Standing on the shoulders of giants: two centuries of struggle against meningococcal disease

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Meningococcal disease was first clinically characterised by Gaspard Vieusseux in 1805, and its causative agent was identified by Anton Weichselbaum in 1887, who named it *Diplococcus intracellularis menigitidis*. From the beginning, the disease was dreaded because of its epidemic nature, predilection for previously healthy children and adolescents, and high mortality. In the last decade of the 19th century, the concept of serum therapy for toxin-related bacterial diseases was identified. This concept was applied to meningococcal disease therapy, in an independent way, by Wilhelm Kolle, August von Wasserman, and Georg Jochmann in Germany, and Simon Flexner in the USA, resulting in the first successful approach for the treatment of meningococcal disease. During the first three decades of the 20th century, serum therapy was the standard treatment for meningococcal disease. With the advent of sulphamides first and then antibiotics, serum therapy was abandoned. The great challenges that infectious diseases medicine is facing and the awaiting menaces in the future in terms of increasing antibiotic resistance, emergence of new pathogens, and re-emergence of old ones without effective therapy, make passive immunotherapy a promising tool. Acknowledging the achievements of our predecessors might teach us some lessons to bring light to our future.

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Introduction

> If I have seen further it is by standing on the shoulders of giants
>
> *Isaac Newton (1643–1727)*

Meningococcal disease was never described in ancient times despite its distinctive rash in a substantial proportion of patients. In January 1805, Gaspard Vieusseux, a general practitioner, first clinically characterised meningococcal disease in a short epidemic at the Eaux Vives quarter in Geneva, Switzerland.[1] Post-mortem examination of some cases was later described by Andre Matthey,[2] and the disease received the name *fièvre cérébrale maligne non contagieuse* [non-contagious malignant cerebral fever].

New epidemics of the disease described by Vieusseux were subsequently reported in Medfield, MA, USA in 1806,[3] and from 1806 to 1809 in other New England states, Virginia, Kentucky, Ohio, and Pennsylvania in the USA, and Canada.[4–6] Throughout the 19th century, epidemics of meningococcal disease spread to most countries in Europe, North and South America, colonial Africa, and western Asia.[7] In these epidemics, the mortality of the disease ranged from 69% to 100% of cases.[7]

Theodor Klebs, in 1875, was the first to observe cocci in cerebrospinal fluid (CSF) of patients who died from meningitis.[8] His findings were subsequently confirmed by many other authors from 1886 onwards. *Diplococcus pneumoniae* (Albert Fränkel's *Pneumoniekokkus*) was considered the cause of epidemic and sporadic meningitis.[8] In the years 1885–87, Anton Weichselbaum, a pathologist from Vienna (Austria-Hungary), while studying germs that caused meningitis, found in the post-mortem examination of eight patients who died from sporadic meningitis, was able to culture *Diplococcus pneumoniae* from two of them, whereas in the other six patients he observed a different micro-organism, and he named it *Diplococcus* on the basis of its morphology, *intracellularis* on the basis of its location, and *meningitidis* due to its potential to cause meningitis.[9] The bacteriological study of meningitis epidemics occurring after 1897 led to *Diplococcus intracellularis meningitidis* being established as the main cause of epidemic cerebrospinal meningitis.[10–16]

Therapeutic attempts before serum therapy

The high fatality of the meningococcal disease epidemics observed during the 19th century meant that this disease was considered one of those with the worst prognosis, only comparable to the plague and cholera.[17] Therefore, countless methods were tested over this century with a therapeutic intent, replacing one another in accordance with the theories predominant at each period on the postulated cause of the disease.

Vieusseux[1] recommended emetics and, occasionally, bloodletting. Lothario Danielson and Elias Mann[3] observed the harmful effect of bloodletting and advised the administration of Fowler's mineral solution and wine, whereas Nathan Strong Jr[6] maintained that the best treatment was a nutritious diet and stimulant medicines. Alcoholic beverages, opium (either pure or as laudanum), potassium iodide, quinine, and many other compounds were extensively used and subject to heated scientific discussions. Opium was believed to be a specific remedy for meningococcal meningitis because of its stimulant properties.[4–6,18–21] The most popular of the compounds initially used was mercury, administered as an ointment or orally as calomel (mercury chloride).[6,22]

With the aim of relieving the severe headaches of patients with meningitis, compresses soaked in cold water or sulphuric ether were applied to the head and rachis.[22,23] The immersion of the patient two or three times a day in warm or hot water was likewise recommended.[23,24] None of these remedies succeeded in modifying the course of the disease, although some of them could provide symptomatic relief.

Figure 1: **Professor August von Wassermann, from the *Königlich Preußische Institut für Infektionskrankheiten* [Royal Prussian Institute for Infectious Diseases], one of the first developers of antimeningococcal serum in Germany**
Prof Wassermann portrait by an anonymous photographer (before 1925). Reproduced from National Library of Medicine, US National Institutes of Health.

At the end of the 19th century, Walter Essex Wynter[25] was already using repeated lumbar punctures to treat tuberculous meningitis. Starting from 1891, CSF drainage, whether by means of repeated punctures, the insertion of trocars or catheters on a subarachnoid, lumbar, or cisternal level, with or without concomitant laminectomy, was one of the therapeutic pillars for bacterial meningitis for over a decade. The idea was to reduce the pressure of the CSF and to diminish its bacterial load. Other surgical procedures were also used for therapeutic purposes in the acute phase of meningococcal meningitis, including suboccipital decompression with the aim of ensuring the permanent drainage of the cisterna magna and trepanation in various locations. Subsequently, the practice of so-called intrathecal washings was advocated, done with repeated punctures of the subarachnoid space and the subsequent instillation of normal saline, distilled water, or sodium citrate solution.[26]

In what was intended to be a therapeutic step forward, antiseptic substances were instilled intrathecally, such as lysol, protargol at 0·2%, carbolic acid solution at 0·5%, flavin, eusol, hexamine, helmitol, and hydrogen peroxide.[26] In the beginning of the 20th century, colloidal silver, salvarsan, neosalvarsan, antimony tartrate, soamine, the subcutaneous injection of turpentine with the consequent formation of the so-called fixation abscesses, and the bilateral intracarotid injection of Pregl's iodine solution were also used.[18,26–28] All these treatment methods were shown to be completely ineffective, despite some specific successes alleged by the authors.

The dawn and golden age of serum therapy

In 1890, Emil Von Behring and Kitasato Shibasaburō[29] laid the foundations of serum therapy for infectious diseases, because they generated serum containing antibodies capable of neutralising the effects of *Clostridium tetani* and *Corynebacterium diphtheria* toxins after immunising horses with these bacterial toxins. In 1891, Georg and Felix Klemperer[30] showed that serum therapy protected rabbits from *Streptococcus pneumoniae* infection and paved the way for this type of treatment and for the development of similar serum-based treatments for other human infections.

On April 19, 1906, Wilhelm Kolle and August von Wassermann (figure 1), from the Berlin *Königlich Preußische Institut für Infektionskrankheiten* [Royal Prussian Institute for Infectious Diseases], announced that they had obtained, starting from the immunisation of horses, a serum which protected guinea pigs against meningococcal disease.[31] On the basis of the results obtained with animal experimentation, they recommended its use for meningococcal disease in humans. On May 17, 1906, Georg Jochmann[32] described an equine antimeningococcal serum that protected guinea pigs from intraperitoneal meningococcal infection. Jochmann, who worked in Breslau (Wroclaw, in present-day Poland), had been experimenting with this serum since 1905, when the meningococcal disease epidemic still persisted in Upper Silesia (now part of Poland). The antimeningococcal serum was administered to 38 patients from Breslau and to 17 from Ratibor, and the results obtained were presented at the Internal Medicine Congress held in Munich, in April, 1906. 12 of the 17 patients from Ratibor presented a clinical benefit. This paper drew attention to the preference for the intrathecal over the subcutaneous route for its administration.

Simon Flexner (figure 2), from the New York Rockefeller Institute for Medical Research (NY, USA), began to study antimeningococcal serum therapy in 1905, independently from the German researchers. Flexner had researched the biological properties of meningococcus and was capable of producing experimental meningococcal meningitis in *Macacus rhesus,* thus obtaining a model to validate the effectiveness of the serum.[33] Flexner immunised two *Macacus nemestrinus* to produce homologous serum. In a subsequent experiment,[34] he injected meningococcal culture intrathecally into ten *M rhesus*. Five of them were treated, also intrathecally, with the previously obtained serum, whereas the other five animals were used as controls. All the controls died, but four of the animals treated with homologous antimeningococcal serum survived. Flexner continued his experimental studies and immunised horses for the production of serum intended for the treatment of humans.

The first serums available were those of Kolle and Wassermann,[31] Jochmann,[32] and Flexner.[34] At the same time, other antimeningococcal serums appeared, such as that of Ruppel in Germany, that of Markl in Austria-Hungary, and subsequently that of Charles Dopter in France.[18,27] The antimeningococcal serum was obtained by immunising horses with various slightly different methods (figure 3). Basically, the serum-obtaining procedure consisted of the subcutaneous or intravenous administration of increasing doses of initially dead meningococci and, in a subsequent phase, of living organisms. The differences in the results were based on whether or not the researchers immunised the horses with soluble autolytic products of the meningococcal culture, on the age of the strains administered, and on the use of strains from just one or numerous patients. Depending on the era, the success of immunisation of the horses was determined by different methods, including opsonic, complement fixation, agglutination, and animal protection studies with the immune serum.[18,27]

From the first observations of meningitis treated with antimeningococcal serum, it was obvious that the intrathecal route of administration was the most effective.[32] For the treatment, lumbar puncture was used to extract a volume of CSF equal to or slightly higher than the volume of serum to be administered (around 30 mL). The serum, previously heated to 37°C, was introduced into the spinal canal by means of repeated injections or using a gravity infusion system, consisting of a container and a rubber tube equipped with a shut-off valve.[35] After introducing the intrathecal serum, the patient was placed in the Trendelenburg position. In the event of the blocking of the subarachnoid space or when impossible to practise the lumbar puncture, the serum administration was done on a cisternal or ventricular level.[36] The daily administration of the serum continued until disappearance of the fever or of the diplococci from the CSF.[18] In patients with meningitis, some authors also recommended the simultaneous administration of the serum by the intravenous route at high doses and, in the cases of meningococcal sepsis without meningitis, only intravenous administration.[27,37] Hypersensitivity reactions were the most frequent side-effect following administration of the antimeningococcal serum, occurring in up to 75% of cases.[18,38]

Table 1 summarises the results of the treatment with antimeningococcal serum in the first epidemics in which it was used. A marked reduction in mortality represented by serum therapy was apparent.[24,35,39,40] It was also soon appreciated that the effectiveness of serum therapy was directly proportional to how early it was administered. The analysis of data from the epidemics outlined in table 1 shows a substantial reduction in the mortality for patients treated with the serum compared with that for untreated patients. However, these were not case-control studies but, rather, they were reports of survival of serum-treated compared with survival of untreated patients in the same meningococcal disease epidemic. Therefore, given the important limitations of the study design, data should be interpreted with great caution. Notwithstanding that limitation, the results were compelling enough, at the time, to settle serum therapy as the treatment of choice for meningococcal disease, and antimeningococcal serum continued to be the standard therapy, being recommended until the 1940s.[41]

Figure 2: **Dr Simon Flexner, from the New York Rockefeller Institute for Medical Research (NY, USA), who developed and applied antimeningococcal serum in the USA**
Dr Flexner portrait by Elias Goldensky (Philadelphia, PA, USA), in 1904. Courtesy of the Rockefeller Archive Center.

The subsequent history of antimeningococcal serum therapy runs parallel to the advances made in relation to the antigenic characteristics of meningococcus, which finally allowed its classification in serogroups. Flexner[39] had already shown the existence of cases of meningococcal meningitis in which the strain responsible was shown to be resistant to serum therapy. At the beginning of serum therapy, the serum was prepared with, in an empirical

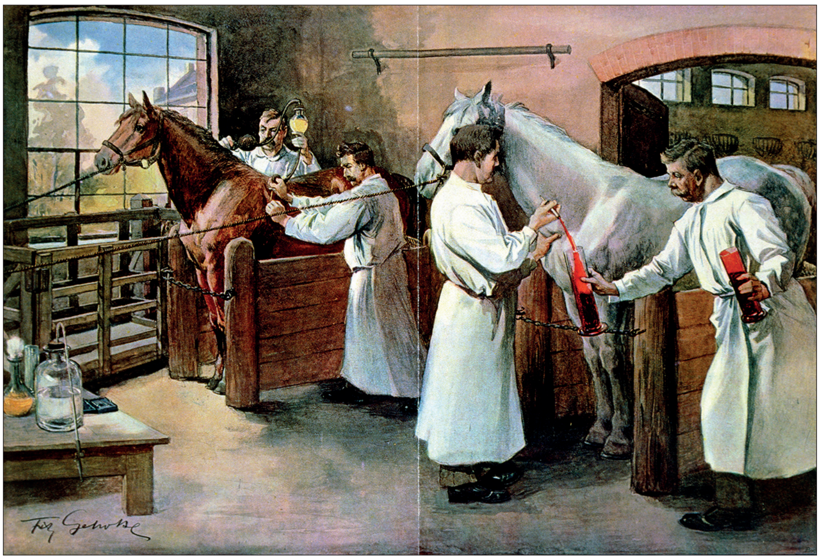

Figure 3: **Horses being inoculated and bled for their serum containing diphteria antitoxin (1900), a method basically identical to that used for obtaining antimeningococcal serum.**
Painting from Jean-Loup Charmet (1900). Reproduced by permission of AgeFotoStock.

	Serum-treated patients		Untreated patients	Type of serum
	Number	Mortality (%)	Mortality (%)	
Steiner	2280	37·0	77·0	Flexner
Flexner	1294	30·9	75·0	Flexner
Robb	300	30·0	72·0	Flexner
Sophian	161	15·5	No available data	Flexner
Netter	100	28·0	49·0	Dopter
Dopter	402	16·4	65·0	Dopter
Levy	165	18·2	52·1	Dopter
Krohne	59	40·6	66·0	Kolle and Wassermann
Leick	34	32·4	55·0	Kolle and Wassermann
Neglein	30	26·6	50·0	Kolle and Wassermann
Tobben	29	34·0	56·0	Kolle and Wassermann
Kleinschmidt	21	19·0	62·5	Kolle and Wassermann
Quenstedt	18	22·2	56·2	Kolle and Wassermann
Jehle	41	45·0	70·0	Markl
Weiss and Eder	23	39·0	85·0	Markl
Schoene	30	25·0	53·0	Jochmann
Total	4987	28·7	60·1	..

*Data from Heiman and Feldstein,[24] Sophian and colleagues,[35] Flexner and colleagues,[39] and Worster-Drought and Kennedy[26]

Table 1: **Outcome of meningococcal disease and treatment with serum therapy***

and random manner, cultures of meningococcus isolated from multiple patients. In 1909, Dopter[42] described the so-called parameningococci α, β, and γ, which he isolated from the nasopharynx of individuals who had been in contact with patients affected by meningococcal meningitis, and which were morphologically and culturally identical to classic meningococcus but distinguishable from it because of agglutination reactions. In the same year, Harry Elser and James Huntoon[43] specified the biochemical and serological characteristics of meningococcus culture, and the preparation of monovalent and polyvalent serums, the clinical use of which was often sequential, began. At the time of diagnosis, polyvalent serum was used first and, after typing the causal agent, treatment continued with the corresponding monovalent serum.

In the cases that appeared in 1914, a high percentage of failures of the serum therapy was recorded, the mortality thus rising to 65–70%, a figure similar to those of the pre-serum therapy era. These disappointing results were attributed to the fact that the serum available came from previous years, to the fact that presumably it did not contain antibodies against the strain responsible, and to deficient storage conditions. Serogroup-specific antimeningococcal serums were, therefore, obtained, and began to be applied in 1915, leading to a reduction in mortality similar to that of the beginning of the serum therapy era.[44]

An attempt to enhance the effect of serum therapy was its complementation with fresh human serum obtained from the patients themselves or from individuals recovering from meningococcal disease,[18,27,38,45] a method called complement therapy. During early 20th century, Ehrlich's side-chain theory of antibody formation and the mechanisms of antibody neutralisation by toxins that induced bacterial lysis with the help of complement was already known.[46] Serum therapy was also combined with bacteria therapy or autologous vaccination, consisting of the administration (by the intrathecal route, subcutaneous route, or both) of CSF from the patient, enriched with glucose and subsequently heated with the aim of obtaining a liquid with 50–100 million dead meningococci per mL.[47–49]

In 1931, Newell S Ferry and colleagues[50] isolated specific soluble toxins from culture mediums of various kinds of *Neisseria meningitidis*. The injection of these toxins in guinea pigs and rabbits gave rise to the development of homologous antitoxins; these two antitoxins combined were called meningococcal antitoxin.[51,52] This antitoxin was administered intravenously, intramuscularly, or intrathecally, as a monotherapy or together with the antimeningococcal serum.[53] Although the initial results with Ferry's antitoxin showed more efficacy than those with standard serum therapy, in subsequent years no differences were observed in relation to the mortality between the two therapeutic options, although the patients treated with antitoxin presented fewer complications.[54,55]

The availability of antimeningococcal serum starting from 1906 and its proven therapeutic effectiveness meant that Jochmann,[32] and subsequently Ruppel,[27] recommended its prophylactic use in close contacts of patients with meningococcal disease. However, this measure was only used in isolated cases.[35] The first evidence that there were asymptomatic carriers of *N meningitidis* and of the fundamental role that they played in the epidemiological chain of the disease[12,56] meant that, in the beginning of

	Number treated with sulphamide	Mortality (%)	Number treated with sulphamide and serum	Mortality (%)	Number treated with serum therapy	Mortality (%)
Roche and McSweeney[61] (1935–39)	11	9·1%	56	57·1%	36	75·0%
Waghelstein[62] (1937–38)	72	15·3%	140	19·3%	368	26·9%
Banks[63] (1937–40)	310	6·1%	70	15·7%	..	..
Goldring et al[64] (1937–44)	209	9·1%	..	..	..	..
Davis et al[65] (1937–45)	..	..	352	6·8%	..	..
Banks[66] (1938)	16	6·2%	59	11·8%	38	16·0%
Feldman et al[67] (1938–41)	24	8·3%	..	..	..	..
Hodes and Strong[68] (1938–42)	110	11%	..	..	..	..
Somers[69] (1939)	143	10·2%	..	..	..	..
Bryant and Fairman[70] (1939)	189	4·8%	..	..	..	..
Beeson and Westerman[71] (1939–41)	2455	9·5%	965	18·7%	..	..
Banks et al[72] (1939–44)	33 450	22·2%	..	..	..	..
Banks et al[72]* (1939–44)	4222	8·4%	..	..	..	..
Jubb[73] (1940)	2357	9·2%	849	13·8%	2279*	36·6%
Scheld and Mandell[74] (1940–45)	14 054†	3·8%	..	..	..	..
Horwitz and Perroni[75] (1941–43)	450	11·1%	..	..	..	..

*Data from 1931 to 1934 only. †Data from service personnel.

Table 2: **Outcome of patients with meningococcal meningitis treated with sulphamides, serum therapy, or both**

the 20th century, attempts were already being made to eradicate carrier status. In 1906, Wassermann used sprays of dried antimeningococcal serum, injecting it through the nostrils. However, the results obtained were discouraging, unlike the experiences described by Karl Kutscher, and Paul Carnot and Cayrel, who also used sprays.[57,58]

The twilight of serum therapy

In the mid-1930s, Gladwin Buttle and colleagues,[59] and Perrin Long and Eleanor Bliss[60] described favourable experimental results in the treatment of meningococcal disease with 4-sulphamide-'2-'4-diaminoazabenzene or Prontosil (ie, sulfamidochrysoidine). The first application of sulphamides in the treatment of human meningococcal disease took place in 1937 when Francis Schwentker and colleagues[47] treated ten patients with meningococcal meningitis and one with sepsis without meningitis with sulphanilamide intrathecally and subcutaneously. All ten patients survived. The authors specified that subsequent studies were required to define the role of sulphanilamide as monotherapy or as adjuvant to serum therapy. Starting from 1937, numerous studies were done on the treatment of meningococcal disease with sulphamides, and the good results obtained endorsed them as the treatment of choice for the following 25 years. Table 2 shows the results of the treatment of meningococcal disease with sulphamides in the 9 years following their introduction.[61–75]

In 1937 and 1938, strains of meningococcus with variable degrees of resistance to sulphamides were isolated in Baltimore, MD and Washington DC, USA.[76] In 1941–43, Emanuel Schoenbach and John Phair,[77] in a study of 430 strains of meningococcus from army patients and carriers, found that eight (1·9%) of these strains were not inhibited in vitro by a concentration of sulphadiazine of 0·5 mg/μL. The first epidemic due to serogroup B meningococcus resistant to sulphadiazine occurred in the spring of 1963, in the US Naval Training Center of San Diego (CA).[78,79] Shortly afterwards, in Fort Ord (Marina, CA, USA), another epidemic of meningococcal disease occurred, also caused by serogroup B meningococcus; 50% of whose isolates were resistant to sulphamides.[80,81] These findings were reproduced shortly after in the civilian population.[82] Therefore, in the USA, sulphamides ceased to be the treatment of choice for meningococcal disease starting from 1965. In 1968, an epidemic was detected caused by sulphamide-resistant *N meningitidis* in Meknes (Morocco),[83] and in 1971–72, in São Paulo (Brazil).[84] The epidemics were caused by serogroup C meningococcus with resistance to sulphamides in 95% of the isolates.[84,85] The geographical dispersion of sulphamide resistance in *N meningitidis* determined the generalised abandonment of sulphamides and the beginning of the era of treatment with penicillin.

In 1944, David Rosenberg and Phillip Arling[86] treated 65 patients with meningococcal meningitis, using intrathecal penicillin, at doses of 1×10^4 units of penicillin every 24 h, associated with concomitant administration by intramuscular or intravenous route. Only one of the patients died, and all the other patients recovered without sequelae. In the same year, Manson Meads and colleagues[87] treated nine patients with similar doses of penicillin and all survived. Despite these results, it was believed that treatment with sulphamides was superior, given that the response to penicillin was slower than to sulphamides, the carrier status remained after treatment,

	Number treated with penicillin	Route used	Mortality (%)
Rosenberg and Arling[86]	65	Intrathecal, intramuscular, or intravenous	1·5%
Meads et al[87]	9	Intrathecal, intramuscular, or both	0
Lepper et al[88]*	40	Intramuscular	2·5%
Keefer et al[89]	5	Intrathecal, intramuscular, or intravenous	20·0%
Herrell and Kennedy[90]	2	Intrathecal, intramuscular, or intravenous	0
White et al[91]	12	Intrathecal, intramuscular, or intravenous	50·0%

*Lepper and colleagues also reported that 38 patients were treated with sulphamide, with a 0% mortality.

Table 3: **Early reports of the outcome of meningococcal meningitis treated with penicillin**

and that treatment with penicillin was difficult because of the need for daily lumbar puncture. In 1952, Mark Lepper and colleagues[88] compared treatment with penicillin and with sulfisoxazole in 78 patients with meningococcal meningitis. The doses of penicillin were higher than those previously used[86,87] by the intramuscular or intravenous route, without intrathecal administration. It was concluded that penicillin at high doses was at least as effective as sulfisoxazole for the treatment of meningococcal meningitis and that its intrathecal administration was not essential. The first series of patients with meningococcal meningitis treated with penicillin is summarised in table 3.[86–91]

In 1965, Theodore Eickhoff and Maxwell Finland[92] isolated strains of meningococcus with a minimum inhibitory concentration for penicillin of 0·1–0·2 μg/mL. In October, 1985, a strain of meningococcus was isolated in Madrid with an minimum inhibitory concentration of 0·2 μg/mL for penicillin from a blood culture of an 8-month child affected by sepsis and meningitis, who was cured with penicillin.[93] Overall, in Spain, the frequency of isolations with decreased susceptibility to penicillin increased from 0·4% in 1985, to 46% in the first 4 months of 1990. Among these strains with decreased susceptibility to penicillin, serogroup C, and serogroups and serotype or subtype B4P1.15 and C2b were initially shown to be predominant.[93] In 1988, Enid Sutcliffe[94] reported the isolation of strains of meningococci with decreased susceptibility to penicillin in the UK.

The penicillin susceptibility decrease mechanism in *N meningitidis* is the modification of the penicillin binding proteins, and only exceptionally the production of β-lactamases.[95,96] Of the strains with reduced sensitivity, penicillin binding protein 3 shows an affinity 30–80 times lower for penicillin by comparison with that of sensitive strains.[97] No alteration whatsoever has been shown in the permeability of the external membrane and no production of inactivating enzymes[98] or of β-lactamase has been shown in the pathogenic strains of neisseria isolated in Spain, although it has been shown among saprophytes.[99]

In 1951, Fred McCrumb and colleagues[100] used, for the first time, chloramphenicol in the treatment of meningococcal disease. 15 patients with meningococcal meningitis received this drug orally or intravenously. They were all cured without sequelae. However, since 1952, the serious side-effects of chloramphenicol have been shown, in the form of aplastic anaemia[101–103] and, in 1959, grey baby syndrome was described with high doses of chloramphenicol.[104–107] These serious adverse effects limited its use and relegated it to a secondary role in the treatment of meningococcal disease.

The development of second-generation and third-generation cephalosporins yielded compounds with a great spectrum of antimicrobial activity and a greater capacity to cross the blood–brain barrier compared with older antibiotics, including penicillin. In 1974, José Correa and colleagues[108] treated meningococcal meningitis with cefacetrile with a good therapeutic response. Since then, excellent results have been published in the treatment of meningococcal meningitis with second-generation and third-generation cephalosporins.[109] At present, the empirical treatment of bacterial meningitis acquired in the community always includes a third-generation cephalosporin.[109–111]

From passive serum therapy to active immunisation

In 1966, Irving Goldschneider and colleagues[112] began their pivotal studies on human immunity against meningococcus and its increasing incidence due to the absence of serum bactericidal antibodies. Furthermore, they showed that the capsular polysaccharides of certain serogroups induced the formation of protective antibodies against the disease due to meningococci from the same serogroup.[113] The following study[114] in vaccine research was the isolation and purification of polysaccharides, thus beginning the path to obtain antimeningococcal vaccines.

The monovalent C antimeningococcal vaccine was obtained by Emil Gotschlich and colleagues[114] in 1969, based on specific capsular polysaccharides of serogroup C, and was capable of inducing bactericidal antibodies in the serum of six volunteers. The C vaccine was the first to be administered on a large scale, initially being tested in US basic military training centres.[115–119] The monovalent A antimeningococcal vaccine was also obtained by Gotschlich and colleagues[114] in 1969, and was associated with high effectiveness in numerous tests.[120,121–129] The bivalent A and C antimeningococcal vaccine was composed of specific capsular polysaccharides of the serogroups A and C, and became necessary when epidemic outbreaks occurred and which were caused simultaneously by both serogroups in São Paulo and in regions of the African savannah.[128,130] No significant differences were found in the concentrations of antibodies induced by the bivalent A and C vaccine when comparing them with those induced separately by the A and C vaccines.[129]

Macleod Griffiss and colleagues[131] obtained the bivalent Y and W135 vaccine in 1981, which finally led to the tetravalent A, C, Y, and W135 antimeningococcal vaccine, tested for the first time by William Hankins and colleagues[132] in 1982. In several studies[132–135] on volunteer adults, results showed that the immunogenicity and the adverse effects of the tetravalent vaccine were similar to those presented by the A, C, or bivalent A and C vaccines and that the immune response was serogroup specific.

However, plain polysaccharide vaccines, although effective and safe in the short term in close community settings, had several shortcomings. These vaccines are poorly immunogenic or not at all in young children (younger than 2 years), do not elicit immunological memory, and are ineffective against carriage.[136,137] The development of conjugate vaccines in the 1990s was a major breakthrough in vaccinology; they contain a polysaccharide molecule, chemically conjugated to a T-cell-stimulating antigen, such as the diphtheria or tetanus toxoids.[138] They are immunogenic in children and adults, elicit immunological memory, and eliminate the carrier status, thereby making them suitable for population-scale interventions.[139] Monovalent conjugate serogroup C and A, and quadrivalent conjugate meningococcal vaccines have been licensed to date, to our knowledge.[139]

The last addition to the vaccine armamentarium against meningococcus is the multicomponent serogroup B meningococcal vaccine, which is immunogenic and safe in children (older than 2 months), adolescents, and adults (no data for people older than 50 years).[140] Results from clinical trials[141] suggest that serogroup B meningococcal vaccine, like the other conjugate vaccines, might lead to herd immunity, reducing not only carriage of the serogroup included in the vaccine but also of other serogroups. Therefore, high population immunity caused by the efficacy of the vaccine against transmission and the coverage achieved might herald the removal of meningococcus and meningococcal disease eradication or extinction.[142]

Back to the future: antibodies for infectious disease therapy

The discovery of sulphamides and later of antibiotics, and their subsequent introduction in the 1930s and 1940s, led to dereliction of serum therapy for a period of 10 years, given that these new compounds were broadly effective, had fewer side-effects, and were cheaper treatment options. However, the field was not completely abandoned for meningococcal disease, although greatly restricted to experimental research and isolated clinical experiences.[143–147] Passive antibody therapy for infectious diseases then became limited to infections not treated with antibiotics, such as the treatment and prevention of hepatitis B virus, rabies virus, respiratory syncytial virus, *Clostridium tetani*, *Clostridium botulinum*, anthrax, *Clostridioides difficile* colitis, vaccinia virus, echovirus, and enterovirus.[148]

However, looming threats in the field of infectious diseases have made the scientific community turn its sight back to the use of antibodies for therapeutic use. These threats include the development of multidrug-resistant bacteria with limited or no response to existing treatments, caused by the broad and general use of antibiotics in veterinary and human medicine, which according to the WHO and Centers for Disease Control and Prevention cause more than 25 000 deaths in Europe and similar numbers in the USA because of antibiotic-resistant infections.[149] Moreover, the emergence of new pathogens, such as severe acute respiratory syndrome, Middle East respiratory syndrome, or the re-emergence of old known pathogens without available vaccines (such as Ebola virus and its 2014 epidemic in west Africa), further highlights the need for new therapeutic approaches, including passive immunotherapy.[150] Furthermore, the problems encountered when treating infections in immunosuppressed patients, such as transplant or HIV-infected patients, show how difficult the role of antimicrobial chemotherapy is in the absence of effective immunity.

For more on **antibiotic or antimicrobial resistance** see https://www.cdc.gov/drugresistance/

The revolution in technologies for the development, selection, generation, and purification of fully human antibodies has eased the means of producing an unlimited supply of homogeneous monoclonal antibodies. Thus, in the past few decades, a huge number of monoclonal antibodies have caused a dramatic effect in the fields of oncology, autoimmune diseases, allergy, bowel inflammatory diseases, and in a few orphan diseases. However, only palivizumab for the prevention and treatment of respiratory syncytial virus, and bezlotoxumab for the prevention of recurrence of *C difficile* infections, have been approved for infectious diseases.[151,152]

Given the growing challenges in the infectious diseases field, new therapeutic options are greatly needed. In this setting, antibodies and antibody-derived treatments

Search strategy and selection criteria

For this Historical Review, our search strategy involved the review of original historical records, either journals or books, mainly from European and American sources, from 1805 to 2018. From these sources, we identified additional records. We also searched some official records of the Prussian and Swiss Governments, and even non-scientific journal articles. Most of the records from governments and non-scientific journals have not been included in this Historical Review. However, reports, manuscripts, and records cited in the bibliographies have been searched as well. All the compiled information has been reviewed as accurately as possible to depict the period between the first clinical descriptions of meningococcal disease to the discovery of its causative agent, and to the evolving ways of therapy against meningococcal disease, from the symptomatic period to the antibiotic therapy and the discovery of vaccines. Our search has inherent limitations due to century-old data sources and some unprecise descriptions. We have searched PubMed and Google Scholar from inception to Oct 23, 2018, for records, journals, and books for the terms "meningococcal disease", "*Diplococcus intracellularis meningitidis*", "*Neissera meningitids*", "cerebro-spinal meningitis", "epidemic meningitis", "spotted fever", "cerebro-spinal fever", "meningococcal meningitis therapy", "sulphamide treatment", "penicillin", "chloramphenicol", "third-generation cephalosporins", "meningococcal vaccine", and "monoclonal antibodies". References were examined in English, German, French, and Spanish.

might offer hope to address these challenges, and perhaps the lessons learned by our predecessors in the past might help us to find new answers for the future. Like the philosopher George Santayana said "Those who cannot remember the past are condemned to repeat it".[153]

Contributors

PD and NB designed the review. PD, VP, AM, and NB searched for the bibliography. The manuscript was drafted by PD, VP, AM, and NB. All authors provided input to the report and approved the final version of the manuscript.

Declaration of interests

We declare no competing interests.

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