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REVIEW

Vaccines against Emerging Sexually Transmitted Infections: Current Preventive Tools and Future Perspectives

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SUMMARY

Vaccines have historically played a pivotal role in reducing the burden of infectious diseases and now play a crucial role in the setting of sexually transmitted infections (STIs). However, there remain several unmet goals: vaccines are available only for viral STIs, vaccination accessibility and uptake remain disproportionate worldwide, and no effective vaccine has been developed for HCV. Moreover, there are no vaccines against bacterial STIs: fewer investments in research have been made, because vaccines are not a top priority due to the availability of effective treatments. However, higher rates of resistance to all available antibiotics has led to a shift in research priorities. Several promising vaccine candidates have been identified or are being investigated in pre-clinical or clinical trials, although further understanding of the immunogenicity, effectiveness and delivery strategies of already licensed vaccines is needed. This paper focuses on current research efforts to develop vaccines against bacterial (*e.g.* gonorrhoea, chlamydia and syphilis) and viral (*e.g.* HCV) STIs. We also review current indications and evidence of effectiveness of already available vaccines (*e.g.* HAV, HBV and HPV) and discuss open issues.

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INTRODUCTION

Sexually transmitted infections (STIs) are a major public health problem worldwide, affecting the quality of life and causing high levels of morbidity and mortality. STIs also have a direct impact on reproductive and child health, causing infertility and pregnancy complications. It has been estimated that the prevalence of STIs in pregnancy can be comparable with that of malaria (Chico *et al.,* 2012). Some STIs, such as the human papilloma virus (HPV), are directly linked to various forms of cancer. Moreover, most STIs also play a role in facilitating transmission of human immunodeficiency virus (HIV). Thus, they affect both national and individual economies. Addressing both prevention and control of STIs is therefore a public health priority, as curable diseases account for a loss of more than 11 million disability-adjusted life years (DALYs) every year. Worldwide, it has been estimated that more than a million STIs are acquired every day: chlamydia, gonorrhoea, syphilis, hepatitis B (HBV), hepatitis C (HCV) and HPV belong to the broad list of STI infections. Chlamydia is the most common STI, followed by gonorrhoea, resulting in substantial morbidity and economic costs worldwide. Unsurprisingly, the World Health Organization (WHO) identified the health sector's response to the STI epidemic as critical to the achievement of universal health coverage in the Sustainable Development Goals (SDGs) identified in the 2030 Agenda for Sustainable Development.

The Agenda includes three key priorities to be achieved by 2030:

- 90% reduction in *N. gonorrhoeae* incidence globally;
- 50:100,000 maximum congenital syphilis cases per live births in 80% of the world;
- 90% HPV national vaccine coverage.

Primary prevention of STIs consists of comprehensive sex education and condom promotion. However, these strategies often fail in the long term due to difficulties in maintaining safe sexual behaviours over time. Considering the expanding use of HIV pre-exposure prophylaxis (PrEP), individuals belonging to

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high-risk groups are at far greater risk of acquiring STIs other than HIV. Secondary prevention is based on surveillance and screening programmes: detection of asymptomatic cases, with prompt treatment, significantly reduces negative outcomes and infertility cases, although it is clear than in a long-term scenario these methods are frail and new prevention strategies are needed (Global Health Sector Strategy on Sexually Transmitted Infections. Geneva, WHO, 2016-2021). Vaccines have historically played a pivotal role in reducing infectious diseases burden and now play a crucial role in this specific setting (Value Attribution Framework for Vaccines against Antimicrobial Resistance. Geneva, WHO, 2019). However, focusing on STIs, there remain several unmet goals: effective vaccines are available only for STIs caused by viruses, such as HAV, HBV and HPV. Given that viral STIs are often highly persistent despite available therapeutic options, the development of effective vaccines has historically been a key priority. However, vaccination accessibility and uptake remain disproportionate throughout the world. Despite all research efforts, and although some promising candidates are currently being investigated, an effective vaccine for HCV and HIV has not yet been developed. Bacterial STIs such as chlamydia, gonorrhoea and syphilis are often effectively treated with antibiotics and no vaccines are currently licensed. As a consequence, fewer investments in research have been made to develop effective vaccines, because vaccines against bacterial STIs are not a top priority due to the availability of effective treatments. However, higher rates of resistance of bacterial STIs, especially gonorrhoea, to all available antibiotics, has led to a shift in research priorities. Several clinical trials are investigating new vaccine candidates or repurposing already licensed vaccines, which may show activity against bacterial STIs. Hence, ongoing efforts to develop vaccines against STIs may prove to be successful in the near future. The WHO's key priorities identified in the Agenda for Sustainable Development are a clear example of the pivotal role that vaccines can play in the fight against STIs: 2 out of 3 goals focus on reducing the incidence of STIs and the last one refers specifically to HPV vaccination programmes. The ongoing epidemic of antimicrobial resistance, the lack of new antibiotics, the persistence of some viral STIs and the high rates of condomless sexual intercourse support the idea that vaccines are the best candidates for effective STI prevention programmes.

NEISSERIA GONORRHOEAE

Epidemiology and disease spectrum

Gonorrhoea infections are common worldwide, with an estimated global burden of 87 million new cases in 2016. The aetiologic agent of gonorrhoea is a bacterium, *N. gonorrhoeae* (also known as gonococcus). It belongs to the genus Neisseria, together with *N. meningitidis* (also known as meningococcus), the aetiologic agent of one form of bacterial meningitis. The disease spectrum includes genital, rectal, pharyngeal and conjunctival infections, which can be either asymptomatic or cause an acute syndrome. Uncomplicated infections can progress to adverse outcomes such as disseminated gonococcal infection (DGI), pelvic inflammatory disease (PID), infertility and adverse pregnancy outcomes.

Gonococci's success as human pathogens is the result of several combined factors:

– The plethora of bacterial virulence factors that allows efficient colonization of both male and female mucosae;
– The chameleon-like ability determined by high-frequency antigenic and phase variation of core surface structures, which causes clonal variability;
– The ability to subvert and hide from the immune system by directly suppressing and interacting with immunological effectors and regulators.

N. gonorrhoeae infections encompass a multi-step strategic process: highly-efficient pathogen transmission, localized mucosal adherence, local proliferation and invasion, local inflammatory response and external or systemic dissemination (Quillin *et al.,* 2018).

Therapy and open issues

Gonorrhoea is often treated effectively with a dual antibiotic treatment: ceftriaxone 250 mg intramuscular as a single dose plus azithromycin 1 gr orally as a single dose (WHO Guidelines for the Treatment of *Neisseria gonorrhoeae*. Geneva: WHO, 2016) or ceftriaxone 500 mg intramuscular as a single dose plus doxycycline 100 mg orally twice a day for 7 days (CDC 2020 Guidelines: St Cyr Barbee *et al.,* 2020). However, since the introduction of antibiotic therapy, gonorrhoea has developed high-level antimicrobial resistance to all drug classes (Drug Resistant *Neisseria gonorrhoeae* report. CDC, 2019). Ciprofloxacin resistance is now common worldwide, azithromycin resistance is present and stable, and decreased susceptibility and resistance to ceftriaxone (DS/R) are emerging. Cases of treatment failure with the currently suggested dual therapy have been reported, with subsequent isolation of extensive drug-resistant (XDR) specimens (Eyre *et al.,* 2018; Fifer *et al.,* 2016). No effective vaccine directly targeting *Neisseria gonorrhoeae* is currently available and, given the rise of multi-drug resistant (MDR) specimens and the lack of new antibiotics, it has become urgent to find an effective vaccination, as the growing risk of untreatable gonococcal infections poses a global health threat. Gonorrhoea is one of the three prioritized STIs requiring immediate action for control by WHO in the

SDG agenda. However, the sustainable limitation of infections might not be achievable with current interventions, and thus new methods are needed.
Given these premises, *N. gonorrhoeae* was included in the "WHO Priority Pathogens List for Research and Development of New Antibiotics". The list is structured in 3 priority categories, and *N. gonorrhoeae*, in the second category, is the only bacterial STI included (Global Priority List of Antibiotic-Resistant Bacteria. WHO, 2017).

Vaccines against gonorrhoea

The feasibility of developing a vaccine specifically targeting *N. gonorrhoeae* has been historically questioned. The high antigenic variability of the bacterium, the lack of protective immunity granted after one exposure and, therefore, the possibility of re-infection, has undermined the idea of creating a vaccine (Mehta *et al.,* 2003). However, thanks to advancing insights into *N. gonorrhoeae* immunopathogenesis, new candidate targets have been identified, paving the way to new and promising approaches (Vincent, 2019). In the past, chimpanzees were the only available animal model, which posed a limit to accessible research tools. The development of mice models made it possible to screen systematically for potential candidate antigens (Jerse *et al.,* 2011). Nevertheless, no *de novo* designed vaccines are currently in clinical trials and only a few have been assessed in the past in humans, all without success. The first clinical trial included a whole-cell *N. gonorrhoeae* vaccine, tested in a Canadian Inuit, resulting in an infection rate of 30% (*versus* 24% in the placebo group) (Greenberg *et al.,* 1974). The second, tested in American soldiers servicing in Korea in the '90s, was a parenteral vaccine based on the gonococcal pilus antigen, resulting in a cumulative infection rate of 6.9% (*versus* 6.5% in the placebo group) (Boslego *et al.,* 1991). In an unpublished clinical trial, a PorB-based vaccine also proved unsuccessful (Rice *et al.,* 2017). A partially autolyzed vaccine was tested in 1974 and a protein I-based vaccine in 1989, both failing. These failures discouraged research, funding and commercial interest in gonococcal vaccines. However, new insights into *N. gonorrhoeae* immune-pathogenesis and new available tools, such as genomics, proteomics and glycomics, justify new efforts in vaccine research.
Antigens showing promise in different pre-clinical stages are listed in *Table 1* (Vincent *et al.,* 2019).
Furthermore, the list of possible vaccine candidates is even broader. More than 168 surface proteins, highly conserved in *N. gonorrhoeae*, have been described thanks to proteomic analyses (Zielke *et al.,* 2016). Given the specific immunologic evasion of gonococci, it is paramount to identify suitable adjuvants and boosters in order to induce long-lasting immunity. One promising strategy, which has shown to be effective in mice, consists of administering intravaginal IL-12, which prevents TGF-β and IL-10 production and Th1 lymphocytes stimulation, which are the main actors of *N. gonorrhoeae* immune-escape (Liu *et al.,* 2013).
Given the absence of a specific vaccine targeting *N. gonorrhoeae*, in 2020 the WHO published a report of the preferred product characteristics for an ideal gonococcal vaccine, underlining the urgency of finding a safe and effective preventive tool in the short term. These guidelines are intended to facilitate product innovation and vaccine development, focusing attention especially on low-income countries, which suffer the highest burden of STIs.
Based on revision of the published literature, two main vaccine approaches were identified:
1) Developing a new vaccine
Suggested strategies include: outer membrane vesicles (OMVs)-based vaccines, LOS epitopes, purified-protein subunit vaccines, whole-cell formalin-inactivated vaccines, virus-like particles, DNA- or mRNAs-based vaccines.

Table 1 - *Gonococcal vaccine candidates showing promise in pre-clinical stages.*

Candidates	*Pre-clinical evidence*
2C7 epitope mimetic + MAP1 adjuvant	Reduced infection duration and bacterial burden in mice; induced bactericidal antibodies and Th1 response; passive protection with anti-2C7 monoclonal antibodies
OMV + IL-12	Reduced infection duration and bacterial burden in mice challenged with homologous or heterologous strains; induced Th1 responses and serum and vaginal IgG and IgA; protection dependent on INF-γ and B cells
Viral replication particle vector (rrPorB-VRP) + rrPorB + Ribi-700	Reduced infection duration in mice and induced Th1 response
TbpA, TbpB	Induced bactericidal antibodies and antibodies that block the capacity of *N. gonorrhoeae* to grow with human transferrin as the sole iron source
AniA	Induced bactericidal antibodies and antibodies that block AniA nitrite reductase activity
MetQ	Induced bactericidal antibodies and antibodies that block gonococcal adherence to epithelial cells
MtrE	Induced bactericidal antibodies

2) Expanding the indications of an already-licensed vaccine

The WHO identifies OMVs vaccines targeting *N. meningitidis* as the best candidate for this approach. Given that developing and licensing a new vaccine may take more than a decade to become available for use, this pathway seems the most effective in the short term, even if vaccine efficacy is less than optimal (WHO Preferred Product Characteristics for Gonococcal Vaccines. Geneva: WHO, 2020).

Meningococcal vaccines against gonorrhoea

Some evidence has suggested a possible role of the multicomponent meningococcal serogroup B (4CMenB) vaccination as a potential tool for reducing the gonorrhoea burden. 4CMenB, was developed by means of reverse vaccinology, is an OMV-based vaccine, currently used worldwide to prevent invasive meningococcal diseases (IMD) caused by serogroup B *N. meningitidis*. 4CMenB is made of OMVs from *N. meningitidis* group B strain NZ98/254, recombinant Neisserial Heparin Binding Antigen (NHBA) fusion protein, recombinant group B Neisseria adhesin A (NadA) protein, and recombinant factor H binding protein variant 1 (fHbp) fusion protein (Bexsero Product Information. EMA, 2012).

The first evidence of the effectiveness of a meningococcal-B vaccination against *N. gonorrhoeae* comes from Cuba, where a large epidemic of meningococcal disease during the 80s and the 90s created an urgent the need for an anti-meningococcal vaccination campaign. VA-MENGO-BC vaccine, which is based on OMV, was included in the Cuban Immunization Program: a decrease in gonorrhoea incidence was observed from 1989 to 1993. The reduction can be related specifically to the vaccination because, while the incidence of gonorrhoea decreased, other STIs increased (Azze, 2019).

Another retrospective ecologic study in Norway investigated the effectiveness of MenBVac against *N. gonorrhoeae*. Vaccine coverage during 1988 and 1992 was compared to laboratory-confirmed gonorrhoea rates from 1993 to 2008 in people more than 16 years old. Three cohorts were compared: unvaccinated people born between 1965-1972 (pre-vaccination, pre-VC), vaccinated people born between 1973 and 1976 (vaccination, VC) and unvaccinated people born after 1976 (post-vaccination, post-VC). Gonorrhoea rates dropped in men from 1993 (27.3:100,.000) to 1995 (12.3:100,000) and in women from 1993 (20.7:100,000) to 1999 (3.1:100,000). Moreover, in men and women 20-24 years of age, a significant reduction in the adjusted incidence rates was observed in individuals in the VC group. No effect was seen in other age groups (Whelan, *et al.,* 2016).

The most solid evidence of cross-protection against *N. gonorrhoeae* following an OMV-based meningococcal B vaccination comes from New Zealand. A retrospective case-control study was carried out in young adults 15 to 30 years of age living in New Zealand who had a laboratory-confirmed diagnosis of gonorrhoea or chlamydia in a sexual health clinic between 2004 and 2016 and were eligible to receive an MeNZB vaccination. Although no longer routinely used in clinical practice, it was paramount for controlling previous serogroup B outbreaks and for the development of 4CMenB. Adjusted vaccine effectiveness against *N. gonorrhoeae* among fully-vaccinated individuals 15 to 30 years of age was 31% (95%CI=21-39, p<0.001), with no significant differences between men and women. This study demonstrated that MeNZB provides solid protection against *N. gonorrhoeae* infection and suggested that decreased efficacy may occur over a short period of time (Petousis-Harris *et al.,* 2017).

Furthermore, a retrospective cohort study was conducted in New Zealand, assessing MeNZB effectiveness against hospitalizations caused by gonorrhoea. Adjusted MeNZB effectiveness against *N. gonorrhoeae* hospitalizations was calculated at 24% (95%CI=1–42%), with effectiveness of 47% (95%CI=18-66%) if only teenagers (median age 13) were considered in the analyses (Paynter *et al.,* 2019).

This study emphasises that OMV-based meningococcal vaccination is effective not only in the outpatient setting, but can also play a role in reducing gonorrhoea-related hospitalizations. Its effectiveness in reducing hospitalizations seemed a little lower (24% *versus* 31%) than that for patients presenting at sexual health clinics. One hypothesis could be that in some cases the cross-protection is sufficient only to experience mild-symptoms, but not to fully prevent infections, and that in high-risk populations this is not sufficient to prevent hospitalizations.

The above-mentioned evidence considers anti-meningococcal B vaccinations which are no longer available (MeNZB) or not routinely used in Italy (VA-MENGO-BC). The only study that investigated the 4CMenB vaccine was performed in Canada. After an increase in serogroup-B *N. meningitidis* cases in the SLSJ region of Quebec, Canada, a vaccination campaign with 4CMenB was conducted from May to December 2014, targeting individuals from 6 months to 20 years of age. *N. gonorrhoeae* and *C. trachomatis* case notifications and incidence rates (IRs) were analysed, comparing the pre-vaccination period (2006 - June 2014) to the post-vaccination period (June 2014-2017). The vaccination's impact on *N. gonorrhoeae* risk reduction was estimated to be 59% (Longtin *et al.,* 2017). However, the size of the study population being small and the disease rare, no statistical significance was found. The results of this ecologic study are consistent with previous data on OMV-based MeNZB vaccine effectiveness and may demonstrate that the 4CMenB vaccine could

Table 2 - *Summary of evidence of protection against N. gonorrhoeae by N. meningitidis vaccines.*

Vaccine	*Evidence*
VA-MENGO-BC, Cuba	Ecologic study. Reduction of gonorrhoea incidence during vaccination programme years.
MenBVac, Norway	Ecologic study. Significant reduction of the adjusted incidence rates of gonorrhoea among those vaccinated.
MeNZB, New Zealand	Case-control study. Vaccine effectiveness against gonorrhoea infection: 31%.
MeNZB, New Zealand	Case-control study. Vaccine effectiveness against gonorrhoea hospitalization: 24%.
4CMenB, Canada	Ecologic study. Reduction of gonorrhoea incidence rates (IRs): 59% (not statistically significant).
4CMenB, Italy	Case-control study among PLWH. Vaccines effectiveness against gonorrhoea infection: between 33 and 72%.

give higher protection against gonorrhoea compared to MeNZB. Moreover, a retrospective case-control study conducted in Italy confirmed that 4CMenB could grant cross-protection against gonorrhoea in the setting of PLWH (Raccagni *et al.,* 2021). 4CMenB vaccination exposure was associated with lower risk of gonorrhoea infections in MSM with HIV infection, at high risk of STIs, especially among young people (effectiveness between 33 and 72%).

A summary of evidence of anti-meningococcal vaccines effectiveness against *N. gonorrhoea* is presented in *Table 2*.

Rationale of effectiveness of meningococcal vaccines

The evidence supporting that a vaccination with 4CMenB could protect against gonorrhoea infection raises questions about its possible mechanisms of action. Although gonococcal strains show extensive variability, genetic homology between *N. meningitidis* and *N. gonorrhoeae* has been demonstrated. More than 80-90% of primary strains are shared between the two species and some meningococci virulence factors find an equivalent in gonococci (Tinsley *et al.,* 1996). OMVs are one example of antigens that have strong similarities and common epitopes between the two species. Research on OMVs identified that 20 of the 22 core proteins can be found in different *N. gonorrhoeae* strains. However, 4CMenB not only includes OMVs, but also three other recombinant proteins (NHBA, fHbp and NadA) that are, to some extent, also shared with *N. gonorrhoeae (*Jongerius *et al.,* 2013). NHBA is the only one exposed on the bacteria's surfaces and, therefore, is accessible to vaccine-induced antibodies; *Nhba*, which is the NHBA encoding gene, has been identified in 100% of *N. gonorrhoeae* strains. Thus, NHBA is a relatively highly conserved gonococcal protein that may provide another cross-protection against gonorrhoea, in addition to the one predicted for MeNZB (Hadad *et al.,* 2012). A study evaluated the ability of MeNZB- and 4CMenB-immunized rabbit and human serum to recognize gonococcal proteins by performing Western blot (WB) and ELISA analyses. *N. gonorrhoeae* OMVs and NHBA were all recognised by the sera of rabbits and humans who received the 4CMenB vaccination (Semchenko *et al.,* 2019).

The ability of 4CMenB to reduce *N. gonorrhoeae* disease burden, even if it was not primarily designed to target this specific bacterium, can be explained by the fact that the sterilizing immunity conferred by the meningococcal vaccine is probably not entirely required to prevent gonococcal transmission, as *N. gonorrhoeae* rarely causes invasive, life-threatening diseases. A less effective vaccine that targeted key factors contributing to pathogen colonization, transmission and pathology would be sufficient to prevent infections and onset of symptoms (Craig *et al.,* 2015). However, the selection of more appropriate and specific target-proteins is a future challenge: since only one out of the 3 recombinant proteins of 4CMenB is thought to be implied in the cross-protection process, it would be ideal to develop a new vaccine candidate where all components show specific gonococcal recognition.

Even a partially-protective vaccine, delivered with a realistic targeting strategy, could have a substantial impact and public health value by reducing gonorrhoea incidence, emergence of MDR strains, HIV infections and both direct and indirect costs (Whittles *et al.,* 2020; Régnier, 2014).

To better understand the real effectiveness of the 4CMenB vaccine against *N. gonorrhoeae*, clinical trials are currently or will soon start evaluating both the immune response and the disease prevention occurring after vaccination. The results will surely better define 4CMenB effectiveness against gonococcal infections, and will also provide ample evidence of cross-protection mechanisms as a result of laboratory analyses. When these data are available, it will finally be possible to define, from a public health perspective, the cost-effectiveness and feasibility of using 4CMenB as a tool in a real-world scenario to actively prevent *N. gonorrhoeae*. Moreover, thanks to better understanding of gonorrhoea pathogenesis and to new vaccine antigens showing promise in different pre-clinical stages, it is likely that new studies investigating vaccines that directly target *N. gonorrhoea* will be conducted in the near future.

CHLAMYDIA TRACHOMATIS

Epidemiology and disease spectrum

Chlamydia is the most common STI worldwide, with an estimated 131 million incident cases in 2012 (Newman *et al.,* 2015). The aetiologic agent of gonorrhoea is a bacterium, *Chlamydia. Trachomatis*.

Infections include genital, rectal, pharyngeal and conjunctival involvement, which can be either asymptomatic or cause an acute syndrome. Uncomplicated infection, similarly to gonorrhoea, can progress to adverse outcomes such as PID, which can lead to long-term complications such as infertility and adverse pregnancy outcomes. As most infections tend to be asymptomatic, most diagnoses are missed, still bearing the potential for long-term negative outcomes. Strains of *C. trachomatis* are divided into three biovars and are further subtyped by serovars. The trachoma biovar, *i.e.,* serovars A-C, causes non-congenital blindness, whilst the genital biovar, *i.e.,* serovars D-K, causes STIs. The lymphogranuloma venereum (LGV) biovar, *i.e.,* serovars L1-L3, causes invasive genital infections, which can result in serious adverse events such as ulcerations and lymphatic drainage obstructions. The chlamydia developmental cycle encompass a multi-step pathway in which it alternates between the extracellular, infectious elementary body and the intracellular, non-infectious reticulate body, which together with the ability to modify the host response *(e.g.,* host cell survival, death and replication cycle), is the landmark of its pathogenicity (Elwell *et al.,* 2016).

Therapy and open issues

Treatment of uncomplicated infections tends to be effective (doxycycline 100 mg orally twice a day for 7 days, CDC 2020 guidelines: St Cyr *et al.,* 2020), but resistance to azithromycin is rising worldwide (Hammerschlag, Sharma, 2021). Given the increasing risk of treatment failures, an effective vaccine is required. Moreover, this is also supported by the short-lived partial immunity resulting after natural infection (Rank 2010; Batteiger *et al.,* 2010) and the requirement of nucleic acid amplification tests (NAATs) as screening method of choice, which are not routinely available in many settings due to difficulties of implementation and related costs. Indeed, even in advanced settings where NAATs are available, screening programmes have found it hard to achieve high coverage rates and have not appeared to reduce infection rates and transmission (Datta *et al.,* 2013).

Vaccines against chlamydia

Today no vaccines are available against *C. trachomatis*, despite several research efforts, and there are no already-licensed vaccines to be repurposed, as seen for *N. gonorrhoea*. Evidence from pre-clinical animal models, epidemiological studies conducted in humans, and early clinical trials support the idea of the feasibility of developing a vaccine targeting *C. trachomatis*. Moreover, a partial and sterilizing immunity is acquired after natural infection, which however fades rapidly and is not sufficient to provide long-term immunity. However, the ability of natural infection to induce partial protection is promising for vaccine research. Vaccine development has been in the pre-clinical stages for many years, but the first Phase I trials are now underway. Moreover, thanks to scientific advances, a growing number of additional candidates for clinical evaluation are being identified. Several vaccine candidates have been investigated in the past. The first ones were live or formalin-fixed whole bacteria vaccines, which were assessed in the 60s, and targeted ocular trachoma rather than genital infections (Grayston, 1978; Sowa *et al.,* 1969). They demonstrated a partial but still insufficient and short protection (Woolridge *et al.,* 1967). Hence, the results of trachoma vaccine trials support the feasibility of developing an effective vaccine. However, concerns regarding the rise of an exacerbated disease when immunized individuals were challenged, shifted the research focus to vaccines based on subunits, in order to reduce safety issues. Historically there has been a strong bias toward systemic vaccines delivery, despite promising outcomes of mucosal delivery systems. Different pre-clinical trials highlighted that whole cell antigenic targets can induce an effective immune response to *C. trachomatis*, although the production of commercially suited antigen-based vaccines has proved to be challenging. Nowadays the major outer membrane protein (MOMP) has been identified as the ideal substitute to whole cell antigenic targets, and a vaccine based on MOMP entered a Phase 1 clinical trial (Olsen *et al.,* 2015; Boje *et al.,* 2016). Several studies highlighted that MOMP could be ineffective if not combined with carefully chosen adjuvants. After promising results in pre-clinical stages, the safety and immunogenicity in humans of a novel chlamydia vaccine based on a recombinant protein subunit (CTH522), adjuvated with cationic liposomes (CAF01) or aluminium hydroxide have been investigated. Both vaccines appeared to be safe and well tolerated; they were immunogenic, although CTH522 with CAF01 had a better immunogenicity profile, holding promise for further clinical development. The most suitable delivery system appeared to be a combination of both systemic and mucosal (intranasal) administration (Abraham *et al.,* 2019).

Moreover, the immunogenicity and safety of a vaccine made of CT584 epitopes [components of the type 3 secretion system (T3SS) exploited by the pathogen for host cell entry] coupled to a bacteriophage virus-like particle (VLP), was recently investigated in mice (Webster *et al.,* 2022). This vaccine was modelled on the success of HPV vaccines and showed promising results. Furthermore, several oth-

er vaccine candidates entered different pre-clinical stages: intranasal MOMP nanoemulsions (NanoBio Corporation, 2015), UV-inactivated *C. trachomatis* complexed with charge switching adjuvant particles (cSAPs) incorporated with a toll-like receptor 7 (TLR7) agonist (Stary *et al.,* 2015) and an oral vaccine based on an attenuated *Salmonella enterica* vector with insertion of chlamydial genes (Garmory, *et al.,* 2005). Moreover, research on vaccines against ocular *C. trachomatis* may also inform vaccine development for genital infections (Kari *et al.,* 2011).
Although further insight on these vaccines is needed, there are strong expectations for the CTH522 vaccine. Even though this vaccine candidate was proved only partially protective, mathematical models support the idea that, adding to currently used screening campaigns and treatment methods, it would be cost-effective and might substantially reduce the disease burden, adverse outcomes and related HIV transmission (Owusu-Edusei *et al.,* 2013). Moreover, the ultimate goal of a chlamydia vaccine is to reduce sequelae of upper genital tract infections in women: a vaccine candidate showing protection against PID and related adverse outcomes would be cost-effective, even without evidence of high protection against uncomplicated infections.

TREPONEMA PALLIDUM

Epidemiology and open issues

Syphilis, caused by the spirochete *Treponema pallidum spp. pallidum*, is a chronic multistage disease, with an estimated 36 million cases worldwide in 2012 (Peeling *et al.,* 2017). Congenital syphilis still remains the most common infection associated with foetal loss or stillbirth in low-income countries, and symptomatic infections greatly increase the risk of HIV transmission. It continues to be a public health problem in both low- and middle-income countries, where most control programmes focus on reducing congenital syphilis, as identified by one of the goals of the WHO Agenda for Sustainable Development. However, it has proved to be challenging to provide an adequate reduction of infections on a population-wide level. Moreover, it has re-emerged in high-income countries among key populations (especially men who have sex with men, MSM) (Schimdt *et al.,* 2019). All these challenges are compounded by supply chain shortages of benzathine penicillin, the syphilis first-line treatment of choice. Although control programmes and public health interventions are imperative for adequate infection control, disease eradication could be obtained only by implementing a parallel vaccination policy.

Vaccines against syphilis

To date, no effective vaccine is licensed against syphilis and no vaccine candidates are being investigated in human clinical trials, although the above considerations have led to renewed interest in developing an effective vaccine against *T. pallidum*. However, the lack of adequate funding and the challenges of using the existing rabbit model of infection have slowed research. Nevertheless, the evidence that multiple infections of irradiated spirochete have immunized rabbits against infections supports the idea that protection against syphilis is possible (Miller, 1973). Thus, it is the only bacterial STI for which a proof-of-concept vaccine has been developed. The evidence that complete protection against infections was obtained after several challenges with irradiated spirochete, but not with mechanically or chemically treated ones, supports the pivotal role played by bacterial surface proteins in generating protective immunity. Nowadays, research efforts focus mostly on reverse vaccinology to identify candidate antigens: treponemal outer membrane proteins have long been considered optimal targets for vaccine development (Lithgow *et al.,* 2017). Challenges remain to identify the right combination of antigens and choose the adequate adjuvants to develop a viable vaccine candidate. Several preferred product characteristics should be taken into consideration: first, the vaccine should be effective at preventing all stages of infection to avoid treponemal transmission during both primary, secondary and latent syphilis. Second, it has to be safe for use during pregnancy, to reduce the consequences of congenital syphilis. Third, as several *T. pallidum* strains are circulating worldwide, it must induce an effective cross-protection in order to avoid reinfections from different spirochetes: for instance, the study investigating immunity granted by irradiated treponema in rabbits highlighted that immunization with *T. pallidum* does not confer cross protection against heterologous bacteria strains (Cameron, 2018). However, compared to other bacterial STIs, limited research has been conducted due to the difficulties in culturing and genetically manipulating *T. pallidum*. However, several antigens have been identified as vaccine candidates and were assessed in animal models, with discordant results. This highlighted that multiple antigens have to be administered in order to achieve protection against infection, and there is a need for standardization of antigen preparation and immunization methodologies. Members of the *T. pallidum* repeat (Tpr) protein family have been identified as an ideal candidate: some proteins of this family play key roles at different pathogenic steps of infection and are often exposed on bacteria surfaces. However, given their extensive sequence variation and ability to undergo both antigenic and phase variation, it is likely that a multicomponent vaccine, encompassing a cocktail of different syphilis antigens, would be needed to achieve effective sterilizing immunity. Summary of investigated antigens in *Table 3*.

Table 3 - *Selection of individual antigens which have been investigated in animal models as vaccine candidates*.

Antigens	*Authors*	*Antigens*	*Authors*
Tp92	Tomson *et al.*, 2007	Tp0483	Tomson *et al.*, 2007
TprK	Morgan *et al.*, 2003	Tp0956	Tomson *et al.*, 2007
TprI	Giacani *et al.*, 2005	TpN47	Tomson *et al.*, 2007
TprF	Sun *et al.*, 2004	Tp0155	Tomson *et al.*, 2007

Moreover, during vaccine development the altered immune response to *T. pallidum*, which mostly relies on $CD4^+$ lymphocytes, among people living with HIV should be taken into consideration in order to achieve protection in the most prominent target population for vaccination (Stary, Klein *et al.,* 2010; Marra *et al.,* 2016).

HUMAN PAPILLOMA VIRUS

Epidemiology

HPV is a viral agent estimated to be one of the most common STIs in the USA, with a prevalence ranging from 1.3% to 72.9% (Lenzi *et al.,* 2013).

HPV-related morbidity and mortality remain a significant global public health burden despite opportunities for prevention using vaccines. Infection with oncogenic HPV strains is associated with the development of anogenital and oral cancers and precancerous lesions in both males and females (Widman *et al.,* 2018).

More than 95% of cervical cancer, the fourth leading cause of death in the world's female population, is due to HPV. It takes 15 to 20 years for cervical cancer to develop in women with normal immune systems, but it can take only 5 to 10 years among those with weakened immune systems, such as those with an untreated HIV infection.

There is a high rate of cervical cancer in low- and middle-income countries because it is often identified in advanced stages or when symptoms develop; furthermore, access to treatment is limited (WHO, (HPV) and Cervical Cancer, 2022).

HPV is transmitted through any skin-to-skin contact, which can lead to infection in susceptible persons (Centers for Disease Control and Prevention (CDC), 2016).

Several studies reported a higher prevalence of HPV infection in MSM than in heterosexual man (Cai *et al.,* 2018).

The prevalence of HPV infection in men does not vary among different age groups, and its incidence is similar in both genders with fairly rapid clearance. HPV in general may cause different types of diseases ranging from benign lesions to invasive tumours. Injury severity is based on the potential risk of causing malignant lesions: genotypes can be divided into high and low risk. In particular, types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 66 are well-known causes of carcinomas, especially cervical cancer (Cai *et al.,* 2018).

HPV can cause high-grade cervical intraepithelial neoplasia (CIN) and anal intraepithelial neoplasia (AIN), precursor lesions to cervical and anal cancer, respectively. About 60% of HIV-negative and 95% HIV-positive MSM acquire anal HPV; anal cytology is used as the screening method of choice. If any alterations are highlighted, individuals then undergo a more sensitive high-resolution anoscopy (HRA). Similarly, cervical cytology has been used for decades to identify women who require cervical colposcopy to visually identify CIN, biopsy it and treat it (Chin-Hong *et al.,* 2009).

The latest report by the European Centre for Disease Prevention and Control (ECDC) has shown that in the European Union and the European Economic Area (EU/EEA) there are currently about 34,000 new diagnoses of cervical cancer. More than 13,000 deaths are reported each year with a mortality rate of 2.8 per 100,000 women. Concerning other tumours of the anogenital tract, the number of cases per years amounts to 14,700. A significant number also regards head and neck cancers, with an incidence of 13,800 cases per year, mostly in males. (Guidance on HPV Vaccination in EU Countries: Focus on Boys, People Living with HIV and 9-Valent HPV Vaccine Introduction).

HPV vaccines impact

The introduction of vaccination against HPV certainly had a strong impact in terms of reducing the incidence of both HPV infections and related disease. For example, in Norway, Feiring B. *et al.* estimated the impact of the immunization program with the quadrivalent vaccine and observed, in their largely HPV-naive population, a substantial reduction in vaccine and non-vaccine genotypes among vaccinated and unvaccinated girls following introduction of HPV vaccination. The prevalence of infection caused by HPV genotypes contained in the vaccine decreased by 81% in 17-year-old immunized women compared to the unvaccinated cohort (Feiring *et al.,* 2018).

Similarly, in French women between 15 and 18 years of age, the incidence of genital warts decreased in the period 2008-2012 (Judlin *et al.,* 2015).

In Spain, there was an efficacy of 76% against the incidence of genital warts in young women 14-19 years of age after three doses of the 4-valent HPV vaccine (Navarro-Illana, *et al.,* 2017).

A systematic review conducted in 2012 showed that in Italy there was a prevalence of 8% of oncogenic HPV genotypes in the general population, with a peak in <25-year-old women. A second peak in prevalence was observed in the post-menopausal age. HPV 16 was the most prevalent genotype in Italy, present in 5% of the healthy population, followed by HPV 18 (about 1%). (Epicentro Hpv e Cervicocarcinoma i Papillomavirus, Trasmissione e Prevenzione).

Vaccines available in Europe and Italy

Three vaccines are available: a bivalent vaccine containing HPV 16 and 18 genotypes, a tetravalent vaccine also containing HPV 6 and 11 genotypes, and a nonavalent vaccine, which contains genotypes 6, 11, 16, 18, 31, 33, 45, 52 and 58. They have been authorized by the European Medicines Agency (EMA) since 2006-2007. They protect against genital warts, precancerous lesions and cancers of the cervix, vulva or vagina, anus, penis, head and neck. HPV vaccines are formulated to induce humoral immune responses and are well tolerated, effective and safe (Agenzia Italiana del Farmaco Gardasil 9. Allegato I Riassunto delle Caratteristiche del Prodotto).

All these vaccines contain highly purified virus-like particles (VLPs) of the major HPV L1 protein (European Centre for Disease Prevention and Control Prevention and Control Measures for Human Papillomavirus).

The vaccination schedule provides for the administration of two doses at 0 and 6 months for subjects up to 13 or 14 years; for subjects >14 years of age the administration involves three doses at 0, 1-2 and 6 months (Ministero della Salute Piano Nazionale Prevenzione Vaccinale 2017-2019).

In Italy, vaccination against HPV has been proposed and recommended to 12-year-old girls as a primary target since 2007, and additional age groups were then proposed, such as 25-year-old women belonging to HPV screening services already subjected to active call. (Ministry of Health. Consiglio Superiore di Sanità Sessione XLVI - Sezioni congiunte II e III - Seduta del 11 Gennaio 2007; Ministry of Health: Rome, Italy, 2007).

Both sexes were included as candidates for vaccination against HPV in adolescence, preferably before sexual debut, only in 2017-2019; the primary target was immunization of the entire population, and the preferable age for the active and free offer of HPV vaccination in Italy is set at the 12th year of life (Ministero della Salute Piano Nazionale Prevenzione Vaccinale 2017-2019).

HPV vaccination: immunogenicity and safety data

The Cochrane review by Arbyn et al. included data from 26 different randomized controlled trials and evaluated the immunogenicity, clinical efficacy, and safety of prophylactic HPV vaccines in adolescent girls and women. Higher protection rates were observed for lesions associated with HPV-16/18 than for other types, and strong evidence that HPV vaccines protect against cervical pre-cancer lesions in female aged 15 to 26 years was detected.

The evidence that HPV vaccines reduce the incidence of cervical intraepithelial neoplasia (CIN) grade 2+ in older women who are HPV-16/18-negative is moderate; this is not true when they are not selected by HPV DNA status (Arbyn, *et al.,* 2018).

Schwarz Tino F. et al examined the ten-year immune persistence and safety of the AS04- HPV- 16/18 vaccine administered to women up to 55 years of age.

Participants were invited to attend an annual visit to evaluate long-term immunogenicity and safety. Anti-HPV-16/18 antibodies in serum and cervico-vaginal secretions (CVS) were measured: seropositivity rates of anti-HPV-16 remained high (96.3%) in all age groups 10 years after the first vaccination, whereas seropositivity of anti-HPV-18 decreased from 99.2% in groups 15 to 25 years old to 83.8% in groups 45 to 55 years old. However, anti-HPV-16 and anti-HPV-18 titres were at least 5.3-fold and 3.1-fold higher than titres observed after natural infection and were predicted to be persistent above natural infection levels for at least 30 years in all groups described.

This study concluded that vaccinated females 15-55 years of age elicited sustained immunogenicity with an acceptable safety profile up to 10 years after primary vaccination, suggesting long-term protection against HPV (Schwarz *et al.,* 2017).

As for the male subjects, the long-term data are still being studied. Further confirmation of a decrease in prevalence of HPV genotypes included in the quadrivalent vaccine has been observed comparing pre- and post-vaccine period in the vaccinated heterosexual male population in Australia; this decrease was most significant in individuals younger than 21 years (Chow *et al.,* 2017; Chow *et al.,* 2019).

HPV vaccination in high-risk groups

The European Research Organization on Genital Infection and Neoplasia (EUROGIN) 2012 Roadmap made a descriptive overview, suggesting greater rates of female-to-male (F-M) than male-to-female (M-F) transmission. A systematic review and meta-analysis were performed to assess the evidence for the differential transmission rate hypothesis regarding genital-to-genital HPV transmission. They included seven longitudinal studies on heterosexual couples and used several different HPV detection methods, calculating pooled estimates of F-M and M-F transmission rates and their rate differences per 100 person-months, with 95% confidence intervals (CI). They used a random-effects model, counting occurrences of directionality preponderance for each HPV type. The overall rate difference was 0.61 infections

per 100 person-months (95% CI, -0.27 to 0.49): F-M transmission is higher, although the result was not significant. Three studies provided rates by sex and HPV genotype; 2 favoured a preponderance of F-M and 1 favoured M–F transmission. In conclusion, there was a different transmission rate favouring higher F–M than M–F transmission, but these findings must be interpreted with caution due to the presence of substantial statistical heterogeneity across studies (Balaji *et al.,* 2020).

A study including 304 female sex workers (SWs) was conducted in Amsterdam and showed that vaginal and anal high-risk (hr) HPV prevalence was 46 and 55%, respectively; hrHPV L1 seropositivity was 37%. Vaginal and anal hrHPV prevalence is high among female SWS in Amsterdam, the Netherlands. Promotion of HPV vaccination, preferably at the beginning of sex working, may be a useful prevention method against hrHPV infection, and potentially against transmission and disease (Marra *et al.,* 2018).

SWs are at high risk of HPV infection: it is important to promote vaccination among them, because the immunogenicity of vaccines is excellent in all women, even if previously exposed. Hence, women with HPV disease may still benefit from vaccination, as they may not have been exposed to all HPV types covered by HPV vaccines. Finally, it could reduce transmission of HPV to clients. On the other hand, there are also reasons not to offer a vaccine to these individuals, because the current vaccines are prophylactic and have not shown to be therapeutic. It is difficult to demonstrate a woman's previous HPV status and whether HPV was cleared or has gone into latency; moreover, vaccinating after sexual debut may not offer protection against CIN2+ or anal intraepithelial neoplasia (AIN2+) (Silverberg *et al.,* 2018).

MSM are at high risk of HPV infection and associated diseases, and have little to no benefit from the girls-only vaccination programme.

A vaccination programme was recommended for MSM attending sexual health clinics in Scotland and was implemented later for MSM under 45 years as well as for prisoners and transgender women. The uptake of the HPV vaccine in Scotland was higher in the 20-29 age group and was approximately 65% for the first dose, but rates of the completion of the schedule are lower. Data were extracted from the national sexual health database on the number of treatment prescriptions for genital warts. In the case of MSM, there was no decline in the number of prescriptions, contrary to women and heterosexual men. Similarly, rectal swabs were used to assess the impact of vaccination on HPV prevalence. There was a slight and non-significant increase in HPV-6/11 types and a significant decrease in HPV-16/18 types from 37.9 to 31.8% (odds ratio (OR) 0.76, p=0.0014). (Joint Committee on Vaccination and Immunisation; Waheed *et al.,* 2021).

Adherence to HPV vaccination

Provider recommendation may influence HPV vaccine uptake for adults, and it is important to assess patient information needs related to shared decision-making; patients say that they do not have enough information regarding the HPV vaccine and so they can't make a decision on their own and specifically need more information about safety and efficacy (Wheldon *et al.,* 2021).

Galvin et al. conducted a study that evaluated the association between four domains of health literacy and willingness to get the HPV vaccine if a provider recommended it. Participants aged 27-45 years with no history of HPV vaccination were recruited online; the outcome of interest was the willingness to receive the vaccine with a provider's recommendation. Overall, 65.3% of the 636 participants were willing to be vaccinated with a provider recommendation. Furthermore, many participants reported ease with finding (67.9%) and understanding (65.6%) HPV vaccination information. Finally, for the unadjusted bivariate chi-square analysis, willingness to vaccinate with provider recommendation was significantly associated with all health literacy covariates ($p<0.05$). (Galvin, Garg *et al.,* 2022).

Despite recommendations from the Advisory Committee on Immunization Practices (ACIP) for routine HPV vaccination of both females and males at ages 11-12, coverage rates are suboptimal. There is still a lack of education on vaccines, which could be a consequence of the lack of time to discuss prophylactic tools with patients (Palmer *et al.,* 2015).

Christy A. Widman et al. conducted an environmental scan among clinicians and parents to explore opportunities, barriers and resources focused on issues regarding HPV vaccination.

They approached 52 clinicians and 54 parents. Most clinicians discussed the need to communicate cancer prevention information to both adolescents and parents. Furthermore, they said they lacked knowledge pertaining to relevance of the vaccine for boys and the appropriate age to start the vaccination process. Lack of education was the most often reported barrier to HPV vaccination uptake noted by parents. They stressed the misinformation on social media and the fact that education was a means to help increase the uptake of HPV vaccine, including alleviating concerns about safety. Both groups also strongly agreed messages about the HPV vaccine should focus on cancer prevention.

Parents also cited school-based education as a potential venue for sharing all this information.

It is important to empower parents to initiate further dialogue on HPV vaccination with their health care clinicians. Despite this, there are misperceptions among both parents and clinicians that HPV vaccination contributes to sexual promiscuity; this may represent a barrier to conversations during office

Table 4 - *HPV vaccination coverage in Italy, observed in females in year 2020. (Ministero della Salute Coperture Vaccinali al 31 Dicembre 2020 per HPV).*

Birth cohort	*1996*	*1997*	*1998*	*1999*	*2000*	*2001*	*2002*	*2003*	*2004*
% first dose	46.34	65.62	67.77	69.87	72.34	74.56	75.01	74.91	75.4
% complete cycle	42.77	62.84	65.01	66.97	68.92	70.12	67.47	65.42	63.84

Table 5 - *HPV vaccination coverage in Italy, observed in males in year 2020. (Ministero della Salute Coperture Vaccinali al 31 Dicembre 2020 per HPV).*

Birth cohort	*1996*	*1997*	*1998*	*1999*	*2000*	*2001*	*2002*	*2003*	*2004*
% first dose	0.48	0.52	0.67	0.97	1.55	3.33	5.69	13.54	21.37
% complete cycle	0.31	0.38	0.49	0.74	1.2	2.69	4.44	11.3	18.42

visits. The HPV vaccine remains underutilized when compared to other vaccines, but addressing misperceptions and educational gaps is a key strategy to increase vaccine uptake (Widman *et al.,* 2018).
HPV vaccination coverage is illustrated in *table 4* and *5*.

HEPATITIS A

HAV is a virus responsible for 1.4 million cases of infections per year globally (Melnick *et al.,* 1992).
HAV is now classified into five genotypes; only genotypes I, II, and III, further divided into subtypes A and B, infect humans (Pérez-Sautu *et al.,* 2011).
HAV does not cause chronic infections, whereas other hepatitis viruses do. The initial incubation period lasts four weeks; it is often followed by a nonspecific prodromal phase during which a person experiences a flu-like syndrome and intestinal disorders for a few days. The next, icteric, phase is defined by jaundice and hepatic cytolysis with elevated serum aminotransferase activities. Symptoms occur mostly in adults and fulminant hepatitis is rare (Tong *et al.,* 1995).
HAV has a strong physical resistance; this, added to the shedding of high titres of the virus in the faeces of individuals who have been infected, explains why transmission is common in poor hygiene conditions and contamination of wastewater when sanitation is suboptimal (Tjon *et al.,* 2006).
This mainly faecal-oral route of transmission can be direct through contact with an individual who has been infected or indirect by ingestion of contaminated water or food. Several outbreaks have been related to consumption of specific food products (fresh blackberries, frozen strawberries, raw scallops and pomegranate seeds). However, a study in 2017 conducted in four states (California, Kentucky, Michigan, and Utah) showed evidence of a shift toward large community outbreaks with person-to-person transmission. These infections have been seen especially among people with injection or non-injection drug use and/or experiencing homelessness (Foster *et al.,* 2017).
Bloodborne infections can also occur in blood transfusion recipients, although such cases are rare; improvements in virus inactivation and the use of sterilized recombinant clotting factors have ensured that these patients are no longer at high risk (Manka *et al.,* 2016).
In low-middle countries, people are exposed to the virus early in life, so there is a high level of immunization. Lower exposure to the virus in countries with higher sanitary and socioeconomic conditions leads to a greater proportion of susceptible individuals. Infection rates remain low in areas where HAV is rare and there is limited circulation (WHO).
Nowadays, infections are increasing among high-risk groups, such as people who are travelling from low endemic areas to high endemic countries. Despite vaccination recommendations for these individuals, the vaccination rate remains low (Lu P.-J. *et al.*).
Another high-risk group in developed countries is represented by MSM. The major risk factors are represented by oral-anal and digital-anal intercourse, sex with multiple partners, current infections with other STIs, visiting gay saunas, dark rooms and dating apps. More and more MSM use pre-exposure prophylaxis (PrEP) for preventing HIV infection; PrEP requires medical follow-up with regular STI screening. This could encourage vaccination awareness among MSM. It is important to spread health education messages, such as recommending handwashing immediately following any digital rectal intercourse (Hennin *et al.,* 1995).

HAV vaccine

The management of HAV is mainly symptomatic. Prevention is extremely important, as is improving sanitary conditions.
Immunoglobulins have been used for prevention of HAV infections, but their use has largely been abandoned after the availability of an effective vaccine, except in infants below 12 months of age. Post-exposure prophylaxis with the HAV vaccine has been used since 2007 for immunocompetent patients without chronic liver disease, and who are between the ages of 12 months and 40 years of age (Centers

for Disease Control and Prevention. Widespread person-to-person outbreaks of hepatitis A across the United States, 2020).
An inactivated HAV vaccine has been licensed in Europe since 1991 and the United States offers two commercially available hepatitis A vaccines and one combined HAV/HBV vaccine. A live attenuated vaccine has been in use in China with good success since 1992 (Werzberger *et al.,* 1993).
The HAV vaccine is typically administered in two doses, 6 months apart, whereas the HAV/HBV vaccine usually requires three doses (Beran *et al.,* 2010).
The efficacy of both live-attenuated and inactivated vaccines has been well established in large clinical trials across the globe collectively encompassing nearly 750,000 patients. Both vaccines confer a protective effect against HAV when given before exposure (Irving *et al.,* 2019).
An antibody titre greater than or equal to 20 mIU/mL is thought to be protective (Lemon *et al.,* 1983).
Knowledge of HAV risks and prevention including vaccination recommendation was poor among affected MSM; indeed, there is still a low rate of vaccination among this population. The most common reasons for vaccine refusal were fear of side effects, a general reluctance to vaccinations, and the assumption of not being at risk of infection. The number of vaccinations among MSM in an HIV centre is certainly higher than in other clinics. However, it is important to promote awareness of HAV and its complications not only in these contests, but among all people at high risk and to facilitate their vaccination. Furthermore, vaccination should be installed at sexually transmitted infection checkpoints and other low threshold facilities accessed by MSM who are not using the traditional health care system (Zimmermann *et al.,* 2021).

HEPATITIS B

Chronic HBV infection had an estimated prevalence of 257 million people worldwide in 2015. Most cases are registered in the Western Pacific and African regions (68%) and the lowest prevalence is in North America (WHO. Global hepatitis report).
There are ten identified HBV genotypes (A-J) collectively, with 35 sub-genotypes; five of the nine genotypes cause 96% of chronic HBV infections worldwide: genotype C is most common (26%), followed by genotype D (22%), E (18%), A (17%) and B (14%). Genotypes F to I together cause less than 2% of global chronic HBV infections. There is a marked difference in the geographic distribution of carriers (Velkov *et al.,* 2018).
The variation in the genotype distribution and risk factors relies on common factors in high-risk populations, such as vertical transmission, which is associated to higher risk of chronic disease and hepatocellular carcinoma (HCC). In endemic areas, the infection is often acquired during the preschool years. HBV is found not only in blood but also in saliva, semen and vaginal secretions, all of which are capable of transmitting the virus, making HBV a possible STI (Meireles *et al.,* 2015).
In Asiatic countries the most common route of transmission is perinatal, while in African countries it is the horizontal route during childhood (Luo *et al.,* 2012).
Transfusions of infected blood products, contaminated injections, sharing of needles among injecting drug users, and unsafe sexual practices are other ways of transmission that are typical of high-income countries. Furthermore, another route is interfamilial transmission involving non-sexual interpersonal contact over a long period of time (Stefos *et al.,* 2009).
Sexual transmission still accounts for the majority of new infections, which are especially common among unvaccinated MSM. Consequently, hepatitis B vaccination is recommended for all people who are at risk of sexual infections, such as sex partners of persons positive for hepatitis B surface antigen, sexually active persons who are not in a long-term, mutually monogamous relationship, persons seeking evaluation or treatment for an STI, and MSM (Mast *et al.,* 2006).
Moreover, all HIV-infected persons should be vaccinated against hepatitis B, because the natural history of hepatitis B is accelerated in the setting of HIV, and coinfection imposes specific considerations in the choice of antiretroviral therapy (Marrazzo *et al.,* 2011).

Types of vaccines

Three hepatitis B vaccines are currently approved for use. Engerix-B and Twinrix are given as a series of three doses over the course of six months.
The first vaccines produced were plasma-derived and contained purified HBsAg obtained from the plasma of people with chronic HBV infection. In the following years, yeast-derived recombinant HepB vaccines have been developed by cloning the HBV S gene in yeast cells. Recently, a mammalian cell-derived recombinant vaccine was developed. There are three vaccines in this class. One of these contains, in addition to the S antigen, antigen from the pre-S2 region, while the other two contain antigens from the pre-S1 and pre-S2 regions. A controlled trial showed that this class of vaccine was associated with a better immunologic response, but vaccines with pre-S antigens are not widely available. Currently, recombinant DNA hepatitis B vaccines are mainly being used, while plasma-derived hepatitis B vaccines are still being used in most low-income countries (Vitaliti *et al.,* 2013).
HBV vaccines are available not only in monovalent formulations that protect only against hepatitis B,

but also in combination formulations that protect against HBV and several other diseases, such as diphtheria, polio, pertussis, tetanus, and *Haemophilus influenzae* type B; the immunogenicity of these vaccines is similar. The multivalent vaccines are commonly used in childhood immunization programmes and have greatly facilitated compliance and reduced cost. The best method would be to administer the first dose of vaccine as soon as possible after birth (<24 h), in order to avoid early interfamilial transmission, which is around 95%. When immunizing against HBV at birth, only monovalent vaccine should be used (Lavanchy *et al.,* 2012).

Efficacy of HBV vaccination

Hepatitis B is self-limited in most adult patients with acute infection, and 1%-2% of these patients progress to fulminant hepatic failure; <10% progress to chronic infection, which can be associated with liver cirrhosis, hepatic decompensation (ascites, variceal bleeding, hepatic encephalopathy, and spontaneous bacterial peritonitis), HCC, and premature death. The rate of progression from acute to chronic HBV infection is reported to be 90% in new-borns and 5%-10% in adults. The progression of acute hepatitis B to chronic hepatitis is higher in Western countries. The different rates of chronicity are supposedly associated to the different distribution of HBV genotypes (Michitaka *et al.,* 2014).

The HBV vaccine was the first vaccine with a triple target: to prevent two viruses and one cancer, i.e., HBV, hepatitis delta and hepatocellular carcinoma (Meireles *et al.* 2015).

A positive immune response to the vaccine is defined as the development of HBV anti-HBs at a titre of >10 mIU/mL, after a complete and adequate immunization schedule measured preferably 1 to 3 months after the last vaccine administration (FitzSimons *et al.,* 2011).

Long-term follow-up studies of new-born vaccinations demonstrated that antibodies become negative in 15%-50% of vaccine responders within 5 to 10 years. A natural booster effect with activation of memory B cells, due to environmental exposure to HBV, can contribute to persistence of anti-HBs antibodies, particularly in areas of high endemicity. Long-term protection is present despite a decrease in anti-HBs antibodies over time. However, the exact mechanism of long-term protection is not yet fully understood, but is probably due to the priming of memory cells, which are capable of producing an anamnestic response when challenged. This is probably because the immunological memory for HBsAg can outlast antibody detection (Vitaliti *et al.*, 2013).

Currently, decisions to offer a booster dose in case of anti-HBs antibody titre <10 mIU/mL is controversial and not recommended by the WHO. The neonatal period and childhood constitute the high-risk period, because later in life it more likely evolves toward chronicity than toward infections. The next high-risk period of exposure is adolescence, in which the onset of sexual activity increases the risk of transmission. A booster dose can be provided to non-responders and exceptionally to some high-risk individuals (e.g., healthcare workers, couples of chronic carriers). While most recipients of three doses of currently available HBV vaccines produce a strong, protective and long-lasting anti-HBs response, 5%-10% of healthy adults do not produce protective levels of anti-HBs and can be considered non-responders. Inappropriate vaccine storage conditions, administration not following recommendations, age, body mass index, chronic alcoholism, cirrhosis or chronic renal failure, immune suppression, organ transplant recipients, chronic haemodialysis, celiac disease and smoking, drug abuse or infections at the time of vaccination, have been found to be associated with a lower rate of response. A possible genetic predisposition to vaccine non-responsiveness has been demonstrated: variants in HLA-DP, HLA-DQ, HLA-DR influence response to vaccination. Persons unresponsive to a first series of three doses of vaccine are advised to complete a second course of vaccine. Non-responders to the second course could have an underlying chronic HBV infection (Tong *et al.,* 2014).

HEPATITIS C

HCV is an important health burden: in 2015, the WHO estimated that there were at least 71 million people chronically infected with HCV (WHO. Global Hepatitis Report, 2017).

Around 400,000 deaths occurred from infection complications. HCV causes both acute and chronic liver disease, and chronicity is associated with the development of cirrhosis (15%-30%) and hepatocellular carcinoma (HCC) (WHO. Fact Sheet: Hepatitis C, 2018).

The major route of transmission in most countries worldwide is blood transfusion. Countries that have adopted NAAT screenings of blood donations have eliminated the risk of transmission. In some African countries, the adequate sterilization of medical devices or even the use of disposable equipment is not adequately enforced, accounting for a residual nosocomial risk. Intravenous drug use (IVDU) has been the second major route of transmission, initially in industrialized countries, since the 1960s; now it affects many countries in the world, in urban as well as in rural areas. Harm reduction policies, needles exchange programs, and development of opioid substitution treatments have significantly helped reduce the prevalence in industrialized countries (Roudot-Thoraval *et al.,* 2021).

Sexual transmission of the virus occurs when infected body secretions or infected blood are exchanged

across mucosal surfaces. Differences in the rate of HCV infection may reflect differences in at-risk sexual behaviours. Sexual transmission of hepatitis C occurs especially in MSM who adopt rough sexual techniques, such as anal fisting, the use of toys and group sex. These practises increase the risk of exposure to blood or can even cause minimal trauma to the rectal mucosa (Van de Laar *et al.,* 2007).
The use of psychoactive substances, to enhance sexual pleasure and anal sphincter relaxation during receptive anal intercourse or to remove inhibition during rough sexual practices, might also cause mucosal trauma or bleeding, especially when substances are applied anally (Purcell *et al.,* 2005).
Presence of the virus in body secretions is necessary but may not be sufficient for transmission to occur. Other factors that may be implicated in transmission are the titre of virus in body secretions, the integrity of the mucosal surfaces, and the presence of other genital infections (Terrault *et al.,* 2002).
However, quantifying the magnitude of an individual's risk of HCV acquisition by sexual contact is difficult. Epidemiological studies have had several methodological shortcomings that tend to overestimate the proportion of HCV infections attributed to sexual contact. Early studies used first-generation antibody to HCV (anti-HCV) assays, which have a higher false positive rate than second- and third-generation assays. Studies to detect HCV RNA in semen (seminal fluid and cells), vaginal secretions, cervical smears, and saliva have yielded mixed results, because even in studies using optimal methods to isolate HCV RNA, all positive samples were of low titre. This titre of virus in genital secretions may be one reason that HCV is transmitted less efficiently than hepatitis B virus or HIV. Additionally, there may be an absence of suitable target cells in the genital tract to allow infection to occur, or infection may require the presence of abnormal mucosa. Finally, a cell culture system or animal model is needed to prove that the HCV RNA detected in genital secretions represents infectious virus (Leruez-Ville, Kunstmann *et al.,* 2000; Manavi *et al.,* 1999).
There is still no vaccine against HCV. Prevalence of the disease is underestimated, mostly because HCV infections are mainly asymptomatic and this fact does not help achieve the goal of eradication. Concerning treatment, the development of interferon-free (IFN-free) regimens based on direct-acting antivirals (DAAs) has revolutionized HCV therapy (Bartenschlager *et al.,* 2018).
However, there are some limitations and obstacles to keeping the virus in check, especially the cost and practical aspects of treatment access, which leaves underdeveloped regions without treatment (Bailey *et al.,* 2019).
An interesting aspect to emphasise is that eliminating HCV infection with DAAs does not eradicate the risk of developing liver cancer. Furthermore, protective immunity is usually insufficient after natural or treatment-induced viral clearance: the possibility of reinfection remains (Midgard *et al.,* 2016).
Together, these facts make HCV elimination in high-risk groups a very challenging task, and the need for an effective prophylactic vaccine remains the greatest unresolved medical problem in the hepatitis C field (Cox *et al.,* 2020).
Vaccine development continues to be in experimental stages, primarily because of the genetic diversity of the virus. There is also an incomplete understanding of the body's immune response to the HCV and limited appropriate preclinical animal models. While humans are the natural reservoir of HCV, human and even chimpanzee experimental conditions for a vaccine are ethically challenging (Manne *et al.,* 2021).

Prior studies of HCV vaccines

There is a large variety of candidate HCV vaccines targeting humoral and/or cellular immunity, such as virus-like particles, recombinant protein, recombinant protein and peptide, DNA and viral vector, and recombinant protein-based strategies (Manne *et al.,* 2021).
Several studies have been conducted using chimpanzees; one design used an antibody-based vaccine consisting of recombinant E1 and E2 glycoproteins from a genotype 1a virus adjuvanted with MF59. It showed a strong antibody response and delayed onset of viremia, but it failed to provide sterilizing immunity (Houghton *et al.,* 2010).
Another study used a recombinant protein vaccine against genotype 1a E1 and E2 in 21 chimpanzees. The results showed five chimpanzees aviremic, resolution in 14, and chronic infection in two (Choo *et al.,* 1994).
Another study using viral vector vaccine type, using antigen GT1b core, E1, E2, p7, NS2, and NS3 in four chimpanzees showed protection against CHC infection (Youn *et al.,* 2008).
Eight vaccine studies in mice were notable. Three of them were DNA vaccines: the first one, using HCV strain GT1b, with targets E1, and E2 resulted in antibody responses toward GT1a, 1b, 2a, 2b, 3a, 4a, 5, 6, and a CD4+ T-cell response was observed (Masavuli *et al.,* 2019).
Of the three studies using a virus-like particle vaccine, the first was conducted in both mice and pigs. Scientists used target core, E1 and E2, using the HCV strain GT1a H77, GT1b BK, GT2a JFH1, and GT3a, which resulted in a homologous neutralizing antibody response (Christiansen *et al.,* 2018).
Two studies used a rat Hepacivirus infection model to evaluate the effectiveness of T-cell immunization in preventing rodent hepacivirus (RHV) persistence. A simian adenovirus vector vaccine strategy was effective at inducing complete protective immunity in the rat RHV model (Hartlage *et al.,* 2019).

Several clinical trials involving humans have been performed, using varying vaccine types. Frey constructed a randomized, double-blind, placebo-controlled, dose-escalation study over four vaccine doses with HCV E1/E2 in 60 healthy adults (Frey *et al.,* 2010; Law *et al.,* 2013).
This study demonstrated lymphocyte proliferation responses to E1/E2 in participants with no significant difference in adverse effects across groups. Finally, the vaccine was well tolerated overall while stimulating a significant humoral and cell-mediated immune response that was not dose-dependent (Frey *et al.,* 2010).
Page conducted a Phase 1–2 randomized, double-blind, placebo-controlled trial, using a recombinant chimpanzee adenovirus 3 vector priming vaccination (ChAd3- NSmut) followed by a recombinant modified vaccinia Ankara boost (MVA-NSmut) in 68 participants to produce HCV-specific T-cell responses. The study did elicit T-cell responses against HCV proteins, but it did not ultimately prevent CHC infection as the incidence of CHC infection was not lower when compared to the placebo group. This fact was postulated to be associated to lower vaccine immunogenicity innately in the study population of persons who inject drugs (Page *et al.,* 2021).
The vector encoding the NS3, NS4, NS5A, and NS5B proteins of HCV genotype 1B in Swadling's study showed a durable, sustained T-cell response in both CD4+ and CD8+ cells (Swadling *et al.,* 2014).
Unfortunately, all the above studies are still in early phases. An effective vaccine will likely need to integrate both an antibody response and a robust T-cell response.
It is important to understand all the mechanisms by which immune cells mediate short- and long-term protection; furthermore, technological advancements have generated HCV virus vaccine sequences to elicit a cross-reactive T-cell response, which has been shown to be effective (Burke *et al.,* 2012).
It is important to stress that more public education on the widespread nature of HCV and its implication for public health is necessary to progress in research (Manne *et al.,* 2021).

CONCLUSION

An effective vaccine is available for some viral STIs and there is a profound lack of vaccines for bacterial STIs. Further research is needed, as vaccines constitute the ultimate solution for the growing epidemic of STIs. Better insight on HAV and HBV effectiveness is needed, and it is urgent to further develop HPV vaccines aimed at targeting more genotypes, as well as to better define already-licensed nonavalent vaccines effectiveness, duration over time and possible need for booster doses. Research on bacterial STIs must be quickly implemented: the rising risk of untreatable infections, due to increased drug resistance, demands prompt action.
Moreover, several practical points should be taken into consideration.
The target population for newly-developed vaccines aimed at targeting STIs should include both young males and females, 10-24 years of age, and high-risk groups (*e.g.,* sex workers, MSM, transgenders, people in correctional facilities, and vulnerable populations). It is unknown how prior STIs would affect vaccine efficacy, but it is highly desirable that vaccination occur before the first sexual exposure, as already happens for HPV vaccination.
Vaccine delivery strategies should consider the characteristics of the product and the duration of protection. Aligning the target age of the vaccine with that of other widely-used vaccinations, such as HPV, would ease administration, but only if the duration of the granted protection is adequate. Moreover, implementing routine vaccination in HIV prevention programmes (*e.g.,* PrEP and STIs screening campaigns) in sexual health clinics could provide an opportunity to deliver a more focused vaccination to key populations.
Another challenging task would be to develop a vaccine targeting more than one STI, such as both *N. gonorrhoeae* and *C. trachomatis*, due to their similar transmission routes, adverse outcomes and frequent co-infections rates. Nevertheless, to avoid vaccine hesitancy, marketing and communication strategies have to be considered prior to vaccine development. Vaccines against STIs might be stigmatized as being associated with sexual intercourse, affecting their acceptability to the parents of adolescents; thus, public health strategies need to be implemented. Even though, reassuringly, HPV vaccine uptake tends to be high, it is regarded by the general population as a cancer-preventing vaccine and is not clearly associated with STIs. Policy makers should prevent stigma, focusing on the burden of STIs-related complications, thus conveying, for example, the idea of a vaccine against PID, adverse pregnancy outcomes or cancer, rather than a vaccine to prevent STIs.

Transparency declarations

All authors have no conflicts of interest to declare.

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