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Impact of MenB Vaccination on *Neisseria gonorrhoeae* infections: a comprehensive state-of-the-art review

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ABSTRACT

Objective. *N. gonorrhoeae* is a human-restricted pathogen but, nowadays, no effective anti-gonococcal vaccine is available. Several studies showed that OMV-based MenB vaccines may provide a cross-protection against gonococcal infections, so the aim of our study was to investigate, through a review of the literature, the state of art about the potential impact of meningococcal B vaccination on gonococcal infections.

Materials and Methods. In February 2021 we performed a search for original peer-reviewed papers in the electronic database PubMed (MEDLINE). The key search terms were "Meningitis B AND Gonorrhoea", "Bexsero AND Gonorrhoea", "MenB vaccine AND Gonorrhoea", "Trumenba AND Gonorrhoea". Studies that provided clear and sufficient data on the impact of MenB vaccination on gonorrhoea were included.

Results. Bibliographic research yielded 39 publications, but the overall analysis was conducted on 5 studies. Despite the limited number of included studies, and their heterogeneity it was observed a reduced incidence of *N. gonorrhoeae* infections and the elicitation of antibody response.

Conclusions. Although MEN B vaccination could be taken in consideration as an interesting strategy to prevent *N. gonorrhoeae* infection, further studies are fundamental to establish a real and durable vaccine effectiveness.

INTRODUCTION

Gonorrhoea is a sexually transmitted infectious disease caused by *Neisseria gonorrhoeae* bacterium (gonococcus); despite the continuing energies spent to limit its health impact, it still remains a global health problem [1].

N. gonorrhoeae is a human-restricted pathogen that infects the lower genital tract, pharynx, and rectum. The predominant site of infection is the cervix in females and the anterior urethra in males. Gen-

erally, the disease affects young individuals (15–24 years of age), but it can be detected in any sexually active individual [1].

The lack of natural immunity in both symptomatic and asymptomatic patients has impeded the development of an effective anti-gonococcal vaccine. Moreover, it is more and more frequent the phenomenon of antibiotic resistance among gonococcal strains and this phenomenon could lead to untreatable *N. gonorrhoeae* infections in the future [2].

Neisseria gonorrhoeae and *Neisseria meningitidis* are obligate human pathogens that are genetically closely related, sharing between 80 and 90% genome sequence identity [3].

In contrast to polysaccharide-based vaccines targeting *N. meningitidis* serogroups A, C, W, and Y, protein-based vaccines have been developed for *N. meningitidis* serogroup B (NmB) [4, 5].

A meningococcal B vaccine, (4CMenB, Bexsero®) was first licensed for use in Europe in January 2013, and is now licensed in Australia, Canada and the United States of America. The 4CMenB vaccine is able to induce an immune response in children between two and five months which received a 3+1 dose schedule, and is also able to induce an immune response in children over six months and from two to ten years which received a 2+1 schedule. In adolescents and adults, protective antibodies against vaccine antigens are elicited with two doses [6].

Another meningococcal B vaccine (Trumenba®), containing two variants of factor H-binding protein (fHBP), has been approved for persons ≥ 10 years of age [7].

The multicomponent MenB-4C vaccine contains the following 3 immunogenic antigens identified by reverse vaccinology: factor H binding protein (FHbp) fused with GNA2091, *Neisseria* adhesin A (NadA), and *Neisseria* heparin binding antigen (NhbA) fused with GNA1030 supplemented with the outer membrane vesicle vaccine (OMV) of the New Zealand epidemic strain (NZ98/254) to warrant broader immunogenicity [8].

Through a U.S. surveillance system, researchers identified 1,525 proteins that were common to both *Neisseria* species (*Neisseria gonorrhoeae* and *Neisseria meningitidis*), of which 57 proteins were predicted to be OMPs (Outer membrane proteins) using *in silico* methods.

In particular NhbA showed moderate sequence identity (73%) to the respective gonococcal homolog, was highly conserved within *N. gonorrhoeae*, and was predicted to be surface expressed. In contrast, the gonococcal FHbp was predicted not to be surface expressed, while NadA was absent in all *N. gonorrhoeae* isolates [9].

Studies previously conducted in Cuba, Canada, and New Zealand have highlighted a potential cross-protection against *N. gonorrhoeae* infections derived from MenB OMV vaccines [9, 10], so the aim of our study was to investigate, through a review of the literature, the state of art about the po-

tential impact of meningococcal B vaccination on gonococcal infections.

MATERIALS AND METHODS

Search strategy

A research of peer-reviewed literature was conducted in February 2021 in the electronic database MEDLINE (PubMed) using the keywords “Meningitis B AND Gonorrhoea”, “Bexsero AND Gonorrhoea”, “MenB vaccine AND Gonorrhoea”, “Trumenba AND Gonorrhoea”.

Inclusion criteria

We considered eligible for the review all the articles (original articles, conference abstracts, but also letters to the editor if containing original data) written in Italian, English, French, Spanish and without time restrictions.

We decided to include in the review only studies conducted on humans and that reported, at least, information about the type of vaccine and vaccine's effects on the studied sample (reported as estimated vaccine effectiveness against *Neisseria gonorrhoeae* infections, estimated risk reduction or incidence reduction, specific antibodies elicitation). Studies that provided ambiguous or insufficient data on the impact of MenB vaccination on gonorrhoea were excluded.

Data selection and analysis

Studies have been selected in a 2-stage process. Titles and abstracts from electronic searches were scrutinized by 2 reviewers independently (A.N. and G.T.) and full manuscripts and their citations list were analyzed to retrieve missing articles and to select the eligible manuscripts according to the inclusion criteria. The level of agreement between the reviewers was high. Finally, each article was further reviewed to identify the manuscripts suitable for the review.

RESULTS

Bibliographic research yielded 39 publications. After the analysis of the titles and abstracts, 33 stud-

ies were excluded: 14 because were duplicates, 7 because were reviews, 12 because reported data not in line with the aim of the study. The full text of 6 remaining articles was analyzed: 5 articles were excluded because they focused on elements not in line with the study. The analysis of bibliographies let us retrieve further 4 studies suitable for the review. The overall analysis was therefore conducted on 5 studies (see **Table 1** and **Figure 1**) [11-15]. Studies have been conducted in Cuba, Canada, Norway, UK and New Zealand and involved a high number of persons (up to more than 2 million) who received different Men B vaccines.

Studied vaccines

VA-MENGOC-BC: Group B OMV vaccine that included also group C polysaccharide.

Bexsero: 4CMen B vaccine.

MENZB: strain specific OMV meningococcal B vaccine.

MenBvac: another OMV MenB vaccine.

Main results

Clinical evidences

Three studies reported a reduction of *N. gonorrhoeae* infections and hospitalizations; one study by Longtin *et al.* [15] reported that the estimated *N. gonorrhoeae* risk reduction was 59%; one study by Paynter *et al.* [13] reported that estimated vaccine effectiveness (VE) was 24%.

Laboratory evidences

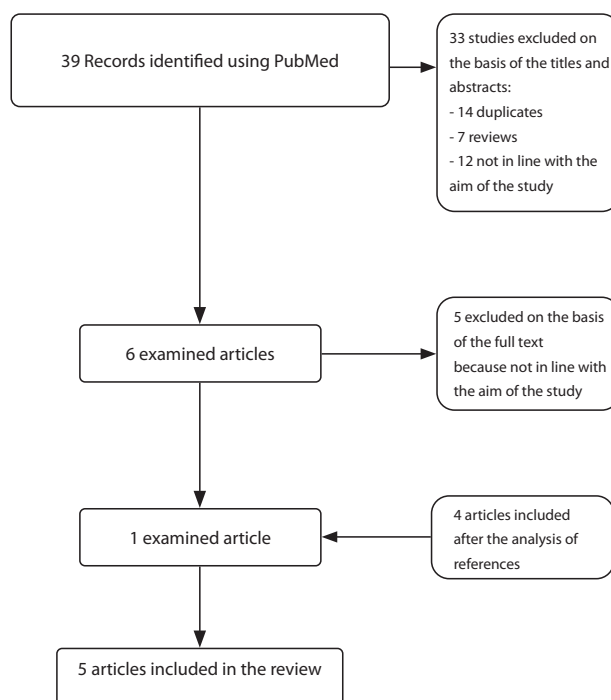
In two studies that reported the datum it was observed specific IgA and IgG cross-recognition between *N. meningitidis* and *N. gonorrhoeae* and a general increase of antibody titers against some *N. gonorrhoeae* antigens.

DISCUSSION

Sexually Transmitted Diseases or Infections (STDs/STI), like those arising from to *N. gonorrhoeae*, are important problems in public health. Their importance is connected to two elements: first, to their high incidence, and then to the complications they may cause and to their role in the HIV transmission [16].

In USA, previous studies showed that half of all new cases of STI are diagnosed among 15–24-year-old persons [17], and this phenomenon is not lim-

Figure 1. Flow diagram.



ited to USA, because worldwide more than a half of these infections are identified in the same age group [18], though this age group represents only ~25% of the sexually active population.

Among the STI, *Neisseria gonorrhoeae* infections are a significant public health problem and represent the second most common reportable diseases in the United States [19].

Most cases of gonorrhoea are identified in the urogenital tract but, among men who report sex with men (MSM), it is also common the pharyngeal gonorrhoea with a prevalence ranging from 2-11% [20, 21].

Previous reviews highlighted that gonorrhoea disproportionately affects marginalized populations. The prevalence of gonorrhoea among sexually-active young adults living in low-income countries, and - in many countries - among sexual and gender minorities, racial/ethnic minorities and indigenous communities, and sex workers is markedly higher than among the general population in high-income countries. The increase in gonorrhoea cases and the increase in antimicrobial resistance will make prevention and control efforts more difficult, and are likely to worsen and aggravate these health inequalities [22]. However, a recently published study conducted in Southern Italy demonstrated, instead, that the prevalence

Table 1. Main characteristics of the studies included in the review.

Author, year	Country	Study period	Sample characteristics	Sample (N)	Vaccine	Main results
Paynter, 2019	New Zealand	- 2004-2008 (years of eligibility for meningococcal B vaccination)	Individuals born from 1984 to 1999 residing in New Zealand	- 327576 (females) and 338061 (males) fully vaccinated (3 doses) - 5343 (females) and 6204 (males) partially vaccinated	MENZB***	- vaccinated individuals were less likely to be hospitalized for gonorrhoea - estimated vaccine effectiveness 24% (95% CI 1-42%) - no significant measurable vaccine effect in the youngest (median age 8) and oldest (median age 18) subgroups
Semchenko, 2019	UK	- n/s	Healthy adults vaccinated with 3 or 2 doses of Bexsero	- 10 (3 doses Bexsero) - 1 (2 doses Bexsero)	Bexsero	Individuals given 3 doses of Bexsero: - significantly increased geometric mean Elisa titer (GMT) from pre- to post-vaccination for whole-cell <i>N. gonorrhoeae</i> (1.8-fold increased GMT, compared to 5.7-fold increase against whole-cell <i>N. meningitidis</i>) and gonococcal NHBA (34-fold increase) - a minor increase in antibodies to meningococcal LPS was observed, but no response to gonococcal LPS in sera from Bexsero-vaccinated individuals Individuals given 2 doses of Bexsero: - antibodies recognizing gonococcal OMV proteins were induced above the pre-vaccination baseline to similar levels at 1 month post-dose 1- and 1-month post-dose 2 - a Western blot analysis indicated that post-dose 2 sera reacted with several gonococcal OMV proteins - antibodies recognizing the gonococcal NHBA were induced after dose 1 (titer of 64 000) and to a very high-level at 1 month post-dose 2 (titer of 512 000) - a Western blot analysis indicated that pre-vaccination serum did not cross-react with gonococcal or meningococcal rNHBA, while post-dose 2 sera reacted equally well with these rNHBA proteins
Longtin, 2017*	Canada	- 2006-2014 (pre-vaccination period) - 2014-2017 (post-vaccination period)	14-20 years old vs 21 years old and older	n/s	4CMenB Vaccine	- estimated <i>N. gonorrhoeae</i> risk reduction of 59% (95% CI -22% to 84%; p = 0.1)
Whelan, 2016	Norway	- 1988-1992 (years of vaccine coverage) - 1993-2008 (years of gonorrhoea notification)	persons >16 years of age during 1993-2008 in Norway	n/s	OMV MenB vaccine (MenBvac)	- overall, rates of gonorrhoea dropped among men and women after the vaccination campaign - a limited age-specific vaccine effect occurred among men and women 20-24 years of age. - no vaccine effect was found among women in other age groups or birth cohorts.
Perez, 2009	Cuba	- 1988-1990 (years of vaccination campaign)	n/s	2692446 (persons vaccinated in 1988-1990)	VA-MEN-GOC-BC**	- drop in the incidence of <i>N. gonorrhoeae</i> (after 1995) - specific IgA and IgG cross-recognition between <i>N. meningitidis</i> and <i>N. gonorrhoeae</i>

*Conference abstract; ** VA-MEN-GOC-BC is a bivalent vaccine of serogroups B and C meningococcal antigens [33]; the MeNZB vaccine was introduced in mid-2004 with the aim of controlling an epidemic of meningococcal disease that had begun in New Zealand in 1991 [34]; n/s: not specified.

of STIs among migrant women was similar to that among non-migrants [23].

Certainly, a different approach, specifically targeting specific populations, should be based on various combinations of biomedical, behavioral and structural interventions. These would ideally involve a pattern of

prevention actions, including communications and practices among sexual partners; improvement of the relationship between individuals and their healthcare providers; comprehensive population-level strategies directed to prevention research, improvement of accurate outcome assessment, and health policy [24].

Sex education and condom promotion are basic prevention elements for gonorrhoea, but condom use among MSM and other populations has decreased during the era of PrEP and other biomedical HIV prevention strategies [25].

One of the brightest chapters in the history of science is the impact of vaccines on human longevity and health [26], but for *N. gonorrhoeae*, several obstacles have challenged the development of gonococcal vaccines for decades.

Observational data related to Men B vaccines have rekindled a slight optimism about the biologic feasibility of gonococcal vaccine development [27].

Our review, tried to outline the state of art about the impact of MenB vaccination on *N. gonorrhoeae* infection. Its main limit was the limited number of included studies. Another limit was the heterogeneity of the included studies in which have been compared different persons (for age, sexual behaviors, etc.), different vaccines and outcomes.

Several studies showed that OMV-based MenB vaccines may provide cross-protection against gonococcal infections [28]. Recognition of gonococcal OMV proteins by MeNZB-like OMV-induced antibodies could explain the previously observed decrease in gonococcal cases following MeNZB vaccination [14].

The first cross-protective *Neisseria meningitidis* B vaccine (the protein-based 4 component meningococcus serogroup B - 4CMenB -), includes the New Zealand outer membrane vesicle (OMV) and three main genome-derived neisserial antigens (GNAs) [29].

However, the major MenB-4C vaccine antigens FHbp, NadA, and PorA are less likely to contribute to cross-protection against *N. gonorrhoeae* infections [9].

The study conducted by Semchenko *et al.* demonstrated, in fact, that FHbp, NadA, and PorA in the MenB-4C vaccine would not be effective vaccine antigens against *N. gonorrhoeae*. Other immunogenic proteins, instead, have a high level of sequence conservation and may therefore serve as potential vaccine targets [9]. In their study, ~98% of common OMPs present in both *Neisseria* species exhibit between 91% and 100% amino acid sequence similarity within 970 *N. gonorrhoeae* isolates [9].

When reading the results, it is important to remember that there are some limitations that should be kept under consideration. First of all, as also evidenced by Kenyon in 2019, vaccine effectiveness declined with the time [30]. Moreover, in the study

conducted in Norway the ecologic study design could not distinguish between long-term trends or behavioral factors and vaccine effects. For example, in the early 1990s, condom use increased in Norway, especially among persons in their early 20s, possibly in response to the evolving HIV epidemic [11, 31, 32].

CONCLUSIONS

Although MEN B vaccination could be an interesting weapon for *N. gonorrhoeae* infection, the limited evidences on this topic cannot lead to completely reliable conclusions. So further studies are fundamental to establish a real and durable vaccine effectiveness (VE) and it is important to interpret the results with prudence, especially if considering a long-term VE [30].

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

All the authors contributed equally to this work.

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Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

N/A.

Informed consent

N/A.

Data sharing

Data are available under reasonable request to the corresponding author.

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