previously identified in Australia and is classified as Class 7 genotype (Blacker et al.,

2011). Investigation into the characteristics of the "new" viruses (Class 8 and Class 9) revealed that they originated from recombination events between the live vaccines based on the local strains and the strain contained in the Intervet vaccine (Lee et al., 2012).

Denmark, 2019: In July 2019, an outbreak of disease in pigs, known as Porcine Reproductive and Respiratory Syndrome (PRRS), was reported in Denmark. The disease is caused by an RNA virus classified as Betaarterivirus suid 1 (genus *Arterivirus*). The disease was initially diagnosed in a boar stud farm and subsequently spread to 38 pig farms through virus-contaminated semen. Phylogenetic analysis of the virus revealed that the strain involved in the outbreak resulted from recombination between two vaccine strains.

The live vaccines implicated in this recombination event were: a live vaccine manufactured by Hipra, named Unistrain PRRS (Amervac strain), and a live vaccine produced by Zoetis, named Suvaxyn PRRS (96V198 strain). The newly emerged recombinant virus demonstrated high infectivity and caused severe disease, despite originating from attenuated strains (Kvisgaard et al., 2020).

Escape of Infectious Agents from Vaccine Production Facilities or Research Laboratories into the Environment (Cases of Laboratory Worker Exposure Are Not Included)

Work involving highly pathogenic viruses requires strict adherence to protocols and the use of appropriate standards according to clearly defined biosafety regulations. Nevertheless, incidents involving laboratory workers becoming infected during work, or the escape of virulent viruses into the environment, have occurred repeatedly. Here, we focus exclusively on events where the infectious agent "escaped" from a production or research facility.

1978, Smallpox, Birmingham, United Kingdom:

Janet Parker (aged 40), a medical photographer, died following infection with smallpox. The event, highly unusual at the time, was thoroughly investigated. It was found that beneath her workplace, located at the Medical School of the University of Birmingham, there was a research laboratory handling the smallpox virus, directed by Professor Henry Bedson (Shooter et al., 1978).

Following the incident, more than 500 individuals suspected of exposure to the virus were vaccinated. On September 5, Janet Parker's father (aged 77) died while in isolation, apparently from a heart attack. The following day, Professor Henry Bedson committed suicide, leaving behind a letter stating:

"I am sorry to have misplaced the trust which so many of my friends and colleagues have placed in me and my work."

Five days later, Janet Parker succumbed to the disease (Fig. 6). In addition to Janet Parker, her mother was also diagnosed with smallpox, though she experienced a relatively mild form of the illness and recovered. Janet Parker was the last recorded victim of smallpox.

Fig. 6: A news report following the death of Janet Parker


BIRMINGHAM
Evening Mail
HOME EDITION
Mystery of city killer virus stays unsolved after probe
SMALLPOX VICTIM DIES
He's back
Soccer boy in sight battle

1966 – Outbreak of Smallpox in West Midlands, United Kingdom:
In 1966, an outbreak of smallpox was recorded in the West Midlands, United Kingdom. The outbreak was caused by a less virulent virus, *Variola minor*. A total of 73 individuals developed the disease, with no fatalities reported. Epidemiological investigation suggested that the index case was a 23-year-old photographer who worked in the Department of Anatomy at the University of Birmingham Medical School. The Department of Anatomy was located one floor above the virology laboratory, which was conducting research involving smallpox viruses.

September 2014 – Belgium:
A virulent poliovirus type 3 (WPV3) escaped into the sewage system and subsequently into the environment from the GSK Rixensart vaccine production facility in Belgium (Duizer et al., 2016).

April 2017 – The Netherlands:
A virulent poliovirus type 2 (WPV2, MEF-1 strain) was released into the environment as an aerosol at high viral concentration from a vaccine production facility in the Netherlands. An employee became infected and subsequently excreted the virus into the environment (sewage system; Duizer et al., 2017).

2019 – Biological Plant, China:
A leak from a brucellosis vaccine production facility led to the infection of more than 3,000 individuals with brucellosis.

September 2020 – The Netherlands:
Media outlets in the Netherlands reported the detection of poliovirus in sewage near a major vaccine production facility, Bilthoven Biologicals. The exact source of the virus remains unclear, and it is unknown whether any workers were exposed. The sewage from which the virus was isolated collects wastewater from additional nearby research centers. The area also houses the Intravacc research institute and the RIVM (National Institute for Public Health and the Environment), which includes laboratories working with poliovirus. Bilthoven Biologicals produces approximately half of the 60 million doses of polio vaccine manufactured globally each year.

The Veterinary Field

In the veterinary field, the most frequent "leakages" involve the Foot-and-Mouth Disease (FMD) virus.

- **1966 – Sweden:** An outbreak occurred in Skaane, Sweden, following the "escape" of FMD virus from a laboratory in Denmark (Gloster et al., 1982).
- **1987 – Germany:** An outbreak of FMD in Germany was attributed to the escape of a virus strain from a nearby vaccine production facility (Strohmaier, 1990).
- **1993 – Russia:** An outbreak of FMD was attributed to the "escape" of a vaccine strain (Valarcher et al., 2008).
- **1995 – Venezuelan Equine Encephalitis (VEE):** VEE is a viral disease transmitted by mosquitoes in the Western Hemisphere, affecting equines (horses, donkeys, and mules) and capable of infecting humans. In 1995, a severe outbreak was recorded in Venezuela and Colombia, with at least 10,000 cases and 11 deaths reported in Venezuela (Brault et al., 2001) and approximately 75,000 cases and 300 deaths reported in Colombia (Rivas et al., 1997). Researchers investigating the outbreak hypothesized that the virus likely escaped from a laboratory in Venezuela, which was also identified as the initial epicenter of the outbreak (Brault et al., 2001).
- **August 2007 – Pirbright Laboratory, Surrey, United Kingdom:**
  A leakage of the FMD virus from either the Merial research facility or the adjacent government research institute led to the infection of eight cattle farms in the Surrey area, causing damages estimated at £200 million.
  A total of 278 infected animals were identified, and 1,578 animals were culled (Cottam et al., 2008). Previous incidents of FMD virus leakage from the government research institute had also been documented in 1960 and 1967 (Hyslop, 1970; Donaldson, 1979).

Conclusions

Vaccines have marked a pivotal advancement in medicine's ability to combat various diseases and represent one of the greatest achievements in public and animal health. Considering the extensive global use of vaccines, it is evident that, even when accounting for the serious events reported over the years, these incidents represent a relatively small and limited number.

The frequency and scale of adverse events associated with vaccines have steadily declined over time. Early deficiencies in manufacturing technologies have been replaced by advanced production methods, improved diagnostic techniques, stringent quality control measures, and robust regulatory frameworks. Collectively, these advancements have significantly reduced the safety risks associated with vaccination.

Major progress in biomedical research has provided science with enhanced capabilities for the development of more advanced, efficient, and safer vaccines. These technological innovations are expected not only to reduce the reliance on animals for research and development—an important ethical consideration—but also to further enhance vaccine safety.

While the development of vaccines has not been without setbacks, failures, and human tragedies, these events do not detract from the profound contribution of vaccines to the health of human and animal populations worldwide.

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