History of Medicine and Ethics

Balto and Togo during the cold winter of Alaska (1925): the two canine heroes in the fight against diphtheria

OMAR SIMONETTI[1], LAVINIA COSIMI[1], MARCO CIGANA[2], ARTURO PENCO[3], STEFANO DI BELLA[4], MARIANO MARTINI[5-7]

[1] Infectious Diseases Unit, University Hospital of Trieste, Italy; [2] Emergency Department, San Jacopo Hospital, Pistoia, Italy; [3] Department of Pediatrics, Latisana-Palmanova Hospital, ASUFC, Udine, Italy; [4] Clinical Department of Medical, Surgical and Health Sciences, Trieste University, Trieste, Italy; [5] Department of Health Sciences, University of Genoa, Italy; [6] UNESCO Chair "Anthropology of Health - Biosphere and Healing System, University of Genoa, Italy; [7] Interuniversity Research Center on Influenza and Other Transmissible Infections (CIRI-IT), Genoa, Italy

Keywords

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Summary

In recent years, diphtheria has re-emerged in areas with inadequate vaccination coverage, and Europe has not been spared with several cases among migrants. Diphtheria is a potentially fatal infection caused mainly by toxigenic strains of Corynebacterium diphtheriae. Due to the high mortality rate, especially among young children, the fight against diphtheria is considered one of the first conquests of immunization. In the history of medicine, there is a unique case of an unconventional response to a diphtheria outbreak in which sled dogs were used to overcome the supply difficulties of diphtheria antitoxin. The mass media followed the medical response to the outbreak and raised audience awareness of public health issues. The facts of Nome, Alaska, in 1925 can serve as a catalyst to rethink conventional responses to diphtheria outbreaks in low-income countries today and promote mass media awareness of public health importance.

Notes on the history of active and passive immunization

Ever since the advent of written evidence, it had always been suspected that a person who had recovered from a certain disease became immune to contracting it again. Indeed, some 2,500 years ago, Thucydides (460 BC-404 or 399 BC; Fig. 1), in his description of an epidemic that struck Athens, observed that "No one has ever been affected a second time, or at least fatally" [1].

As early as the Middle Ages, this conviction prompted attempts to elicit immunity to smallpox by inoculating materials taken from the skin of affected patients into healthy subjects, a procedure that was very risky. However, towards the end of the 18th century, an English doctor named Edward Jenner introduced a procedure that was similar, but much safer (Fig. 2). In 1798, he published an investigation into the causes and effects of "Variolae vaccinae", a disease known as "cowpox", which had been discovered in some counties of England. Jenner described 23 cases of subjects whom he first vaccinated with material taken from patients with cowpox and subsequently contaminated with smallpox and observed that these subjects did not contract smallpox (Fig. 2).

Immunity is the body's ability to resist or fight a particular infection or toxin, *i.e.* to defend itself against diseases caused by certain bacteria or viruses; it may occur naturally (following exposure to bacteria or viruses), or it may be elicited through vaccination. Those who are vaccinated against a given disease do not usually contract that disease or else contract it only in a mild form.

As immunization consists of the acquisition of a state of immunity against a specific antigen, it helps the organism to defend itself against diseases caused by certain bacteria or viruses, enabling the subject to resist attack by microorganisms that would otherwise cause an infectious disease (this usually occurs through inoculation) [2]. When immunization results from the administration of a vaccine, it is known as active immunization. By contrast, when the process is activated through immunoglobulins, we have passive immunization.

In the history of public health and the prevention of serious diseases, vaccines have proved very effective, improving people's health worldwide [3]. In countries where vaccines are widely used, many diseases that were once frequent and lethal (*e.g.* polio and diphtheria) [4] have now become rarer or have been brought under control [5]. Indeed, in the case of smallpox, vaccination has enabled the disease to be eradicated.

Background and aims of the study

In recent years, diphtheria has reappeared in areas with poor vaccination coverage. Renewed interest has been raised after the outbreak in the Rohingya migrant camp in Bangladesh in 2017 [6]. In addition, outbreaks have been recorded on the African continent in the last two years. Specifically, at least 13416 suspected cases and

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Fig. 1. Tucidide (Θουκυδίδης, Thūkydídēs) (Alimunte, 460 a.C. - Atene, after 404 a.C., o 399 a.C.) (Adapted by the authors. Public domain – wikipedia commons).

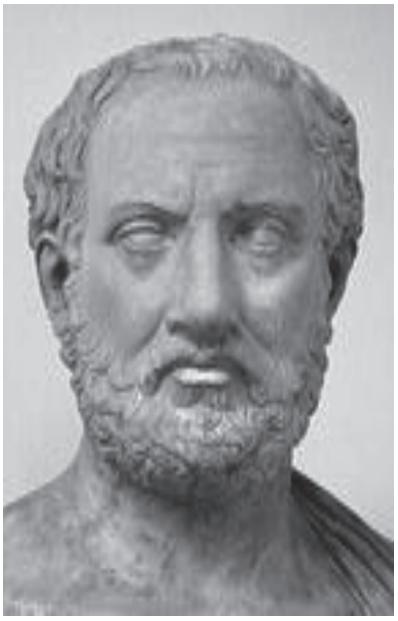
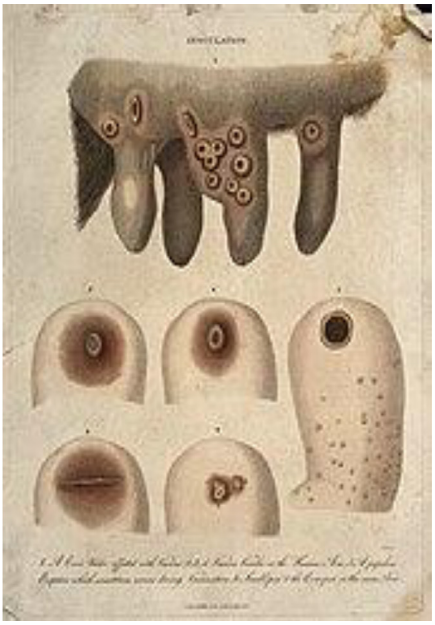


Fig. 2. Jenner's discovery of the link between cowpox pus and smallpox in humans helped him to create the smallpox vaccine. (Adapted by the authors. Public domain - wikipedia commons).



8576 confirmed cases of diphtheria have been registered in Nigeria since May 9, 2022. People with confirmed diphtheria were unvaccinated or partially vaccinated in 63-9% of cases. The main reason for this epidemic is an historical gap in immunization coverage [7]. Europe has not remained untouched. Indeed, between 2022 and 2023 an increase of reported diphtheria cases among migrants in Europe has been recorded. Such disease was correlated to a high volume of asylum seekers arriving by small boats to England and among migrants in Germany during 2022 [8, 9].

The aim of this work is to provide a comprehensive narrative review about the diphtheria epidemic of Nome, Alaska, in 1925. It will provide a new perspective on the success of an unconventional approach to public health emergencies in the history of medicine and may stimulate reflection on the responses to diphtheria outbreaks faced by low-income countries today. Scientific databases (*e.g.* PubMed and Google Scholar) and historical records have been reviewed.

Dogs in medicine

Throughout history, dogs have played significant roles in medical practice, providing emotional support, therapy, and even contributing to disease diagnosis and treatment. The evolution of their involvement in medicine reflects the deep connection between humans and animals, as well as the recognition of their extraordinary sense of smell and emotional sensitivity [10].

In medicine, dogs have been called "medical dogs", serving various roles. They have been used to assist people with visual impairments, to detect diseases such as cancer and epilepsy, to improve human mental and physical health [11, 12].

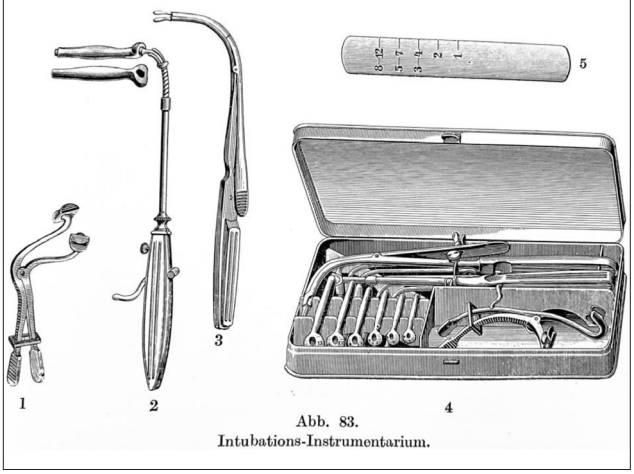
In addition, some dogs are trained to alert their owners in case of imminent emergencies and play an important role in search and rescue, helping to locate people who are lost or buried under rubble following natural disasters or accidents [13, 10]. In summary, dogs' involvement in medicine reflects their versatility, intelligence, and ability to form deep bonds with humans. As further discussed, their presence brought tangible benefits also in the history of preventive medicine.

Notes on diphtheria and the history of its antitoxin

Diphtheria is a potentially fatal infection caused mostly by toxigenic strains of *Corynebacterium diphtheriae*. The disease is usually an acute respiratory infection characterized by the formation of a pseudomembrane in the throat [14]. It spreads easily as the basic reproductive number is 1.7-4.3 [15]. The progression of the respiratory form typically involves prodromal symptoms leading to membranous inflammation of the pharynx, tonsils, or larynx within 2 days. If left untreated, death may occur within 1-2 weeks due to asphyxia resulting from airway obstruction. Toxic cardiomyopathy emerges 1-2 weeks after the onset of respiratory symptoms in 10-25% of patients and contributes to 20-25% of deaths in untreated cases [15, 16].

Diphtheria can be fatal today, as it was at the beginning of the 20th century. The case-fatality ratio for untreated, non-vaccinates cases has been estimated at 29%, and it is estimated to be still 5-10% if treated. Notably, children

Fig. 3. Image representing the instruments used in the early 20th century for intubation. Taken from the chapter on diphtheria of Handbuch der inneren Medizin. Infektionskrankheiten (1911). Imaged revisited by the authors from an hardcover copy of the manual.



under 5 years old face a higher likelihood of death due to symptomatic infection compared to adults over 20 years old, with a relative risk [RR] of 1.5 [95% CrI, 1.4-1.6], due to smaller airways [15, 17, 18].

As can be seen from the manuals of the time, diphtheria was one of the main indications for endotracheal intubation due to airway complications (Fig. 3) [19]. Moreover, systemic manifestations such as myocarditis and neuropathy may also occur. These are due to the diphtheria toxin, an exotoxin produced by the pathogen that inhibits protein synthesis and causes cell death. Skin infections are also possible [14]. Diphtheria toxin is the major known virulence factor of *C. diphtheriae*; the structural gene encoding diphtheria toxin (tox) is carried in the genome of a family of corynebacteriophages. The most virulent strains may carry two or three copies of tox inserted into the genome. Even though tox is of bacteriophage origin, the regulation of toxin production is under bacterial control [14].

C. diphtheriae, a gram-positive bacterium, was one of the first bacterial pathogens to be isolated and cultivated in pure culture. The diphtheria exotoxin is also one of the first toxins to be discovered [20].

As a matter of fact, Edwin Klebs (1834-1913) proved that *C. diphtheriae* was the causative agent of diphtheria in 1883. One year later, Friedrich August Johannes Loeffler (1852-1915) postulated that the damage to the internal organs was caused by a soluble toxin. By 1888, Émile Roux (1853-1933) and Alexandre Yersin (1863-1943) demonstrated that a potent exotoxin was the most important virulence factor for the disease [21].

The control of diphtheria, which was one of the most feared childhood infectious diseases, is considered the first conquest of immunization [22]. Diphtheria antitoxin (DAT) was developed after the demonstration that the blood of diphtheria-immunized animals (mainly horses) was effective in treating sick patients. After the introduction of antitoxin in 1894, the decline in the mortality rate accelerated to an average of over 10 percent per year, and a similar decline was observed after the introduction of vaccination at the end of 1918 in the United States [23]. Interestingly, a recent systematic review found that DAT can reduce mortality by 76%. Thus, antibiotics must be paired with diphtheria antitoxin to limit morbidity also in actual management of the disease [15].

In the late decades of the 19th century, knowledge of hygienic measures, such as isolation, for diphtheria cases was poor. It was common practice to keep the patient in quarantine for 30 days after the onset of symptoms. A 30-day isolation was also required for the re-admission of children to school. Nevertheless, the topic was hardly discussed, as stated in an original paper from Bristol, Great Britain, 1898 [24].

The facts of Nome, Alaska, 1925

The frontier town of Nome in Alaska was settled after the discovery of a gold mine in 1898. The village, located near the Arctic Circle and the Yukon River, was not served by the railroad, and was isolated from the state's major cities during the long winters. In fact, there was no train from Nenana (the local main city) to Nome and horses were unsuitable due to the cold. In addition, traveling by bicycle was too risky, as evidenced by some original diaries of that time [25].

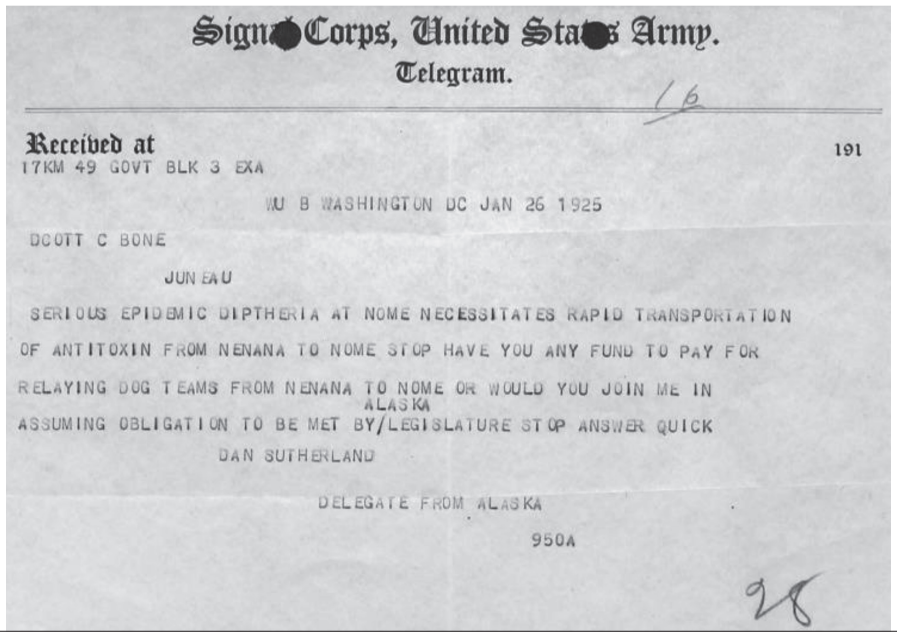
In January 1925, some children of the local Eskimo population began to show symptoms that Curtis Welch, the local doctor, soon recognized as diphtheria. Specifically, he noted a fatal case of tonsillitis and soon thereafter other upper respiratory illnesses in children with pathognomonic membranes. Unfortunately, the only DAT available, manufactured by Lilly's, had expired years earlier. Nevertheless, Welsh decided to use a few thousand units of it [26].

He immediately recognized the need for more DAT, as the Inuit, the indigenous people of Alaska, had little or no immunity to the disease. The first patient was diagnosed on January 11. He immediately notified the fact to Mayor George Maynard and a temporary board of health was set up. Welch continued to make recommendations, which the board implemented, such as closing all public buildings, restricting all public gatherings, restricting the movement of children on all roads, and restricting the movement of adults to official business [26]. From the correspondence of Governor Scott C. Bone (Governor of the Alaska Territory from 1921 to 1925), it is known that expedited transportation of DAT from Nenana to Nome was required beginning January 26, 1925 (Fig. 4).

The H.K. Mulford Co., Philadelphia, had the legal license for the production of medical products such as diphtheria antitoxin. The company was asked to manufacture and ship DAT for the urgent demand in Alaska [27].

In the region of Nome temperatures frequently dropped below -40 °C [28]. Prolonged exposure to these temperatures may result in hypothermia, defined as a body temperature of 35 °C or less. When body

Fig. 4. Bone's correspondence files on the 1925 Serum Run to Nome. Alaska. Office of the District and Territorial Governor. Courtesy provided by Alaska State Library Historical Collections.



Signal Corps, United States Army.
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DCOTT C BONE

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SERIOUS EPIDEMIC DIPTHERIA AT NOME NECESSITATES RAPID TRANSPORTATION OF ANTITOXIN FROM NENANA TO NOME STOP HAVE YOU ANY FUND TO PAY FOR RELAYING DOG TEAMS FROM NENANA TO NOME OR WOULD YOU JOIN ME IN ALASKA ASSUMING OBLIGATION TO BE MET BY/LEGISLATURE STOP ANSWER QUICK

DAN SUTHERLAND

DELEGATE FROM ALASKA

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temperature falls below 32°C, depression of the central nervous system and altered mental status are reported [29]. In case of trauma, mortality increases also because a low body temperature interferes with clotting, impairing platelet adhesion and enzymatic coagulative function, worsening ongoing bleeding [30]. Moreover, prolonged exposure to subfreezing temperatures, can cause tissue ischemia and necrosis through an immediate

Fig. 5. Celebrated sled dog Balto with Gunnar Kaasen, the Norwegian immigrant musher that finally and successfully delivered diphtheria antitoxin to Nome, Alaska in 1925 (Pictures of Public domain - wikipedia commons).

Fig. 6. Leonhard Seppala posing with six of his sled dogs, the first from left to right is the heroic Togo (Pictures of Public domain - wikipedia commons).

cold-induced cell death or after the reperfusion-related inflammatory process [30, 31]. These injuries include the loss of fingers or part of the limbs [32, 33].
The transportation of DAT from Nenana – where the last train station was available – under such extreme environmental conditions required an unconventional method. At such an extreme point in the history of medicine and humanity, dogs were asked to help humans where advances in technology felt short. Indeed, Governor Bone made the decision to deploy a relay of several sled dog teams for the cross-country run. The dog sled trek was not scheduled to begin until January 27, when the train full of DAT units arrived in Nenana. In the end twenty riders and dog teams took part in the voyage. The two most notable teams (Figs. 5, 6) were: Leonhard Seppala (1877-1967) with his lead dog Togo, a Siberian Husky (1913-1929), and Gunnar Kaasen (1882-1960) with his famous lead dog Balto (1919-1933). From January 27 to February 2, the teams covered 674 miles (1085 kilometers) bringing DAT units from Nenana to Nome [27].

Balto in medical mass media and science

Since the success of the DAT run in 1925, commemorative events and memorials have been organized in its honor. The famous statues of Balto and Togo, which can be seen every day in Manhattan's Central Park and Seward Park, show the importance of this collaboration between humans and non-humans in the history of science. In addition, at least 5 films commemorate the history of these sled dogs [34].
Both science and fiction love this unique experience. In fact, in 2023, Moon KL and colleagues published an article in the journal Science entitled: "Comparative genomics of Balto, a famous historic dog, captures lost diversity of 1920s sled dogs" [35]. Thanks to this unconventional approach to preventive medicine, the diphtheria vaccination and the DAT have been known worldwide since 1925.

Conclusions

The history of vaccinology has been considered as the chronicle of medical contributions of vaccinologists and public health practitioners coupled with unconventional methods such as human-animal cooperation [27]. The steady supply of diphtheria treatment, including diphtheria antitoxin, to achieve the best clinical outcomes of high-risk patients was a priority in 1925 as it is in 2024; as recently emphasized [7]. As well described in the recent diphtheria epidemic in Nigeria, the main causes of the outbreak were low vaccination coverage, inadequate availability of drugs, an inefficient cold chain system and cultural barriers combined with environmental factors [36]. Interestingly, in 1925 Alaskans natives believed the disease was caused by an angry supernatural spirit; depicting how cultural beliefs impact health practice acceptance in the present and in the past [37]. It is our opinion that rethinking unconventional approaches to DAT and antibiotics delivery could shape the ongoing diphtheria epidemics in developing countries. Unconventional methods could be hypothesized also to reduce vaccination hesitancy of local populations.
Moreover, as the paper indicates, the facts of Nome were discussed daily by the American public and later left their mark on popular culture. The mass media, then as now, had a major impact on curbing the spread of infectious diseases by raising public awareness and limiting the occurrence of future outbreaks in the years to come [38]. Newspapers and radio that time as modern mass media now follow vaccination campaigns in high-income countries with interest and enthusiasm. Nevertheless, there is a media gap in some parts of the world that are heavily affected by infectious diseases.
We believe that the lessons learned from the 1925 Nome outbreak should both enhance the dissemination of epidemic-related information and promote unconventional approaches to managing and mitigating the ongoing diphtheria epidemics in developing countries. Nevertheless, vaccination must be strengthened worldwide as the most important prevention goal to avoid extreme remedies such as the one of Nome. As a matter of fact, vaccination is able to mitigate epidemic and pandemic respiratory diseases such as influenza; still related to respiratory and cardiovascular mortality also in people under 65 years [39].

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Informed consent statement

Not applicable.

Data availability statement

Not applicable.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' contributions

OS, MM: designed the study. OS: conceived the manuscript. OS, LC, MM: drafted the manuscript. MC, AP, OS, MM: revised the manuscript. OS, LC, MC, AP: performed a search of the literature. SdB, MC, AP:

critically revised the manuscript; conceptualization, and methodology. OS, MM; investigation and data curation. MC, AP, OS, SdB: original draft preparation. OS: review. All authors have read and approved the latest version of the paper for publication.

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Correspondence: Mariano Martini, Department of Health Sciences, University of Genoa, IRCCS San Martino Polyclinic Hospital. Genoa, Italy. Largo Rosanna Benzi, 16132 Genoa.

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