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Review

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Sexually transmitted infections in Spain: Current status

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ABSTRACT

Sexually Transmitted Infections (STI) are a major public health problem. The problems inherent to their diagnosis, treatment and prevention have to do not only with their nature, but also with organizational issues and overlapping competencies of the different health authorities in Spain.

The real situation of STI in Spain, at present, is poorly known. For this reason, the Scientific Committee on COVID and Emerging Pathogens of the Illustrious Official College of Physicians of Madrid (ICOMEM) has formulated a series of questions on this subject which were distributed, not only among the members of the Committee, but also among experts outside it. The central health authorities provide very high and increasing figures for gonococcal infection, syphilis, *Chlamydia trachomatis* infection and lymphogranuloma venereum (LGV). Both HIV infection and Monkeypox are two important STI caused by viruses in our environment, to which it should be added, mainly, Herpes simplex virus (HSV) and Human papillomavirus (HPV) infections. Emerging microorganisms such as *Mycoplasma genitalium* pose not only pathogenic challenges but also therapeutic problems, as in the case of *N. gonohrroeae*.

The pathways that patients with suspected STI follow until they are adequately diagnosed and treated are not well known in Spain. Experts understand that this problem is fundamentally managed in public health institutions, and that Primary Care and Hospital Emergency Services, together with some institutions that deal monographically with this problem, are the recipients of most of these patients. One of the most serious difficulties of STI lies in the availability of the microbiological tests necessary for their diagnosis, particularly in this era of outsourcing of microbiology services. Added to this is the increased cost of implementing the latest generation of molecular techniques and the difficulties of transporting samples.

It is clear that STI are not diseases to which the entire population is equally exposed and it is necessary to have a better knowledge of the risk groups where to focus the necessary interventions adapted to their characteristics. It should not be forgotten that STI are also a problem in the pediatric age group and that their presence can be a marker of sexual abuse with all that this implies in terms of health care and medicolegal activity.

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Finally, STI are infections that are associated with a high cost of care for which we have very little information. The possibility of expanding the automatic performance of laboratory tests for STI surveillance through laboratory routines is encountering ethical and legal problems that are not always easy to solve.

Spain has created a ministerial area of specific attention to STI and there are plans to improve the diagnosis, treatment and prevention of these problems, but we still lack the necessary evidence on their impact. We cannot forget that these are diseases that transcend the individual and constitute a Public Health problem.

Keywords: Sexually Transmitted Infections, Sexually Transmitted Diseases, STI, STDs, HIV, Monkeypox, Herpes simplex virus, Human Papillomavirus, Mycoplasma genitalium, syphilis, Neisseria gonorrhoeae, Gonococcal infections, High risk groups, Public Health.

Infecciones de transmisión sexual en España: Situación actual

RESUMEN

Las Infecciones de Transmisión Sexual (ITS) constituyen un problema de Salud Pública de primera magnitud. Los problemas inherentes a su diagnóstico, tratamiento y prevención tienen que ver no solo con la naturaleza de las mismas, sino también con problemas de organización y de solapamiento de competencias de las distintas autoridades sanitarias.

La situación real de las ITS en España no se conoce bien en el momento actual. Por este motivo, el Comité Científico sobre COVID y Patógenos emergentes del Ilustre Colegio Oficial de Médicos de Madrid (ICOMEM) se ha formulado una serie de preguntas sobre este tema que ha distribuido, no sólo entre los miembros del Comité, sino también entre expertos ajenos al mismo. Las autoridades ministeriales aportan cifras muy elevadas y crecientes de infección gonocócica, sífilis, infección por *Chlamydia trachomatis* y Linfogranuloma venéreo. Tanto la infección por VIH como Monkeypox son en nuestro medio dos importantes ITS causadas por virus a las que deben añadirse, principalmente, las infecciones por el Virus herpes simplex (VHS) y el Virus del Papiloma Humano (HPV). Emergen patógenos como *Mycoplasma genitalium* que plantean no sólo retos patogénicos si no también problemas terapéuticos, como ocurre en el caso de *N. gonohrroeae*.

Los caminos que siguen los pacientes con sospecha de ITS hasta su adecuado diagnóstico y tratamiento no se conocen bien en España. Los expertos entienden que este problema es fundamentalmente manejado en instituciones sanitarias de titularidad pública, y que los servicios de Atención Primaria y de Urgencias Hospitalarias, junto con algunas instituciones monográficamente destinadas a este problema, son los receptores de la mayor parte de estas enfermedades. Una de las dificultades más serias de las ITS estriba en la disponibilidad de las pruebas microbiológicas necesarias para su diagnóstico, particularmente en esta época de externalización de servicios de Microbiología. A ello se suma el aumento de costes de la implantación de técnicas moleculares de última generación y las dificultades del transporte de muestras.

Está claro que las ITS no son enfermedades a las que esté igualmente expuesta toda la población, por lo que es necesario conocer mejor los grupos de riesgo donde centrarse las necesarias intervenciones, adaptadas a su idiosincrasia. No hay que olvidar que las ITS son también un problema en la edad pediátrica y que su presencia puede ser un marcador de abuso sexual con lo que supone de actividad asistencial pero también medicolegal.

Las ITS son, finalmente, infecciones que se asocian a un elevado gasto de cuyas cifras disponemos de información muy escasa. La posibilidad de la realización automática de pruebas de laboratorio para su detección tropieza con problemas éticos y legales que no siempre tienen una fácil solución.

España ha creado un área ministerial de atención específica a las ITS y existen planes para mejorar el diagnóstico, tratamiento y prevención de estos problemas, pero carecemos todavía de la necesaria evidencia sobre el impacto de los mismos. No podemos olvidar que se trata de enfermedades que trascienden al individuo y constituyen un problema de Salud Pública.

Palabras clave: Infecciones de Transmisión Sexual, Enfermedades de transmisión Sexual, ITS, ETS, VIH, Monkeypox, Virus Herpes simplex, Papilomavirus Humano, Mycoplasma genitalium, sífilis, Neisseria gonorrhoeae, Gonococia, Grupos se alto riesgo, Salud Pública

INTRODUCTION

Sexually Transmitted Infections (STI) have accompanied mankind throughout its history and have been particularly prevalent in turbulent times. They are more frequent in periods of war or when major social movements and changes occur, and it can be said that this group of infections have transformed history by affecting, and sometimes limiting, the lives of many prominent people in the arts and sciences.

The revolution brought about by the discovery and introduction of antibiotics created the mirage of a rapid end to diseases such as syphilis or gonorrhea, but it was only a few decades before the great pandemic of Human Immunodeficiency Virus (HIV) infection appeared, with its tragic consequences for millions of people. The HIV pandemic showed that there were still causative agents of STI to be discovered. The darkest years of the pandemic were associated with a decline in other STI, which soon rebounded with the discovery of agents capable of controlling HIV infection and the consequent abandonment of some prevention measures.

The recent epidemic of Monkeypox Virus infections has shown once again that microorganisms that were not previously considered to be typically sexually transmitted can become so only through changes in human movements and habits. The recent Coronavirus pandemic has also taught us lessons in the STI universe by proving the impact that a state of confinement can have on human-to-human relationships.

What is happening with STI is poorly understood outside

Table 1 **Epidemiological situation of gonococcal infection, syphilis, *C. trachomatis* infection and LGV in Spain 2021. Adapted from reference [2].**

Indicators	Gonococcal infection	Syphilis	*C. trachomatis* infection	Lymphogranuloma venereum
Number of Autonomous Communities that notify	19	19	15	11
Number of cases reported	15,338	6,613	20,507	649
Rate per 100,000 inhabitants*	32.41	13.97	48.36	1.66
Male: female ratio	5.0	9.6	0.9	80.1
Percentage of men	83.0%	86.6%	49.8%	98.8%
Percentage of cases in people under 25 years of age	23.1%	12.0%	39.5%	7.4%
Rate between 20-24 years per 100,000 inhabitants*	110.02	28.02	251.49	2.28

*** Calculated for all the Autonomous Communities that have a surveillance system and that notified in 2021**

very specialized circles and, even within these circles, very important gaps in information and data recording are recognized. The professionals closest to this problem reflect their concern at the "chilling" figures of the increase in the incidence of these diseases, affecting not only groups at particular risk but also the general population.

For this reason, the Illustrious Official College of Physicians of Madrid (ICOMEM) has formulated a series of questions about the situation of STI in Spain, summoning to answer them, not only members of the COVID-19 and Emerging Pathogens Committee, but also experts from outside the Committee. The following pages attempt to answer some of these questions, without pretending to cover a vast area, but trying to clarify some aspects of what is happening, preferably in Spain, at the present time.

AT PRESENT, WHAT IS THE BEST DEFINITION OF "SEXUALLY TRANSMITTED INFECTION" AND WHICH ARE THE MOST PREVALENT, PARTICULARLY IN SPAIN?

STI are a group of diseases of infectious etiology that produce heterogeneous clinical pictures and whose reservoir is human. Transmission occurs mainly from person to person, during sexual intercourse, although many of the microorganisms that cause them can also have other transmission mechanisms such as the perinatal or parenteral route. The probability of transmission from an infected patient varies according to the STI and its stage.

One of the important problems of this group of infections is that, in general, suffering from them does not generate immunity and, therefore, reinfections are possible and frequent. There is also no mutual exclusion between them, since the same individual can have more than one STI at the same time.

Although there are several infections that can be transmitted sexually, not all of them constitute an STI. In addition to the route of sexual transmission, the epidemiological context related to each microorganism must always be taken into account, since this context defines the necessary prevention and control measures to be applied from the health point of view. We can therefore conclude that the concept of STI does not extend to all infections that can be transmitted during sexual intercourse, but only to those in which the sexual route is the main mechanism of transmission and, moreover, this route of transmission is of special epidemiological interest [1].

Table 1 shows data on the epidemiological surveillance of STI that are notifiable diseases for 2021, published in 2023 by the HIV, STI and hepatitis B and C Surveillance Unit of the National Epidemiology Center of the Carlos III Health Institute (Instituto de Salud Carlos III) [2]. The data establish incidence rates ranging from 1.66 episodes per 100,000 population for LGV to 48.36 episodes per 100,000 population for *C. trachomatis* infection. There is a clear predominance of males among reported cases and rates are particularly high among the population aged 20-24 years. National incidence data for other STI are not known, since they are not diseases subject to surveillance through the National Epidemiological Surveillance Network (RENAVE).

TO WHAT EXTENT IS HIV STILL SEXUALLY TRANSMITTED IN SPAIN?

During the 1980s and 1990s, at the onset of the HIV pandemic, the most frequent mechanism of HIV transmission in Spain, unlike in most countries of the world, was not sexual transmission but injecting drug use (IDU). The measures adopted to prevent HIV transmission among IDUs, among other causes, decreased the incidence of infection associated with this risky practice and unprotected sex became the transmission mechanism for virtually all new infections since the mid-1990s.

Official epidemiological surveillance in Spain confirms that this trend continues today [3]. In the latest report on HIV infection in Spain, 81.7% of new HIV diagnoses in 2021 were sexually transmitted and only 2.2% had another route of transmission documented (in 16% the route of transmission

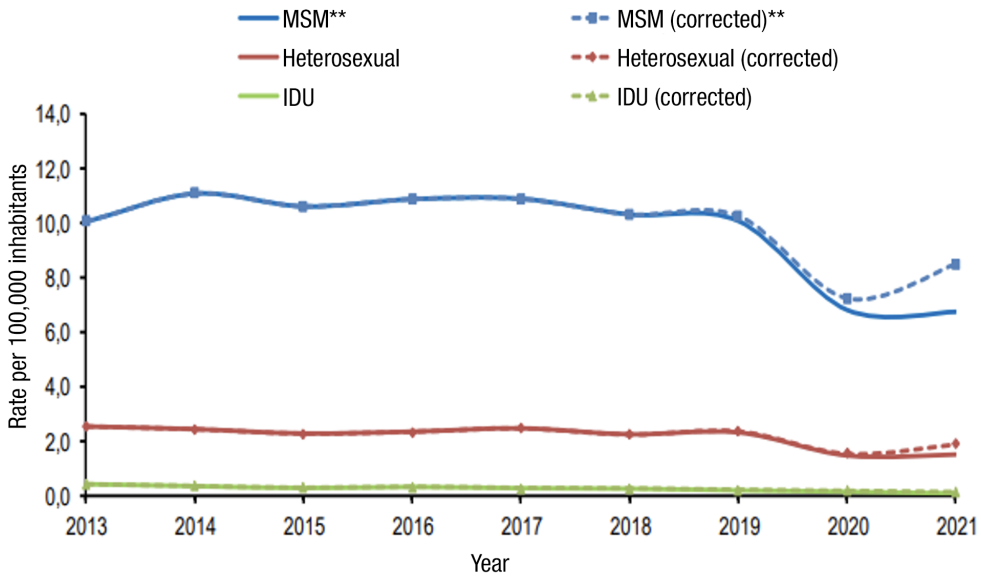

Figure 1 | **Rates (per 100,000 population) of total annual new HIV diagnoses and by mechanism of transmission (2013-2021). Data corrected for delay in notification. Source: HIV, STI and hepatitis surveillance unit. Adapted from reference [3].**

** Rate per 100.000 men, MSM: Men who have sex with men; IDU: injecting drug use

was not recorded). Transmission in men who have sex with men (MSM) was the most frequent, 56.3%, followed by heterosexual transmission, which accounted for 25.4%, overall. The importance of sexual transmission is maintained when broken down by sex. Among men, MSM transmission accounted for 65.4% of new HIV diagnoses and heterosexual transmission for 16.6%. Among women, heterosexual transmission constitutes the vast majority, accounting for 79.9% of new diagnoses.

It is important to note that the sexually transmitted route has remained responsible for the highest number of new infections throughout the period 2013-2021, where all the infections reported by the Autonomous Communities are collected (Figure 1). The number of cases reported in this period was 35,019. Interestingly, both the overall rate and the rate by sex and by mode of transmission show a statistically significant downward trend. In summary, HIV infection is an infection that is mostly transmitted sexually. This fact is of enormous importance because it indicates that, without neglecting other forms of transmission, it is necessary to implement and reinforce effective actions to prevent transmission by this route. Within sexual transmission, the MSM group is a priority for prevention programs (Figure 1).

IS MONKEYPOX (MPOX) AN STI AND DO WE HAVE THE SPANISH FIGURES?

From the start of the current "Monkeypox" (Mpox pandemic, in June 2022, until March 1, 2023, WHO has reported a total of 86,231 cases of which 84,858 cases have been reported in countries that previously had not reported Mpox cases [4,5]. This incidence declines since the end of 2022 [5].

In Europe, 25,745 cases of Mpox have been reported to the ECDC from 47 countries as of February 28, 2023, through the European Surveillance System (TESSy). Ninety-eight percent were men, the vast majority (96%) being MSM. Thirty-eight percent were co-infected with HIV, 6% required hospitalization (6 in the ICU) and 5 people died as a direct result of this disease [6]. To date, WHO and ECDC have been informed of five cases of occupational exposure.

As of March 1, 2023, 7,541 cases of Mpox have been reported to the Spanish Ministry of Health's Center for Health Alerts and Emergencies, in 17 Autonomous Communities (the most affected were Madrid, Catalonia, Andalusia, Valencia and the Basque Country). Ninety-eight percent were men with a median age of 37 years. Of the cases, 46.1% were born in Spain. Excluding cases with no information, 95.5% were MSM. Regarding the route of transmission, of the 5,725 reported cases, 82.6% were attributed to close contact in the context of sexual intercourse, 6.1% to non-sexual close contact (including cases in children) and 2 cases were due to occupational exposure in the healthcare setting. About 70% of the cases had general symptoms and in more than 60% the most common presentation was rash in the anogenital region (Figure 2). Overall, 9.1% presented complications, the most frequent being bacterial infections, pneumonitis, encephalitis, keratitis and oral ulcers. Three people have died: two cases due to meningoencephalitis and one case due to causes unrelated to Mpox. Since September 2022, there has been a clear decrease in the number of new cases of Mpox in Spain [7,8].

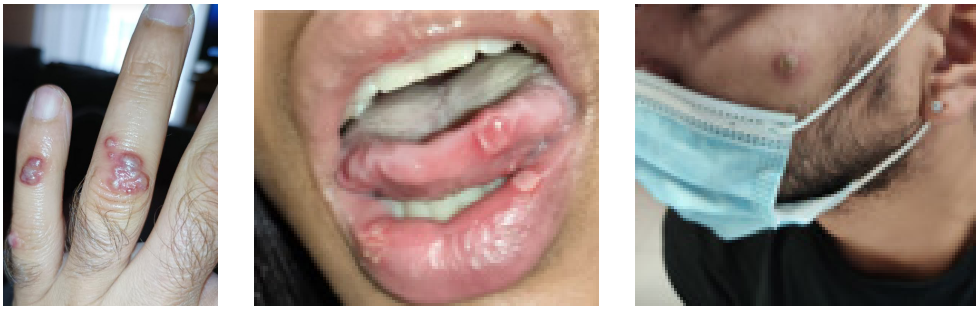

Figure 2 | **Some examples of lesions caused by Mpox.**

In Madrid, among the 435 first diagnosed cases of Mpox in an STI clinic (Centro Sandoval), 98% were MSM. Their median age was 37 years and 38% were co-infected with HIV. Thirty-eight percent of the Mpox patients were users of HIV Pre-Exposure Prophylaxis (PrEP) and 23% were HIV-uninfected MSM not receiving PrEP [9,10].

With respect to categorizing the Mpox pandemic as STI or non-STI, the epidemiological data reported in countries where data exist unquestionably confirm that it is an STI that has particularly affected MSM. The Mpox pandemic of 2022 would probably not have occurred in the absence of sexual transmission [4], although there is much evidence that not all cases have been transmitted in the context of sexual intercourse. The main route of spread has probably been different in previous outbreaks of Mpox.

Some public health officials and community representatives have expressed concern regarding the stigmatization of MSM by the spread of the large proportion of Mpox cases in that population. However, both the HIV and COVID-19 pandemics have demonstrated the need to provide clear and accurate information to the public as a preventive strategy (behavioral and vaccine) that raises awareness among individuals and the most affected population groups.

WHAT IS THE REALITY OF OTHER STI CAUSED BY VIRUSES IN SPAIN?

STI of viral etiology, in addition to HIV, include genital herpes and human papillomavirus (HPV) infection. Other viruses such as the causative agents of viral hepatitis, cytomegalovirus (CMV) or poxvirus, although they can be sexually transmitted, are not genuinely STI.

Genital herpes is caused by herpes simplex virus (HSV), usually HSV2. Transmission occurs through sexual contact, either vaginally, anally or orally. Clinically it is characterized by the presence of vesicles on the vulva or vagina, penis, anus, rectum and, more rarely, in the mouth, which can lead to the appearance of very painful abrasions and ulcers. Many people with genital herpes infection have no symptoms, but transmission from asymptomatic individuals is possible.

It is estimated that between 400 and 500 million people between 15 and 49 years of age worldwide are carriers of HSV [11,12]. In Spain, experts estimate that between 10-15% of the adult population may be carriers of HSV. As for the incidence of the disease, since it is not a notifiable disease, the figures can easily be underestimated. It is the most common sexually transmitted viral disease. There has been an exponential increase since the 2010s, which seems to have stabilized at around 50,000 cases per year in Spain [13] (Figure 3). In a multicenter study carried out during the state of COVID-19 alarm in our country, in a population of 674 subjects with STI, microbiological results were obtained in 519, 10% corresponding to HSV [14]. As in the rest of STI, the risk of genital herpes is higher in MSM, sex workers and people with greater sexual promiscuity. Although the disease is more frequently linked to HSV-2, in recent years a progressive increase in HSV-1 infection is being observed in cases of genital herpes [15]. The diagnosis of genital herpes can be made clinically and confirmed by PCR techniques, replacing cell culture. A topic currently under discussion is the usefulness of performing serology to detect antibodies at least in the at-risk population. It would be indicated in couples in which one of them has a history or lesions of genital herpes and the serological status of the other is unknown. Also, in pregnant women with no history of genital herpes, whose partners do have it. Treatment is aimed at reducing symptoms and their duration, as well as preventing outbreaks. Acyclovir, valacyclovir or famciclovir may be used for treatment [16]. In patients with repeated outbreaks (more than 5 per year), preventive treatment, maintained for 12 months, is recommended, without the Cochrane review published in 2014 showing superiority of any of these drugs [17].

Anogenital HPV is the most common STI worldwide. The peak prevalence of HPV infection usually occurs between the ages of 15 and 25 years in most Western countries. It has been estimated that at least 80% of sexually active people are exposed to HPV at least once in their lifetime [18].

Most individuals exposed to HPV infection manage to clear the virus without developing lesions in less than two years [19]. Some of these viruses manage to integrate into the genome of the host cell and this fact contributes to oncologic transformation following the sequence of dysplasia, high-

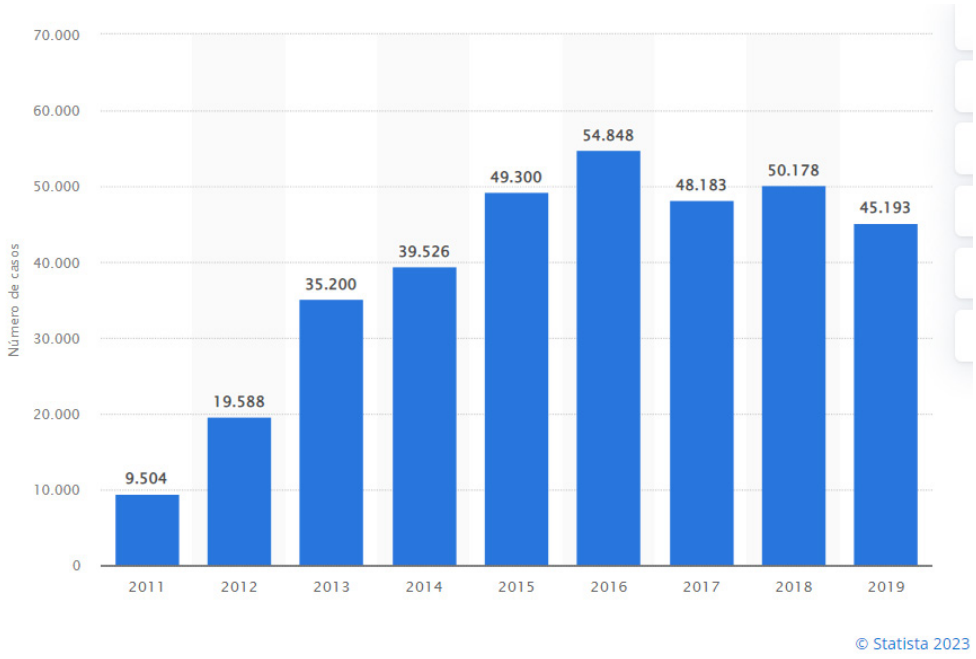

Figure 3 | **Evolution of the incidence of genital herpes in Spain. Adapted from reference [13].**

grade dysplasia and carcinoma. The role of HPV as a carcinogenic agent has been highlighted by the International Agency for Research on Cancer and the WHO [20]. Carcinogenic serotypes such as HPV-16 are the causative agents of multiple cancers (penis, anus, cervix, vagina, vulva, oropharynx, etc.) [20]. This makes it necessary in high-risk populations, such as people with HPV lesions in the anal canal, to carry out periodic diagnostic screening, as is done for the early detection of cervical carcinoma [21].

Routine HPV vaccination of adolescents and young adults is recommended in many countries. Following these vaccination programs, many studies have reported a decrease in the prevalence and incidence of HPV infection and HPV-related diseases [22-24].

WHAT ARE THE FIGURES FOR *CHLAMYDIA* SP INFECTION AS AN STI?

Chlamydia trachomatis is a bacterium that is the most common cause of bacterial STI in both men and women [25-28]. In the United States, it is the most frequent notifiable disease after SARS-CoV-2 infection (COVID-19).

The most common clinical manifestations of *C. trachomatis* infection are urethritis, cervicitis and proctitis (serotypes D-K). Lymphogranuloma venereum (LGV) (serotype L) is much less common. Local complications of these infections are orchi-epididymitis in males and tubaritis, ectopic pregnancy and pelvic inflammatory disease (PID) in females. They can also produce systemic complications, reactive arthritis being one of the best known. *C. trachomatis* infections can cause vertically transmitted infections during delivery that may manifest as conjunctivitis or pneumonia in the newborn.

Seventy percent of *C. trachomatis* infections in women and 50% in men are asymptomatic, which is a further complication in preventing transmission.

The incidence of *C. trachomatis* infection has increased in Europe over the past 20 years (Figure 4), where 434,184 cases were reported in 2019, of which two-thirds occurred in persons under 25 years of age. In 2019, 3,112 cases of LGV were reported, mainly (87%) from 4 countries: France, the Netherlands, the United Kingdom, and Spain [28bis]. These patients, almost without exception (>99%), were MSM and 64% were co-infected with HIV.

In Spain, genital infection by *C. trachomatis* has shown a progressive increase in incidence in recent years (Figure 5) [3]. There were 17,718 cases reported in 2019, representing a rate of 44.18 episodes / 100,000 population (54.4% in women). In our country, more than 40% of cases are under 25 years of age [3]. As for LGV, 453 cases were reported in Spain in 2019. As in Europe, 99% were MSM and 70% of the cases have been reported in Catalonia (rate 1.24/ 100,000 inhabitants).

The treatment of choice for common *C. trachomatis* infections is the combination of doxycycline (100mg/12h x 7 days) and azithromycin (1g in single dose). In the case of LGV, the association of doxycycline (100mg/12h x 21 days) and azithromycin (1g/week x 3 weeks) is recommended.

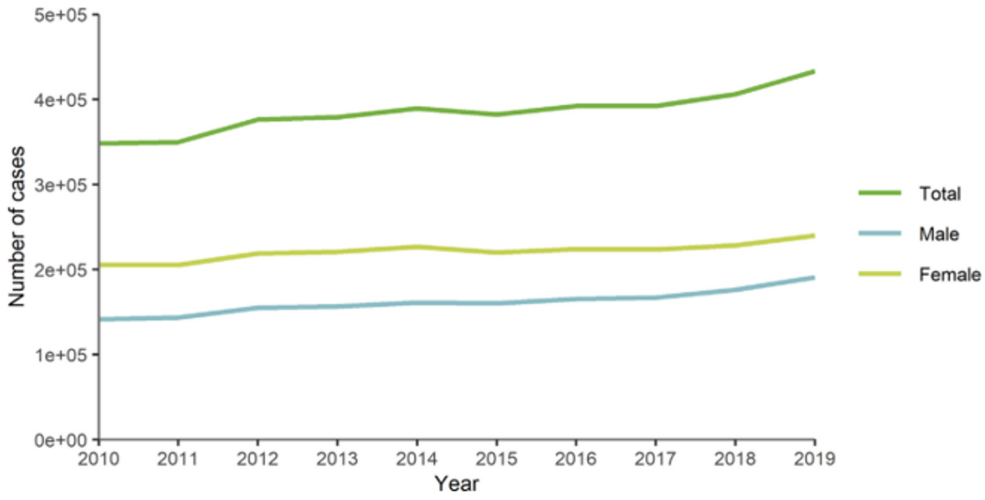

Figure 4 Number of confirmed cases of *C. trachomatis* infection in the European Union (from countries reporting consistently). Obtained from reference [28bis].

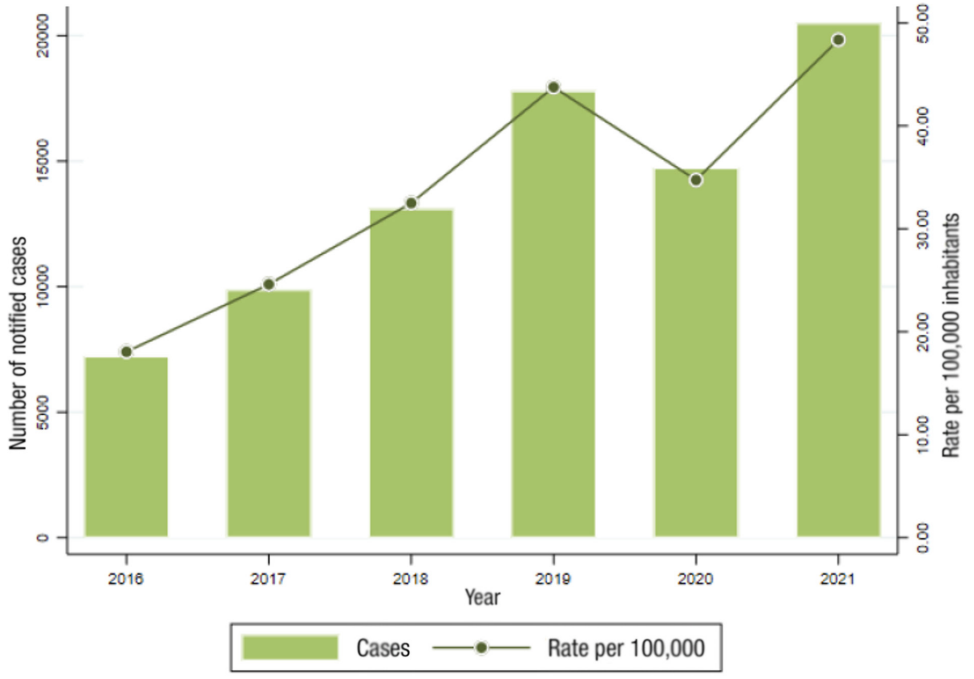

Figure 5 Evolution of the number of cases and rates of *C. trachomatis* infection in Spain 2016-2019. Obtained from reference 2.

WHICH MYCOPLASMAS PLAY A ROLE AMONG THE IMPORTANT STI IN SPAIN?

Among the Mycoplasmas, it is *M. genitalium* (MG) that is of increasing interest. Since 2015, it is considered by WHO as an emerging sexually transmitted pathogen. It was isolated for the first time in 1980 from specimens from patients with urethral syndrome [29]. The overall prevalence of MG is estimated to be between 1 and 3.3% of the general population, a frequency that increases in at-risk populations (35%) [30,31].

The infection initially appeared to be limited to a symptomatic or asymptomatic genitourinary condition, primarily

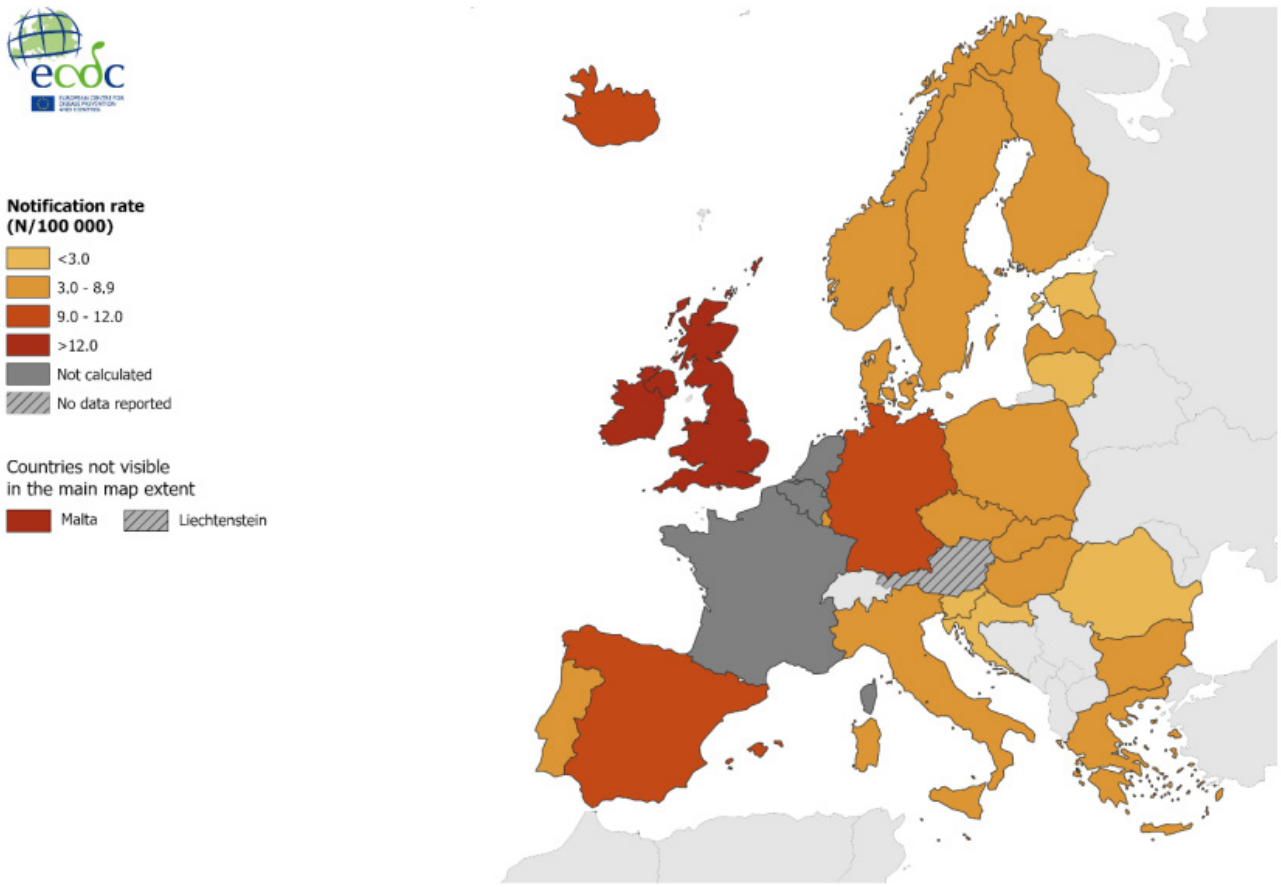

Figure 6 | **Distribution of syphilis cases in Europe in 2019. Obtained from reference [42].**

urethritis (accounting for 40% of persistent or recurrent urethritis), but has been shown to cause cervicitis, pelvic inflammatory disease, and has been associated with preterm delivery, miscarriage and infertility. Its role as an agent of proctitis is under discussion at this time. Its presence in the pharynx is asymptomatic and does not appear to be associated with disease or subsequent complications [30-32].

Traditional microbiological methods are not useful for diagnosis. Culture is very difficult, requires a long incubation and has a low sensitivity (50%). Its detection is therefore based on the use of molecular techniques [30,32-34]. However, these techniques are not implemented in all laboratories, leading to a major problem of underdiagnosis.

MG is intrinsically resistant to antimicrobials acting at the cell wall level (beta-lactams, glycopeptides or fosfomycin), as it lacks a cell wall. The frequency of cure with doxycycline remains stable at 30-40%, although early studies showed in-vitro activity [35]. The first line of treatment is azithromycin at present, but mutations have been detected in 23S rRNA (polymorphism in 2058 and 2059) that produce changes in the 50S ribosomal subunit and confer a high level of resistance to macrolides. These mutations can appear immediately after treatment in 10% of the isolated microorganisms that were initially sensitive. The prevalence of azithromycin resistance is increasing significantly in recent years [36], although it differs greatly from one geographical area to another. Data collected in Spain place it between 20-35% [37]. Recent studies show that an extended regimen with an increased dose (1 g on the first day followed by 500 mg/d for 3 more days) achieves a higher response rate (85-95% in sensitive MG infections) and decreases the selection of resistance mutants [30,32,36-39].

Moxifloxacin (400 mg/d for 1 week) is the alternative treatment of choice in case of detection of macrolide resistance mutations. Resistance to quinolones has been associated, although less consistently, to mutations in the genes encoding DNA topoisomerase IV, mainly at parC level (S83 and D87), with a much lower prevalence [30, 32,37,39]. Coexistence of macrolide and quinolone resistance mutations leaves few treatment options [40].

A sequential treatment is recommended, starting with doxycycline to reduce the bacterial load, followed by azithromycin or moxifloxacin, according to the macrolide resistance

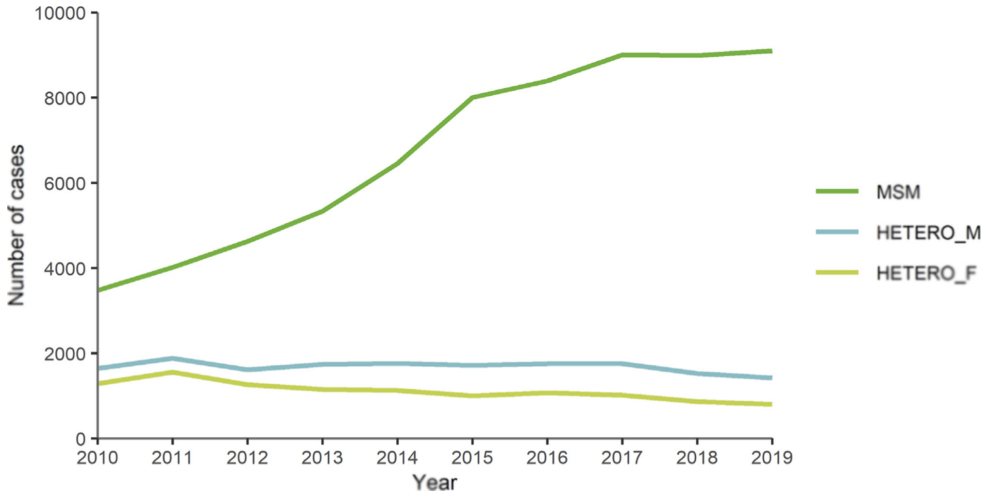

Figure 7 | **Number of confirmed syphilis cases by gender, transmission, category and year in EU/EEA countries reporting consistently, 2010-2019. Obtained from reference [42].**

study. This allows to have a greater response and decrease the selection of resistances [30,32,39]. Pristinamycin could be an alternative in case of failure [30,32,40,41].

WHAT IS HAPPENING WITH SYPHILIS IN THE WORLD, IN EUROPE AND IN SPAIN?

In 2020, WHO reported 7.1 million cases of syphilis worldwide. In 2016, approximately one million pregnant women had syphilis causing obstetric complications in more than 350,000 deliveries. All this despite the recommendation of rapid testing for syphilis screening in pregnant women, especially in pregnant women less than 28 weeks pregnant and during the third trimester in women with risk factors. WHO's goal is to drastically reduce syphilis cases in any population group and particularly congenital syphilis.

In a communication from the European Centre for Disease Control in Stockholm [42], 35,039 new confirmed cases of syphilis were reported in 29 EU/EEA Member States in 2019, with a crude notification rate of 7.4 cases per 100,000 population. Reported syphilis rates were nine times higher in men than in women, peaking in the male age group 25-34 years (31 cases per 100,000 population). The majority (74%) of syphilis cases with transmission category information were reported in MSM. Between 2010 and 2017, the trend in syphilis notifications among men increased steadily, mainly due to an increase in the number of cases among MSM. However, this increase appears to have slowed in 2018 and 2019. During the same period, there were very small fluctuations in syphilis notifications among heterosexuals at the EU/EEA level. In 2019, the number of MSM cases with seropositive status decreased by 1%, while the number of MSM cases with seronegative status increased by 2% compared to 2018.

In Figure 6, the distribution of reported cases can be seen, in which Spain appears as one of the countries with the highest rates. In that European report, the evolution of the figures in the last decade can be appreciated, with a very significant increase in incidence attributable mainly to the MSM population that represents 74% of all episodes (Figure 7) [42]. In European data, HIV coinfection in patients with syphilis is 23%, which rises to 34% in MSM.

In Spain, syphilis data reported by the central health authority are 5,822 cases (88.7% male) in 2019, which is a rate of 13.29 cases per 100,000 population. The figures rise to 30.81 cases in the population aged between 20 and 24 years (Figure 8) [3]. This impressive increase may be due in part to improved data collection methods.

WHAT ARE THE PROBLEMS POSED BY GONOCOCCAL INFECTION IN OUR ENVIRONMENT?

Neisseria gonorrhoeae (NG) infection remains a major public health problem today. It mainly affects the epithelium of the urethra, cervix, rectum, oropharynx and conjunctiva. In cases of genital involvement, it can ascend and cause PID in women and orchi-epididymitis and prostatitis in men. Other complications such as disseminated infection, bacteremia, skin lesions, arthritis and tenosynovitis, perihepatitis (Fitz-Hugh Curtis syndrome), meningitis or endocarditis are not frequent.

In recent years, we are experiencing a continuous increase in the incidence of gonococcal infection. The latest data published globally in Spain report a rate of 28.88/100,000 inhabitants in 2019, an increase of 25.2% over 2013 (Figure 9) [3]. The rate in men (79.7%) is higher than that observed in women. The trend is upward for both sexes, with an annual percentage

Figure 8 | **Evolution of syphilis rates in Spain between 1995 and 2021. Adapted from reference [2].**

change of 26.6% in men and 35.7% in women, and a significant increase in all age groups (Figure 10) [43]. The analysis of data from subsequent years will allow to assess the real impact that the COVID-19 pandemic has had on the incidence of gonococcal disease. In the experience of the Gregorio Marañón Hospital, a decrease in cases was observed in 2020 with respect to the previous year (x0.65) and a progressive increase thereafter (x1.63) (María Palomo, unpublished data).

Therapeutically, NG is a microorganism that has become resistant to the different antimicrobial regimens used over time, with the result that treatment possibilities are increasingly reduced. In 2011, due to the appearance of the first cephalosporin-resistant strains, it was decided to add azithromycin to the cephalosporin regimen for uncomplicated gonococcal infections in order to optimize treatment and preserve sensitivity to these drugs. Surveillance studies in subsequent years have shown high rates of resistance to ciprofloxacin (between 30-70% in Spain), so it is not, any more, an option for empirical treatment, although it could be a good choice for susceptible strains [44,45]. Resistance rates to azithromycin have been progressively increasing in Spain, and are estimated at 5-30%. It is likely that its use is also related to the increased resistance of other microorganisms, including *M. genitalium*. Data on cephalosporin resistance in Spain remain low at present (<5%) [45,46].

In this context, the different international organizations recommend treatment with cephalosporins at an increased dose, although there is no established consensus. The United States guidelines opt for cephalosporins in monotherapy, as in the United Kingdom, although at higher doses; while the European and Australian guidelines continue to opt for doble therapy [45,47,48]. As an alternative, gentamicin can be used (in combination with azithromycin), which has been shown to be useful in patients allergic to beta-lactams, when there is no data on sensitivity to ciprofloxacin or the isolate is resistant to ciprofloxacin [32,44,47]. Recent studies have shown that ertapenem could be a therapeutic option in cases of resistance to cephalosporins [49-51].

The application of molecular techniques for the detection of resistance determinants is under development, but for the moment they have limitations and are not incorporated into daily practice [52]. It is therefore essential not to stop using bacteriological culture techniques in order to be able to carry out subsequent resistance studies.

Prevention is the basic pillar in the fight against this disease. There are no specific vaccines available, although studies carried out with the serogroup B meningococcal vaccine show promising results of cross-protection [52].

WHAT ARE THE GROUPS OF PEOPLE AT GREATEST RISK OF STI IN SPAIN?

DO ANY OF THESE GROUPS HAVE AN ORGANIZATION AS A PATIENT GROUP?

The groups with the highest risk of acquiring and trans-

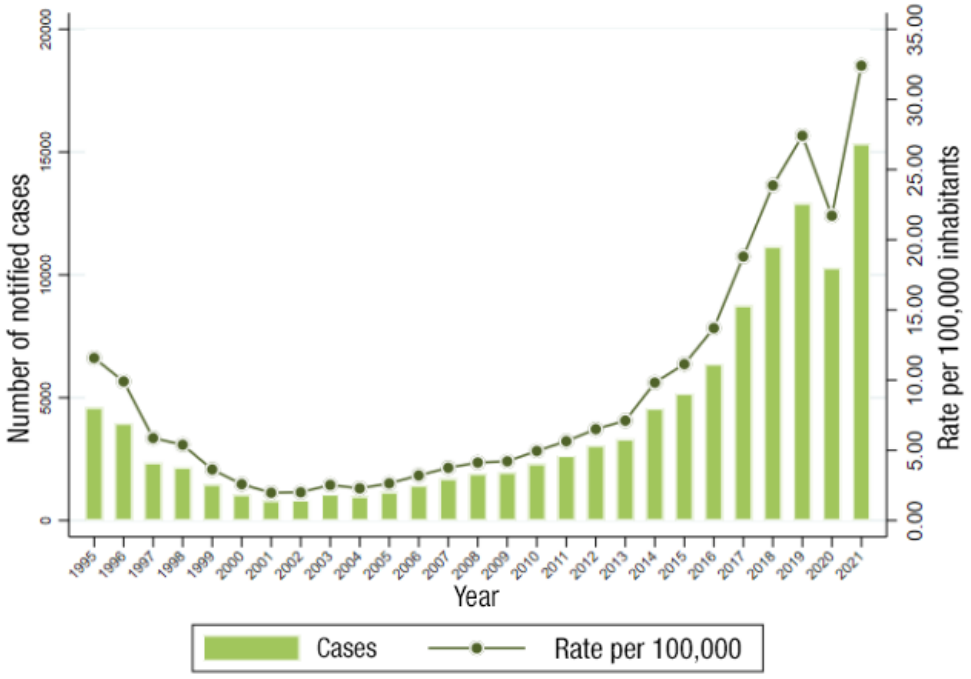

Figure 9 | **Evolution of the incidence of gonococcal infection in Spain between 1995 and 2021. Adapted from reference [2].**

mitting an STI in our environment are MSM, sex workers and people with previous STI.

In Spain, there are several non-governmental organizations (NGOs) and community-based associations (ABC) that work to promote equal rights, the promotion of healthy sexuality without discrimination, and also to make LGBTQ+ people visible. Some of the most prominent are: Fundación Triángulo; COGAM (Colectivo de Lesbianas, Gays, Transexuales y Bisexuales de Madrid); FELGTB (Federación Estatal de Lesbianas, Gais, Trans y Bisexuales); Chrysallis (Asociación de Familias de Menores Transexuales); CESIDA (Coordinadora Estatal de VIH-SIDA); Spanish Red Cross; Gais Positius; Stop Sida; Apoyo Positivo; Barcelona Checkpoint and Sevilla - Checkpoint.

Historically, these entities have played a crucial role in the fight against HIV/AIDS. At the beginning of the epidemic, the organization of people to provide support and care to these patients played a fundamental and indispensable role in the progress and improvement of the global response to this disease. NGOs and ABCs play a vital role in the detection and prevention of HIV and STI. Their work, together and in collaboration with government and other institutions, lies in improving public health at the grassroots level, advocating for gender equality and promoting the elimination of discrimination [53].

The UNAIDS 2021-2026 strategy proposes that up to 30% of diagnostic testing and treatment services involve the community by 2026, with a focus on access to testing, linkage to treatment, and support for adherence and retention [54]. For this reason, the new Strategic Plan 2021 presented in Spain aims to work in a complementary manner with institutions and civil society organizations that promote actions that foster education, training, knowledge, and empowerment of people with HIV/STI infection and other population groups with risk practices in order to promote a positive, healthy sexuality and put an end to the HIV epidemic, its stigma and discrimination. From the National Public Health System, community participation has been granted in the decision-making processes on the response to the HIV epidemic and other STI, acquiring a cross-cutting and interdisciplinary approach: civil society, medical personnel, researchers and politicians, joining and adding tools to better address the response to this public health problem [53].

WHAT ARE THE PATHWAYS FOR A PATIENT WITH SUSPECTED OR CONFIRMED STI IN SPAIN?

Between 2013 and 2020, the Strategic Plan for the Prevention and Control of HIV Infection and other STI developed by the Ministry of Health has been in force in Spain [55]. In the 17 Autonomous Communities (AC) and the 2 Autonomous Cities (Ceuta and Melilla), there is a high degree of heterogeneity and variability in the development of local plans, with an insufficient level of development of specific actions for STI [55].

In most of the ACs, care for patients with suspected or confirmed STI in Spain is provided by different actors, in hos-

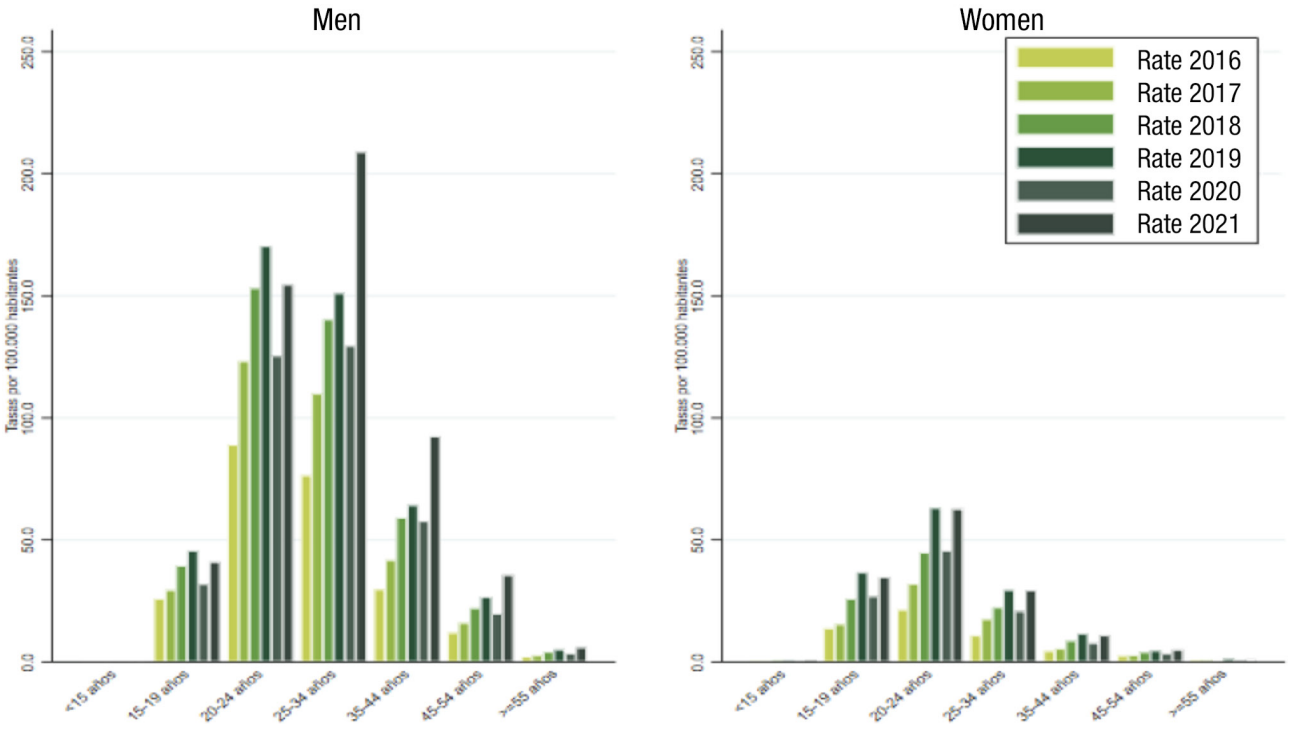

Figure 10 | **Evolution of the incidence of gonococcal infection in Spain between 2016 and 2021 by age group and sex. Adapted from reference [2].**

pital and community settings (primary care and community services) and in clinical and non-clinical settings. Despite the heterogeneity of the Autonomous Communities, in general, the majority of registered STI cases are diagnosed through the public health network. In this health care network, primary care plays a special role and, due to its characteristics of accessibility and comprehensive treatment of the pathology, it is in a privileged position for the detection and clinical management of most STI cases and contacts. Clinical care for STI patients is provided within the primary care clinic, but not exclusively. STI cases are also seen in hospital care, mainly in the emergency department and during hospital admissions, in specialties such as gynecology, urology, dermatology, internal medicine, and through the infectious disease and microbiology services. Access to these centers can be at the patient's own initiative or on demand from primary care or other community facilities. The STI care consultation will be carried out in the corresponding Specialized Care service, but not exclusively. There are also monographic care consultations, created within a Specialized Care service, dedicated exclusively to the health care of patients with STI. In addition to the conventional centers of the healthcare network, the Autonomous Regions have developed a series of centers for the prevention and early diagnosis of HIV and other STI, in clinical and non-clinical settings [56]. These devices are varied and include monographic community care centers (outpatient and/or inpatient) dedicated exclusively to STI health care, community STI rapid detection and counseling services, or mobile information or detection units. These facilities provide anonymous, confidential and free care, and have fewer administrative barriers than conventional health centers.

Community units have been designed for the most vulnerable people, who do not have regular contact with the health system and who have a high prevalence of STI and a higher risk of transmission (people who inject drugs, MSM, individuals with risky behaviors or practices, sex workers, immigrants from areas with a high prevalence of certain STI), and are attended by various agents, institutions or organizations that are distributed in centers or units of the community network. These units work with HIV and other STI prevention programs. Most of them operate in non-clinical settings (specific STI care centers, addiction care centers, dual pathology centers, immigrant shelters, day centers, NGOs, municipal health centers, mobile STI detection units, etc.), with or without links to or integration in the public health network. In Spain, this care circuit for people who are less linked to the health system is complex, with regional, provincial and even local differences. Among the intervention strategies of these community devices are direct intervention and clinical-therapeutic management or referral to other health resources, generally to primary care or to specialized units (STI referral center, hospital HIV units, emergency rooms or hospital clinics).

WHAT IS THE BURDEN OF STI IN THE EMERGENCY DEPARTMENT?

U.S. studies show that 1.3/1,000 of the diagnoses recorded in emergency care are for an STI [57]. A recent Spanish study conducted in 250 hospital emergency departments (ED), with a population coverage of around 45.7 million people and 19.4 million attendances, showed that approximately 71,000 of those attendances corresponded to a suspected STI, which means an incidence of 3.7/1,000 in our country [58]. A noteworthy aspect of this study is that only 36.4% of Spanish hospital EDs have a therapeutic approach protocol for STI, which is more frequent in large hospitals and in hospital EDs with a high influx of patients [58]. The protocolization of STI in the ED is important for 5 reasons: 1) clinical protocols improve the quality of care; 2) STI are a public health problem so their proper management has implications not only for the patient; 3) sample collection, transport and processing are especially important in some frequent STI such as gonococcal infection, as *Neisseria gonorrhoeae* is very sensitive to environmental conditions; 4) the successive emergence of antibiotic resistance to gonococcus has forced frequent modifications of empirical treatment guidelines for STI worldwide [59]; and 5) ensuring subsequent follow-up is important in order to ensure clinical cure, screen for other STI, interrupt the chain of transmission and implement preventive and sexual health promotion measures. Seventy percent of EDs frequently or almost always perform exudates for etiological diagnosis, 44% STI serology and 35% HIV serology [58].

Another important aspect of STI is their association with an increased likelihood of occult HIV infection [60]. It is known that 1 in 3 missed opportunities for HIV diagnosis occur in the ED, so they can be key in the fight against hidden infection and late diagnosis of this infection [61], being a strategy that multiple studies have shown to be efficient [62]. Despite the perceived difficulties in the ED in detecting patients with unknown infection, it is not possible to detect patients with unknown infection [63], EDs are getting involved in this task by encouraging requests for HIV serology for STI care and other entities routinely seen in the ED through the "dejatuhuella" program [64].

We have not found reliable data on the proportion of STI patient care provided by the private sector.

WHAT ARE THE PROBLEMS OF ETIOLOGICAL DIAGNOSIS OF STI?

Traditionally, the diagnosis of STI was performed in monographic consultations dealing with the so-called "venereal diseases". In addition to analyzing the symptoms and lesions on the external genitalia and adjacent areas, microscopy techniques were used on the exudates of the lesions observed, including dark field, fresh slides and a few stains (Gram, Giemsa or silver stain) and culture for some of the microorganisms, essentially *Neisseria gonorrhoeae*. Most of these techniques were performed at the place of patient care or with the proximity of the laboratory to the people attending these consultations. Later, useful serological techniques were implemented for some of the pathogens (e.g., syphilis and HIV). More recently, molecular biology techniques were introduced, broadening the spectrum of microorganisms to be investigated, especially with the so-called syndromic or "multiplexed" panels that simultaneously investigate a multitude of pathogens and can be performed in individual formats or with automated high-throughput platforms [65,66].

This evolution has had the benefit of greater precision in microbiological diagnosis and an increase in the diagnosis of the pathogens involved. However, with the implementation of all these new techniques, and with some exceptions, STI monographic consultations have been disappearing in parallel in many centers, dispersing in many cases the care of these patients. Microbiological diagnosis has also been centralized in many cases, making it necessary to establish adequate transport systems and the development of methods independent of microbiological culture.

Microbiology services and laboratories respond in many cases to requests for STI studies in which they do not know the clinical symptoms, so multiplex platforms that cover numerous possibilities are used, without being able in many cases to optimize the available resources. However, this strategy has brought as a benefit the diagnosis of coinfections, in clear increase in recent years [67,68].

At present, the problems faced by Microbiology Services in the diagnosis of STI can be summarized as follows:

- Distance of the patient and the physician responsible for the laboratory, with loss and lack of clinical information, often necessary to guide and optimize the diagnosis.

- Need to organize adequate transport of samples to preserve the viability of microorganisms in case microbiological culture is necessary.

- Reduction of personnel and high rotation with loss of experience in conventional techniques such as culture, use of microscopy or interpretation of stains.

- Use of expensive molecular systems that increase the total costs of diagnosing STI and the laboratory in general.

- Increase in the number of requests due to the implementation of screening programs (HIV, hepatitis).

- Controls in persons with pre-exposure drugs to the HIV virus.

- Discontinuation and, if necessary, stock-outs of certain conventional diagnostic tests because their manufacturing costs are low and the economic margin for the diagnostic company is very small.

- Introduction of point-of-care systems, including self-diagnosis systems, which on the one hand facilitate rapid diagnosis, but steal the results from the patient's or the laboratory's registration systems, making it difficult to declare the case and follow it up [69].

Improvements in the diagnosis of STI are related to the

solution of the aforementioned problems, for which the participation of the clinical microbiologist in the multidisciplinary teams caring for people with STI is important. This attitude facilitates not only the improvement of diagnosis, but also the transmission of results and the implementation of follow-up protocols.

HOW SHOULD CARE TEAMS FOR THESE PATIENTS BE STRUCTURED?

If anything has become clearer in recent decades, it is the need for a multidisciplinary approach to STI. These diseases have ceased to be the preserve of specific groups of specialists and have become almost a paradigm of the virtues of multidisciplinary care by well-coordinated teams. On the other hand, patients do not go to groups, but to physicians or other independent health professionals and, therefore, the interest, knowledge and culture about STI must be very widespread among all the components of the care chain.

STI care teams, whether in primary care or in hospitals, should be multidisciplinary and have immediate access to microbiological diagnostic tools. These units seem to us to be indispensable, at least in general and referral hospitals, with close links to emergency departments, with the capacity to provide care 24 hours a day, 7 days a week and linked to a well-established and coordinated network. STI units must have the facility to care for patients of any condition, without the need for "paperwork" and be able to administer treatments as immediately as possible. In addition, they must be very well connected with social and prevention services to turn each case into the index of a possible chain to be searched for and treated.

Very often, these units are serving a very vulnerable population where the specific STI is linked to social and personal problems of all kinds and physical or mental pathology that require a total response.

WHAT IMPACT IS PrEP HAVING ON STI INCIDENCE?

PrEP is the acronym for the use of antiretroviral drugs to reduce the likelihood of HIV infection in uninfected patients. Its preventive efficacy for sexual transmission of HIV is estimated to be around 99% when there is high adherence [70-73] and 74-84% in people who inject drugs [74,75].

PrEP also shows an impact on other facets of sexuality. It improves self-esteem, sexual satisfaction and reduces anxiety associated with sexual intercourse. In addition, in some cases, it can facilitate access to the health care system and sexual health care. [76].

Numerous studies have shown that the daily oral regimen (for men, women and adolescents), with a co-formulated tablet containing 200 mg of Emtricitabine (FTC) and 300 mg of Tenofovir Disoproxil Fumarate (TDF), is safe and effective in reducing the likelihood of acquiring HIV infection in men and women, adults and adolescents at risk for HIV infection [77]. For men and transgender women (adults and adolescents), daily oral PrEP with a co-formulated tablet containing 25 mg Tenofovir Alanine Fumarate (TAF) and 200 mg FTC (TAF/FTC, Descovy Ò) is also a recommended option for HIV prevention in adults and adolescents at risk for HIV infection. PrEP with FTC/TAF has not yet been studied in cisgender women and is therefore not recommended in them for this purpose.

On December 22, 2021, the FDA approved the use of Cabotegravir, for PrEP, in adults and adolescents with sexual or parenteral risk practices for HIV acquisition. Its dosage is one intramuscular injection every 8 weeks [78].

In Spain, the Ministry of Health guidelines for the implementation of PrEP, updated in December 2021, recommend its use in HIV-uninfected individuals aged 16 years or older who meet one or more of the following criteria [79]:

-MSM and transgender women presenting at least two of the following criteria: More than 10 different sexual partners/year; Unprotected anal sex in the last year; Drug use associated with unprotected sex (chemsex) in the last year; Administration of post-exposure prophylaxis on more than one occasion in the last year; Any bacterial STI in the last year.

Cis or transgender women and male sex workers who report non-habitual condom use.

-Injection drug users with unsafe sexual practices.

Heterosexual women and men reporting non-habitual condom use, presenting at least two of the same criteria as MSM.

In developed countries, especially in the last 10 years, a continuous increase of bacterial STI in PrEP users has been detected. The causes generally related to this increase are: the loss of fear of AIDS due to the preventive efficacy of suppressive ART; the use of drugs for sexual intercourse (chemsex, slamsex,...) and the increased frequency of STI screening in people in these programs.

A study conducted in an STI clinic in Madrid found a significant decrease in condom use 2 years after starting PrEP. The factors that showed an independent association with the presence of an STI after multivariate analysis were: age under 30 years, practicing chemsex and having more than 10 sexual partners/month [80].

A meta-analysis of 17 observational studies conducted in Australia, which included 2,058 participants [81], found that PrEP use was associated with an increase in STI. Multivariate analysis showed that the highest incidence of STI (more than 3 per year) were concentrated in a subgroup of PrEP users, who possessed the following characteristics: being younger than 30 years, having a higher number of sexual partners (more than 10 partners in the last six months), and engaging in group sex [81]. The effect was greater for rectal infections, both for *C. trachomatis* and for other STI. Rates of repeat STI diagnoses during follow-up were high.

In contrast to the studies discussed above, other work in PrEP users found that before starting PrEP, the incidence of STI

was high and increasing in these individuals, and after starting PrEP, STI rates remained high, although they did not increase [14,82].

WHAT IS THE ECONOMIC COST OF STI IN SPAIN?

It is difficult to estimate the cost of STI because they are a heterogeneous set of diseases that are often underreported, partly because they are often asymptomatic and patients do not always seek care for their management or do so outside the health system. An additional reason is that some STI become chronic and have long-term consequences, requiring prolonged follow-ups of patients to assess their costs. Therefore, it is not surprising that not even the Ministry of Health's Plan for the prevention and control of HIV infection and STI 2021-2030 in Spain includes an evaluation of the costs of these processes [53]. We have not found it on the ECDC website dedicated to communicable disease surveillance either [83], although it contains very rich information on the magnitude and distribution of STI in Europe.

The only report we are aware of on this issue in Spain is the one carried out by the group in Public and Health Economics of the University of Cantabria with the sponsorship of Durex Ò [84,85] and Europe [86] questions the effectiveness of available measures, the intensity of their implementation, or both.

HOW IS THE FIGHT AGAINST THIS PROBLEM STRUCTURED AT THE STATE LEVEL? WHAT COULD BE IMPROVED?

Royal Decree 852/2021, of October 5th, modifies the basic organic structure of the Ministry of Health, creating the Division for the Control of HIV, STI, viral hepatitis and tuberculosis (DCVIHT), with the aim of providing an integrated response to these 4 diseases, in line with the international guidelines established by the WHO, UNAIDS and the ECDC. This new structure recognizes the functions assumed in recent years by the former Secretariat of the National AIDS Plan in the prevention and control of the aforementioned diseases and defines a new structure in three distinct areas: primary prevention and community response, secondary prevention and diagnostic innovation, and tertiary prevention and management of chronicity.

This new structure encompasses various functions transversally to all areas of work of the DCVIHT, highlighting the collaboration in epidemiological surveillance and monitoring of the response to these diseases, the implementation of the Social Pact for non-discrimination and equal treatment associated with HIV, as well as actions in teaching and collaboration with the various regional and national administrations, scientific societies and international organizations.

The lines of action for the prevention of STI are reflected in the Plan for the Prevention and Control of HIV infection and STI 2021-2030 in Spain, whose objective is to promote and coordinate actions for the elimination of HIV and STI as a public health problem by 2030, through prevention, early diagnosis and treatment of infections, attention to chronicity and improvement of quality of life, as well as addressing the stigma and discrimination associated with HIV and other STI.

Within strategic objective 1 "Promote the combined prevention of HIV and other STI", in the first line of action, special emphasis is placed on the promotion of comprehensive sexual health from a positive approach, encouraging training, education and promotion of comprehensive sexual health aimed at both the general population and the vulnerable population, especially the young population, as well as the promotion of condom use through specific HIV and other STI prevention campaigns aimed at young people and other groups of special epidemiological interest. In this line, the DCVIHT has carried out collaborative actions with condom distribution companies to facilitate access to condoms among the population, and is currently studying various improvements to promote access to condoms among the most vulnerable sectors of the population and improve their acceptability.

On the other hand, in strategic objective 2 "Promote early diagnosis of HIV infection and other STI", different strategies are addressed to improve the diagnosis of HIV and other STI in order to incorporate them into care and treatment early, cut the chains of transmission and favor the enjoyment of a full sexual life. In the field of secondary prevention of STI, the Ministry is promoting HIV self-testing in collaboration with community entities and important initiatives are being carried out in terms of regulatory changes to promote the implementation of self-testing for the diagnosis of STI in Spain in order to implement a self-care strategy that will promote healthy habits and try to improve the perception of risk of acquiring HIV and other STI, providing various preventive tools to the population to ensure the enjoyment of sexuality in a safe manner.

Prior to the implementation of the Strategic Plan, an integrated review of the HIV and other STI prevention and control plans of the different Autonomous Communities was carried out to determine the actions carried out in the last ten years by the autonomous administrations in the prevention and control of HIV and other STI and to determine the degree of alignment with the national strategy, as well as a characterization of the existing infrastructures dedicated to addressing STI at the national level in order to know the capacity to address STI in our country, as well as the diagnostic capacity of STI and the training of health professionals dedicated to STI care in Spain.

However, as aspects that could clearly be improved, coordination with the different Autonomous Communities for the implementation of measures for the prevention and control of HIV and other STI, the need to incorporate STI as a priority in the political agenda, identifying these pathologies as a public health problem that requires a joint response by the different health administrations, and improving investment in the facilities dedicated to STI care in the different territories to achieve an effective response.

WHAT CAN BE EXPECTED FROM A LARGE STATEWIDE PROGRAM TO CONTROL THESE INFECTIONS?

Actions at three different levels can be expected from a national strategic plan of the characteristics of the one we have mentioned. At the national level, one of the main objectives of the plan is to provide useful information to all the Autonomous Regions on the resources and the state of STI care at the national level in order to facilitate decision-making in the management of this type of pathology, as well as to undertake the necessary regulatory changes to ensure that innovations in the prevention and early diagnosis of these diseases can be implemented throughout the territory and are accessible to the public. At the regional level, this plan aims to provide each territory with a common framework for the development of the activities necessary to curb the STI epidemic in a manner adapted to the territorial particularities and characteristics of the population in each territory. At the community level, this plan aims to integrate the community response in the prevention and control of HIV and other STI, involving the third sector in activities aimed at curbing the different epidemics.

WHAT ARE THE MAIN PECULIARITIES OF STI IN CHILDREN AND ADOLESCENTS?

Their differential characteristics with respect to adults are due to the age of infection in pediatrics (from newborns to adolescents). They adopt various clinical forms of presentation and their morbidity, mortality and sequelae can be permanent. The most important thing to remember is that STI in children and adolescents can be secondary to sexual abuse, with all the personal, family, legal and juridical connotations that this entails.

It is difficult to know the real incidence of STI in children and adolescents because not all of them are notifiable, nor are they always recorded and reported by age group. Recently, on the occasion of the European Sexual Health Day (February 2022), Spanish pediatricians warned of the rising trend of STI in all population groups, including adolescents [53,87].

STI in newborns and infants are acquired through vertical transmission, in children born to infected mothers. The most frequent perinatal STI are syphilis and infections by *N. gonorrhoeae* and *C. trachomatis*. Their clinical forms are varied and complex [88] and sometimes debut with symptoms suggestive of congenital STI such as perinatal mucopurulent rhinitis in syphilis, persistent neonatal ophthalmia secondary to gonococcal infection or neonatal pneumonitis and conjunctivitis secondary to *C. trachomatis*. Early diagnosis and treatment is essential for cure and to avoid permanent sequelae. It is frequent that perinatal infection is the "index case" of STI in the family, with the mother being unaware of her infection and her role as a carrier of the infection [89,90].

The detection of STI in prepubertal children or adolescents who do not admit to having sexual relations leads to the suspicion of sexual abuse in the first place. It is also possible that cutaneous contact or self-inoculation mechanisms are involved, as in the case of anogenital warts [32]. Confirmation, in this age group, of infection by gonococcus, syphilis, HIV or *C. trachomatis* infection, once vertical transmission has been ruled out, is considered evidence of sexual abuse and the corresponding medical (complete personal and family history, diagnostic tests, treatment if necessary, etc.) and legal protocols must be applied [32,91].

Isolation of other STI such as genital herpes (especially HSV-type 2) or *Trichomonas vaginalis* infection are also suspected of sexual abuse and, even if such abuse is not evident, should be officially reported for information and follow-up [32,91].

Adolescents and young adults are currently the most vulnerable population for STI transmission. Globally, STI are the second most important cause of overall morbidity in women aged 15-44 years [90]. According to the report of the National Epidemiology Center between 2016-2019 the incidence of infection by gonococcus, *C. trachomatis* and syphilis have doubled in Spain among young people aged 15-19 years. Their current way of life, initiating early sexual relations with risk factors, and the lack of knowledge of protective measures, condition the increase of STI [92,93]. The main risk factors for contracting STI are: age under 25 years, sexual contact with people with STI, sexual relations with different partners, previous history of STI, drug and/or alcohol use especially associated with sexual relations, inconsistent use of condoms with casual partners, being prostitution professionals or their clients, or being a victim of sexual violence [92-94].

The adequate management of STI in pediatric age is based on five basic aspects: rapid diagnosis, adequate treatment, evaluation of sexual contacts, communication of cases and health education to detect and modify risky sexual behaviors. Treatment will be adjusted to current protocols according to age [89,91,95]. If the STI is secondary to sexual abuse, the protocols will be followed.

Suspected sexual abuse should always be handled as an emergency until the patient is stabilized and the risk is assessed. In all healthcare centers that deal with these cases, there should be protocols for the management of sexual abuse, accessible and known by the professionals, endorsed by the competent authority, which must be complied with for healthcare and legal reasons [94-97].

The American Academy of Pediatrics [97] recommends the progressive inclusion in sex education campaigns of children and adolescents with disabilities who survive their underlying pathology and are frequently able to have sexual relations. They are especially fragile and vulnerable to sexual abuse, STI and unwanted pregnancies.

The decrease and control of STI in children and adolescents will only be possible by addressing sex education programs based on knowledge and prevention. Training programs should be developed to be taught in schools, primary care clinics (pediatrics or family medicine). Training and support for

families on this subject, and their inclusion in treatment and health education groups for adolescents will be a key element in the control of these diseases.

WHAT ARE THE MECHANISMS FOR APPROACHING THE SCREENING AND TREATMENT OF STI IN VICTIMS OF SEXUAL ASSAULT IN SPANISH HOSPITALS?

Sexual assault and abuse not only have an immediate and global effect on women's lives and health, but also have a medium- and long-term impact on sexual life, among many others. One way in which this impact materializes is through the risk of transmission of STI.

In the Community of Madrid the VISEM code is followed [98]. It is a protocol that should be activated with women over 16 years of age who have suffered sexual violence in the form of sexual assault or abuse in the last 72 hours (3 days), or 168 hours (7 days) if there has been vaginal intercourse. Patient consent must be obtained for care and specimen collection.

The care is carried out in the ED, which must have the means to perform the care in a single act, in an urgent, coordinated and comprehensive manner: forensic medical examination, clinical care and specimen collection. The intervention will be governed by a code that standardizes as much as possible the procedures of all those involved with the guarantees of confidentiality and protection of the victim. Once hospital emergency care has been completed, continuity of care must be ensured in primary care, which is essential in the case of STI.

IS IT CURRENTLY NECESSARY TO REQUEST CONSENT FOR PERFORMING AUTOMATED STI DIAGNOSTIC TESTS IN CLINICAL LABORATORIES?

In Spain, the patient's informed consent is a right derived from the fundamental right to information and is protected by Law 41/2002, of November 14, 2002, which regulates patient autonomy and the rights and obligations regarding clinical information and documentation [99]. Obtaining it is a legal requirement to perform any type of medical test, including HIV testing. In addition, in the specific case of HIV testing, the following regulations apply:

- The performance of HIV testing must be justified on clinical and epidemiological grounds, and must be prescribed by a physician.

- The patient must be adequately informed about the nature of the test, its purpose, the risks and benefits of the test and the possible results.

- The patient has the right to refuse to undergo the test, without affecting his or her medical care.

- Information obtained during HIV testing is protected by medical confidentiality, and can only be disclosed with the explicit consent of the patient, or in specific circumstances provided for by law (e.g., in the case of mandatory reporting of infectious diseases).

From an ethical point of view, it could be argued that the trust that presides over the ordinary doctor-patient relationship would justify the possibility for the physician to perform all the examinations necessary to establish the diagnosis, provided that they are not explicitly rejected or prohibited. This would be the case of the determination of the HIV test when making the diagnosis of the patient who comes for suspected STI. However, this interpretation of implied consent would not comply with the necessary free and voluntary consent required by the principle of personal autonomy. The ethical mandate still requires explicit consent to be obtained in these cases, with verbal consent being sufficient, which should be reflected in the patient's clinical history.

Nor would it be appropriate from the ethical-legal point of view to perform routine HIV diagnosis by laboratories on the basis of algorithms or protocols, without the explicit request of the requesting physician.

In the event that the requesting physician includes in the clinical history the patient's verbal consent for the performance of the appropriate examinations for the diagnosis of STI, including HIV, if necessary, the laboratory could extend the corresponding tests that the clinical protocol establishes, as in the case of invasive interventions where this is contemplated in the consent for the intervention itself (for example, in the donation of blood, cells, tissues or organs for transplantation).

However, in the event that the requesting physician records in the medical record the patient's verbal consent for the performance of the appropriate tests for the diagnosis of a specific disease, for example an STI (which by protocol includes all diseases such as HIV infection), if necessary, the laboratory could extend the corresponding tests that the clinical protocol establishes, including HIV, as in the case of invasive procedures where it is contemplated in the consent for the procedure itself (for example, in the donation of blood, cells, tissues or organs for transplantation).

In summary, although the early detection of STI is important for public health, this does not automatically justify the performance of tests without adequate informed consent from the patient (explicit verbal and recorded in the clinical history), and it is advisable to regulate it within the different algorithms or clinical protocols for action.

In spite of this, efforts should be made in the future to standardize HIV diagnosis in our setting and subject it to the same regulations as the other complementary tests requested of the patient, considering the existence today of an effective treatment from which the patient will benefit to a greater extent the earlier the diagnosis is made, in addition to the obvious public health benefits of avoiding secondary cases. In this same sense, safe strategies that respect the patient's rights should be promoted, so that microbiology services can transform situations of missed diagnostic opportunities into gained ones based on well-established clinical protocols.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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Review

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Advantages and disadvantages of maintaining the mandatory use of masks in health centers and nursing homes in Spain. How and when is it justified to maintain it?

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ABSTRACT

We address the advantages and disadvantages of maintaining the mandatory use of masks in health centers and nursing homes in the current epidemiological situation in Spain and after the declaration of the World Health Organization on May 5, 2023 of the end of COVID-19 as public health emergency. We advocate for prudence and flexibility, respecting the individual decision to wear a mask and emphasizing the need for its use when symptoms suggestive of a respiratory infection appear, in situations of special vulnerability (such as immunosuppression), or when caring for patients with those infections. At present, given the observed low risk of severe COVID-19 and the low transmission of other respiratory infections, we believe that it is disproportionate to maintain the mandatory use of masks in a general way in health centers and nursing homes. However, this could change depending on the results of epidemiological surveillance and it would be necessary to reconsider returning to the obligation in periods with a high incidence of respiratory infections.

Keywords: Masks; Health centers and nursing homes; Spain; SARS-CoV-2; COVID-19

Ventajas e inconvenientes de mantener la obligatoriedad del uso de las mascarillas en centros sanitarios y sociosanitarios en España. ¿Cómo y cuándo está justificado mantenerla?

RESUMEN

Abordamos las ventajas e inconvenientes de mantener la obligatoriedad del uso de las mascarillas en centros sanitarios y sociosanitarios en la situación epidemiológica actual de España y tras la declaración de la Organización Mundial de la Salud el 5 de mayo de 2023 del fin de la COVID-19 como emergencia de salud pública. Propugnamos prudencia y flexibilidad, respetando la decisión individual de usar mascarilla y enfatizando la necesidad de su uso ante la aparición de síntomas sugestivos de infección respiratoria, en situaciones de especial vulnerabilidad (como inmunodepresión) o al atender

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pacientes con dichas infecciones. En la actualidad, dado el bajo riesgo observado de COVID-19 grave y la baja transmisión de otras infecciones respiratorias, creemos que es desproporcionado mantener el uso obligatorio de mascarillas de forma generalizada en centros sanitarios y sociosanitarios. No obstante, esto podría cambiar en función de los resultados de la vigilancia epidemiológica y habría que reconsiderar volver a la obligatoriedad en periodos con alta incidencia de infecciones respiratorias.

Palabras clave: Mascarillas; Centros sanitarios y sociosanitarios; España; SARS-CoV-2; COVID-19

INTRODUCTION

The COVID-19 pandemic, particularly in its first waves that produced thousands of deaths in Spain, was an exceptional situation that made necessary, as in most countries, to take extraordinary measures. To limit the transmission of the infection and its serious consequences, measures were adopted such as confinement, the promotion of teleworking, the expansion of telemedicine, hand washing, diagnostic screening tests, and the widespread use of masks [1]. The latter, strongly supported by public health guidelines, was probably very useful in reducing transmission, although, given the simultaneous implementation of all of them, it is not easy to assess the individual effect of each one. The mandatory use of masks in all public spaces, designed to reduce viral transmission, has been progressively abandoned, but it persists in Spain in health centers and nursing homes.

The current situation of widespread immunity acquired through vaccines and infections, combined with the successive mutations of the virus and the widespread availability of rapid diagnoses and effective treatments, has drastically reduced the incidence of serious SARS-CoV-2 infections. Although there are some exceptions [2], most authors agree that the mandatory use of masks should not be maintained indefinitely in hospitals, health centers, nursing homes, pharmacies, dental clinics, and other health centers [3-5]. What is more debatable is the moment to withdraw the obligation, accepting that this decision can be dynamic and reversible (Figure 1). In some countries with vaccination levels similar to Spain, it is no longer compulsory to wear a mask in these centers and this decision does not seem to have led to an increase in infections. Although different climatic, geographic, and epidemiological circumstances may make it difficult to extrapolate those experiences, SARS-CoV-2 infections now appear to be little more severe than those caused by influenza and other respiratory viruses [6].

ADVANTAGES OF MAINTAINING THE MANDATORY USE

Viral respiratory infections are common and potentially serious. Health centers and nursing homes concentrate the population with the highest risk of severe COVID-19, subgroups that continue to have a relatively high risk of serious illness and death in the case of acquiring respiratory infections. In addition, nosocomial and healthcare-related infections by respiratory viruses are common and include not only SARS-CoV-2 but also influenza, respiratory syncytial virus, and others (human metapneumovirus, parainfluenza virus...). Acute respiratory viral infections can cause pneumonia and exacerbations of chronic obstructive pulmonary disease, decompensated heart failure, arrhythmias, acute coronary syndromes, and neurological events [7,8].

Reduced transmission of viral infections. Despite the fact that Jefferson et al [9] have recently questioned the degree of usefulness of masks with respect to the prevention of respiratory virus infections in the latest Cochrane Review, and other authors have questioned its usefulness in other circumstances such as its use in schools [10], several studies have shown that the proper use of masks reduces respiratory viral spread. In fact, its use by healthcare professionals can reduce nosocomial respiratory viral infections by up to 60% [11-14].

Habit persistence. The habit of wearing masks in health centers by professionals, patients and family members has been established, and it could be difficult to recover - in situations similar to those that occurred in the COVID-19 pandemic or due to the increase in other respiratory infections - if masks were no longer mandatory.

DISADVANTAGES OF MAINTAINING THE OBLIGATORY NATURE OF ITS USE

Doctor–patient relationship. Masks prevent seeing people's faces. Its mandatory use has had a negative impact on communication, empathy and closeness, more pronounced in some subgroups such as children [15], the elderly, patients with impaired speech, mental health disorders or cognitive impairment, and patients who do not speak Spanish as their first language or with hearing loss [16-18]. Smiles and facial stimuli are not seen, and are necessary for the relationship with patients. The increased listening effort required when wearing masks is also associated with a higher cognitive load for patients and healthcare professionals [19,20]. The prolonged use of masks has contributed to the harmful trend, already present before the pandemic, of medical practice progressive dehumanization [21].

In some cases, the use of the mask can also make clinical diagnosis difficult, preventing or making it difficult to assess labial cyanosis and perioral infections, facial paralysis, and others [22].

Perception of healthcare and nursing homes users. Patients and, even more so, users of nursing homes perceive the mandatory use of masks as irrational when they are not mandatory in cafeterias, theaters and means of transport. They want to return to a true normality as soon as possible, as they already have in the "outside world".

Advantages

Frequent respiratory infections
Protect the most vulnerable
Reduce transmission of viral infections
Avoid decompensations
Persistence of the habit of its use
Changes in epidemiological situation

Disadvantages

Doctor-patient relationship and dehumanization
Make clinical diagnosis difficult
Teamwork and information transmission
Perception of "irrational" use by users
Environmental impact
Possible damage to user health

Figure 1 | **Advantages and disadvantages of maintaining the mandatory use of masks in health centers and nursing homes.**

Teamwork. The advent of masks has also had a negative impact on interprofessional relations. Masks hide facial expression, can contribute to feelings of isolation, and negatively affect human connection [23]. The transmission of information is more difficult and it is not easy to perceive changes in mood [24]. In some situations, such as in the context of emergencies, masks can hinder clear communication between the professionals caring for the patient, facilitating errors. In addition, there are contexts such as clinical sessions and other training activities in which there is no contact with patients in which the mandatory use of the mask is not justified when there is a high level of vaccination among professionals and outside of the periods of increased circulation of respiratory viruses.

Environmental impact. The detrimental effect of respirator fragmentation on biomass quality is also a cause for concern. Disposable masks can reduce water quality and harm microalgae, inhibiting their growth [25]. In addition, masks contaminated by various microorganisms, after being used, are a potential danger to the environment [26].

Possible damage to the user's health. Although the impact on the user's health is minimal, some studies have shown possible side effects related to prolonged use of masks such as headache, irritation and dry eyes and skin conditions (appearance or worsening of acne and other facial dermatoses, including rosacea, dermatitis seborrheic, and irritant contact dermatitis) [27]. An impact on the subjective appreciation of effort when performing physical activities has also been described [28].

CONCLUSIONS

The individual decision to wear a mask in health centers and nursing homes must be respected and its use is recommended and necessary, as it was before the pandemic, for patients and health workers with symptoms compatible with respiratory infections, in situations of special vulnerability (such as immunosuppression) or when caring for patients with these infections. Given that the observed risk of severe COVID-19 is currently very low, and that there is no high transmission of other respiratory diseases, it seems disproportionate to maintain its mandatory use. However, mandatory use should be assessed - at least in spaces where there is contact with patients - seasonally, for example, from December to February, when the incidence of respiratory infections is high, with epidemic figures in the case of flu. The situation may change in the future and we need an approach that allows for the rapid and effective implementation of prevention policies that adapt to changing circumstances and that can be adopted by the governing bodies of these centers in epidemic situations.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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Adecuación de la prescripción de antibióticos antipseudomónicos tras los cambios en los criterios EUCAST 2019

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RESUMEN

Introducción. En 2019, el Comité Europeo para el estudio de la sensibilidad antibiótica modificó las categorías de los test de sensibilidad antibiótica incluyendo el término "sensible con exposición incrementada". Tras la difusión de protocolos locales recogiendo estas modificaciones, el objetivo de nuestro estudio fue analizar si los prescriptores se han adecuado a los mismos y el posible impacto clínico en los casos de inadecuación.

Material y métodos. Estudio observacional y retrospectivo de los pacientes con infección por *pseudomonas aeruginosa* y que hayan recibido antibiótico antipseudomónico desde enero a octubre de 2021 en un hospital terciario.

Resultados. La inadecuación a las recomendaciones de la guía fueron un 57,6% en planta y un 40,4% en UCI (p<0,05). Tanto en planta como en UCI el grupo con más prescripción no ajustada a las recomendaciones de la guía fueron los aminoglucósidos (92,9% y 64,9% respectivamente) por utilizar dosis subóptimas, seguido de los carbapenémicos (89,1% y 53,7% respectivamente) por no administrarlo en perfusión extendida. En planta, la tasa de mortalidad durante el ingreso o a los 30 días en el grupo de terapia inadecuada fue de 23,3% vs 11,5% en los que recibieron los tratamientos de forma adecuada (OR: 2,34; IC 95% 1,14-4,82); en UCI no hubo diferencias estadísticamente significativas.

Conclusiones. Los resultados muestran la necesidad de implementar medidas para garantizar una mejor difusión y conocimiento de los conceptos claves en el manejo de los antibióticos, con el objetivo de garantizar exposiciones incrementadas y poder ofrecer una mejor cobertura de la infección, así como de evitar la amplificación de cepas resistente.

Palabras clave: *Pseudomonas aeruginosa*, antibióticos antipseudomónicos, Redefinición EUCAST, resistencias

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Adequacy of the consumption of antipseudomonal antibiotics after changes in the 2019 EUCAST criteria

ABSTRACT

Introduction. In 2019, the European Committee for the Study of Antibiotic Susceptibility modified the categories of antibiotic susceptibility tests to include the term "susceptible with increased exposure". Following the dissemination of local protocols reflecting these modifications, the aim of our study was to analyse whether prescribers have adapted to them and the clinical impact in cases of inadequacy.

Material and methods. Observational and retrospective study of patients with infection who received antipseudomonal antibiotics from January to October 2021 in a tertiary hospital.

Results. Non-adherence to the guideline recommendations was 57.6% in the ward and 40.4% in the ICU (p<0.05). In both the ward and ICU, the group with the most prescriptions not by the guideline recommendations were aminoglycosides (92.9% and 64.9% respectively) for using suboptimal doses, followed by carbapenems (89.1% and 53.7% respectively) for not administering an extended infusion. On the ward, the mortality rate during admission or at 30 days in the inadequate therapy group was 23.3% vs 11.5% in those who received adequate treatment (OR: 2.34; 95% CI 1.14-4.82); in ICU there were no statistically significant differences.

Conclusions. The results show the need to implement measures to ensure better dissemination and knowledge of key concepts in antibiotic management, to ensure increased exposures, and to be able to provide better infection coverage, as well as to avoid amplifying resistant strains.

Keywords: ***Pseudomonas aeruginosa*, anti-pseudomonal antibiotics, EUCAST Redefinition, resistance**

INTRODUCCIÓN

En 2019, el Comité Europeo para el estudio de la sensibilidad antibiótica (EUCAST) [1], modificó las categorías de los test de sensibilidad antibiótica (AB), concretamente el término sensible (S) e intermedio (I), siendo con la nueva actualización: sensible con régimen estándar de dosificación (S) y sensible con exposición incrementada (EI). Esta exposición incrementada puede conseguirse de diversas formas, ya sea modificando el modo de administración, la dosis, los intervalos posológicos o el tiempo de perfusión, y requieren la adaptación a los parámetros farmacocinéticos/farmacodinámicos (PK/PD) que mejor optimicen la respuesta para cada tipo de antibiótico.

Tras estos cambios, el Programa de Optimización del Uso de los Antimicrobianos (PROA) de nuestro hospital, elaboró una guía de recomendaciones posológicas de los antibióticos antipseudomónicos [2].

En un medio con una alta prevalencia de aislamientos multirresistentes de PA, se nos planteó la necesidad de evaluar el grado de adecuación del manejo de los antipseudomónicos a lo establecido en la guía referida tras un año de implantación.

Este estudio tiene por objetivo principal detallar la inadecuación del tratamiento antipseudomónico, y, como objetivos secundarios, determinar si el nuevo modo de informar los antibióticos como EI condiciona su uso, así como tratar de analizar las posibles repercusiones clínicas de la inadecuación (sus consecuencias en la aparición de las resistencias durante la hospitalización, recurrencias a los 3 meses y mortalidad).

MATERIAL Y MÉTODOS

Estudio observacional y retrospectivo de los pacientes con cultivo microbiológico positivo para PA y que recibieron tratamiento antibiótico antipseudomónico desde enero del 2021 hasta octubre del 2021 en un hospital terciario. No se incluyeron en el estudio aquellos pacientes sin ingreso o en los que no había datos sobre el antibiótico recibido.

Las variables recogidas fueron género, edad, servicio médico, *índice de comorbilidad de Charlson* [3], puntuación en la escala Apache (para pacientes ingresados en la Unidad de Cuidados Intensivos (UCI)), días de ingreso, foco de la infección, muestra y microorganismo aislado. Los pacientes se clasificaron según lugar donde recibieron el tratamiento (planta o UCI).

También se recogieron variables relacionadas con el proceso infeccioso: tipo de infección, presencia de sepsis/shock séptico, bacteriemia, ventilación mecánica invasiva (VMI), inmunosupresión, y si presentaban infección por el síndrome respiratorio agudo severo coronavirus 2 (SARS-CoV-2) durante el ingreso.

Respecto al antibiótico antipseudomónico recibido, se recogió el tipo de tratamiento (empírico o dirigido), en monoterapia o combinado (uso junto a otro antibiótico antipseudomónico durante más de 48h), pauta de prescripción (dosis, secuencia horaria y forma de administración), ajuste de dosis a función renal y la duración del tratamiento.

Para evaluar los resultados en salud del tratamiento se recogió: curación microbiológica (2 muestras repetidas con cultivo negativo), curación clínica (ausencia de signos/síntomas tras finalizar el tratamiento) y recurrencia de la infección, definida como el aislamiento de PA en un nuevo cultivo microbiológico en los 3 meses posteriores al alta del ingreso. Se recogió la mortalidad durante el ingreso y a los 30 días del alta.

Los antibióticos analizados se clasificaron por grupo terapéutico: aminoglucósidos (amikacina, gentamicina y tobramicina), β-lactámicos no carbapenémicos (NC) (aztreonam, cefepima, ceftazidima, ceftazidima/avibactam (C/A) y piperacilina/tazobactam (P/T)), carbapenémicos (meropenem e imipenem-cilastina (I/C)), quinolonas (ciprofloxacino y levofloxacino) y polimixinas (colistina). Ceftolozano/tazobactam (C/T) no se utilizó por desabastecimiento en ese período.

Además, se comparó la mortalidad durante el ingreso o a los 30 días del alta entre los grupos de terapia Inadecuada (TI) y terapia adecuada (TA). Para ello se establecieron dos criterios de inadecuación: la terapia empírica inadecuada (TEI) cuando el prescriptor no disponía aún de antibiograma (se incluyeron los casos de monoterapia ya que la guía recomienda inicio con biterapia y también aquellos en los que el informe microbiológico establecía que el aislado era resistente al antibiótico usado empíricamente) y la Inadecuación Posológica (IP) en los casos en que alguno de los antibióticos informados como "EI", no se administraban siguiendo las nuevas recomendaciones y por tanto no se garantizaba esa exposición incrementada (recomendaciones de dosificación elaboradas por el equipo PROA en Tablas 1 y 2 del Material suplementario).

Los datos identificativos de los pacientes con aislamientos de PA, así como su perfil de sensibilidad, fueron detallados por el servicio de Microbiología, y la información sobre el tratamiento antibiótico se obtuvo del programa de gestión farmacoterapéutica del Servicio de Farmacia. El resto de las variables se recogieron de la historia clínica electrónica (HCE).

En referencia a la implantación de los cambios en los criterios EUCAST y de las nuevas recomendaciones de dosificación de antipseudomónicos, el grupo PROA elaboró un documento informando con estas nuevas recomendaciones y se realizó una gran difusión de las mismas, mediante avisos en la intranet del hospital, sesiones multidisciplinares realizadas por el equipo PROA en servicios clave y modificaciones en los informes de microbiología para incluir un texto con la definición de "EI".

El análisis estadístico se realizó con SPSS Statistics22®. Las variables cualitativas se dan en porcentaje y se realizó la prueba de Chi-cuadrado; las cuantitativas se representan mediante medidas de tendencia central. Se realizó un análisis de regresión logística binaria (*Odds Ratio* (OR) y sus intervalos de confianza (IC) del 95%) para analizar la mortalidad durante el ingreso o a los 30 días del alta en los grupos de TI y TA.

El estudio fue aprobado por el Comité Ético de Investigación Clínica de Aragón (referencia PI22/003).

RESULTADOS

Del total de pacientes con aislamiento de PA y que recibieron antibiótico (n=340), se incluyeron en el estudio finalmente 313 (19 pacientes fueron excluidos del análisis por tener solo un episodio de urgencias, 4 por ser trasladados a otro hospital y otros 4 por no haber datos sobre el tratamiento recibido). El 33,0% de los pacientes requirieron ingreso en UCI, con una mediana en la escala APACHE de 16 [2-33].

En la tabla 1 se describe las características demográficas de los pacientes, el foco de la infección y variables relacionadas con la misma.

De los 313 pacientes se recogieron 392 aislamientos. En la tabla 2 se recoge el tipo de cepa y la sensibilidad microbiológica de los aislados incluidos en este estudio, según los criterios EUCAST 2021. Para el análisis se ha utilizado solo un aislado por persona, tomando de referencia el de mayor resistencia; en planta 3 pacientes desarrollaron resistencias (XDR) durante su estancia, mientras que en UCI 16 PA se hicieron resistentes (13 MDR y 3 XDR) y 9 MDR pasaron a XDR.

En cuanto al antibiótico recibido, en planta se utilizó sobre todo β-lactámicos NC (38,3%) de forma empírica, mientras que en UCI se usaron principalmente carbapenémicos (38,7%). Cabe remarcar que el 82,4% del meropenem prescrito en UCI fue iniciado empíricamente.

En el tratamiento dirigido predominó el uso de la monoterapia en planta (61,6%) frente a la biterapia en UCI (68,3%). En este caso, los β-lactámicos NC fue el grupo más prescrito de forma dirigida tanto UCI como en planta (36,3% y 35,2% respectivamente).

Respecto a los resultados clínicos, se recogen en la tabla 3 junto con las variables relacionadas con el ingreso hospitalario.

El porcentaje de tratamientos que no seguían las recomendaciones de la guía fueron un 57,6% en planta y un 40,4% en UCI (p=0,02). En el ajuste de dosis según función renal (FR), se observó prescripción no ajustada a las recomendaciones de la guía en el 55,6% de los pacientes de UCI y en el 39,1% de planta.

En pacientes con FR normal, tanto en planta como en UCI el grupo con más TI fueron los aminoglucósidos (92,9% y 64,9% respectivamente) seguido de los carbapenémicos (89,1% y 53,7% respectivamente), siendo este el grupo que más destaca como TI en los pacientes con FR alterada (94,1% en planta y 66,7% en UCI).

En la tabla 4 se muestran los porcentajes de TI para cada antibiótico y el motivo por el cual no se han ajustado (en los pacientes sin necesidad de ajuste renal).

En los pacientes que requerían ajuste por función renal, a parte de la falta de adecuación del meropenem por no administrarlo en perfusión extendida (PE), destacan los β-lactámicos NC en los que el ajuste se realizó siguiendo ficha técnica sin ajustarlo a dosis antipseudomónicas (46,2% planta y 38,5% UCI), y en planta al no espaciar el intervalo de dosificación en el ciprofloxacino (60,0%) y en la amikacina (80,0%).

Tabla 1 **Características demográficas, foco de la infección y variables relacionadas con la misma.**

	Global n=313	Planta n=210	UCI n=103
Edad (DE)	69 (15)	72 (15)	63 (12)
Sexo (%)			
Hombres	212 (67,7%)	141 (67,1%)	71 (69,0%)
Mujeres	101 (32,3%)	69 (32,9%)	32 (31,1%)
Tipo de infección (%)			
Nosocomial	197 (62,9%)	100 (47,6%)	97 (94,2%)
Comunitaria	116 (37,1%)	110 (52,4%)	6 (5,8%)
Bacteriemia (%)	85 (27,2%)	25 (11,9%)	60 (58,3%)
Shock séptico o sepsis (%)	48 (15,3%)	15 (7,1%)	33 (32,0%)
VMI (%)	32 (10,2%)	0 (0,0%)	32 (31,1%)
Inmunosupresión (%)	14 (4,5%)	7 (3,3%)	7 (6,8%)
SARS-Cov-2 concomitante (%)	62 (19,8%)	19 (9,0%)	43 (41,7%)
índice de Charlson (DE)	2,9 (2,1)	2,7 (2,0)	3,5 (2,0)
Perfil Resistencia			
PA XDR	46 (14,7%)	19 (9,0%)	27 (26,2%)
PA MDR	31 (9,9%)	15 (7,1%)	16 (15,5%)
Foco de la infección (%)	n=335	n=214	n=121
Respiratorio[a]	121 (36,1%)	60 (28,0%)	61 (50,4%)
Urinario	91 (27,2%)	65 (30,4%)	26 (21,5%)
Herida quirúrgica	31 (9,3%)	26 (12,1%)	5 (4,1%)
Ulcera	29 (8,7%)	23 (10,7%)	6 (5,0%)
Abdominal	26 (7,8%)	16 (7,5%)	10 (8,3%)
Sin foco[b]	22 (6,6%)	9 (4,2%)	13 (10,7%)
Otro foco	15 (4,5%)	15 (7,0%)	0 (0,0%)

VMI= Ventilación mecánica invasiva; UCI = Unidad de Cuidados Intensivos; PA = *Pseudomonas aeruginosa*; XDR = Extremadamente resistente; MDR = Multirresistente

[a]Foco respiratorio: PA aislado en muestras clínicas de aspirados bronquiales

[b]Bacteriemias de origen desconocido o dos focos diferentes con dificultad para establecer la periodicidad.

8 pacientes presentaron cepas carbapenemasa tipo VIM de los cuales, en planta, 2/5 no se ajustaron a la guía al recibir aztreonam junto con aminoglucósidos a dosis inferiores a las recomendadas. En UCI el manejo fue de acuerdo con las recomendaciones en todos los casos.

En cuanto a la valoración de si el cambio en los criterios EUCAST y la nueva expresión en el antibiograma pudieran resultar en una modificación del uso de antimicrobianos (rechazando los prescriptores aquellos con informe como "EI" si tenían otra alternativa que aparecía informada como S), cabe mencionar que de los tratamientos dirigidos en los que se

Tabla 2 **Perfil de sensibilidad de los aislados (%S) según criterios EUCAST 2021**

ANTIBIÓTICO	PA (N=288)	PA MDR (N=47)	PA XDR (N=57)
Amikacina	98,9	95,1	83,6
Aztreonam	99,1	31,4	26,4
Cefepima	97,8	43,5	0
Ceftazidima	98,6	51,1	5,3
Ceftazidima/avibactam	100	90,5	70
Ceftolozano/tazobactam	100	95,7	82,1
Ciprofloxacino	84,9	43,8	26,3
Colistina	100	100	100
Imipenem	89,3	57,4	10,5
Levofloxacino	78,8	28,3	3,6
Meropenem	96,7	71,4	10,5
Piperacilina/tazobactam	98,2	34,8	0
Tobramicina	96,8	78	61,1

MDR = Multirresistente; PA = *Pseudomonas aeruginosa*;
XDR = Extremadamente resistente;

Tabla 3 **Variables relacionadas con el ingreso y resultados clínicos**

	Global n=313	Planta n=210	UCI n=103
Días de ingreso (DE)	36,7 (35,8)	25,0 (26,4)	60,7 (40,0)
Días en UCI sobre total (DE)	N/A	N/A	37,4 (31,9)
Duración del tratamiento (DE)	15,7 (15,4)	11,5 (10,5)	22,0 (16,6)
Curación microbiológica (%)	248 (79,2%)	184 (87,6%)	64 (62,1%)
Recurrencia a los 3 meses (%)	43 (13,7%)	34 (16,2%)	9 (8,7%)
Curación clínica (%)	248 (79,2%)	184 (87,6%)	64 (62,1%)

prescribió un β-lactámico (incluyendo los carbapenémicos), el 29,0% en planta y hasta el 37,1% en UCI utilizaron meropenem cuando en el informe de sensibilidad aparecían otras opciones como "EI" a cefepima, ceftazidima y P/T.

De los 20 pacientes de UCI en los que los aislamientos iniciales fueron aumentando su perfil de resistencia durante el tratamiento, el 65,0% fue previamente tratado sin ajustarse a las recomendaciones. En la planta solo en 3 pacientes se observa ese aumento de la resistencia frente al aislamiento inicial, pero 2/3 recibieron TI.

Las recurrencias a los 3 meses fueron mayores en planta que en UCI, aunque sin significación estadística (16,2% vs 8,7% p=0,072) de las cuales el 20,6% fueron a cepas resistentes.

En planta, la tasa de mortalidad durante el ingreso o a los 30 días en el grupo de TI fue de 23,3% frente a un 11,5% (p=0,02) en los que recibieron los tratamientos de forma adecuada (OR: 2,34; IC 95% 1,14-4,82), en UCI estas diferencias fueron menores (45,2% TI vs 41,0% TA, p=0,59) sin diferencias estadísticamente significativas (OR: 1,19; IC 95% 0,64-2,21). En el análisis del subgrupo de terapia empírica inadecuada, también se encontraron mayores diferencias en planta en relación a la tasa de mortalidad para el grupo de TEI respecto a los que lo recibieron de forma adecuada (22,4% vs 7,3% p=0,04, OR: 3,64; IC 95% 1,01-13,13).

DISCUSIÓN

De forma global los datos muestran un peor manejo antibiótico en planta que en UCI, con una tasa de TI del 57,6% vs 40,4% en UCI (p<0,05), resultado parecido al obtenido en el estudio de Viceconte et al. [4] donde encontraron un 61,0% de inadecuación antibiótica para bacterias MDR en planta, situando al meropenem como el AB que menos se ajustaba a las recomendaciones, siendo este el segundo en nuestro estudio. No obstante, los criterios de inadecuación en ambos estudios no eran iguales y el estudio italiano estaba referido a distintos microorganismos y no solo a PA.

En planta ha predominado el uso de la monoterapia dirigida frente a la biterapia, representando el 61,6% de las prescripciones. Además, el 78,9% de las quinolonas dirigidas fueron en monoterapia, y a pesar de ser infecciones de carácter más leve que podrían justificar su uso en monoterapia, el 31,6% de ellas no se habían prescrito de forma que se garantizase una mayor exposición, aumentando el riesgo de una peor cobertura de la infección y la amplificación de subpoblaciones resistentes. Tanto la guía local como otras (por ejemplo, la de la Sociedad Española de Quimioterapia [5]), recomiendan, el inicio con un β-lactámico combinado con otro tipo de AB dada la alta prevalencia de cepas resistentes a β-lactámicos.

La combinación β-lactámico-aminoglucósido ha destacado en el manejo de las cepas tanto sensibles como resistentes, pero falta concienciarse sobre la importancia de optimizar los parámetros PK/PD de los aminoglucósidos para conseguir actividad sinérgica. En nuestro estudio y para la amikacina, hasta el 85,2% en planta y el 62,8% en UCI, se administró a dosis subóptimas, siendo los aminoglucósidos el grupo con mayores tasas de inadecuación. A pesar de que en el centro se puede realizar la monitorización de niveles plasmáticos de aminoglucósidos y las guías locales de tratamiento recomiendan el inicio con dosis ajustadas al peso del paciente y posterior solicitud de niveles, es frecuente la prescripción de dosis estándar de 1g/24h por ejemplo para amikacina, y en muchos casos sin llegar a solicitar la determinación de niveles plasmáticos.

Con los β-lactámicos NC encontramos mayores dificultades en aquellos AB en los que se recomienda acortar el intervalo posológico; con aztreonam (AB de elección en cepas resistentes incluso a las nuevas combinaciones de cefalosporinas), solamente el 20,0% de las prescripciones (tanto en planta

Tabla 4 **Porcentaje de prescripción no ajustada a las recomendaciones de la guía y el motivo por el cual no se han ajustado (en pacientes con FR normal).**

			Motivo de no ajuste		
	Antibiótico	% Prescripción que no se ajusta a Guía	Dosis[a]	Secuencia horaria[b]	Modo de administración[c]
PLANTA (373 AB)[d]	Amikacina	85,2%	92,0%	8,0%	
	Tobramicina	100,0%	54,2%	45,8%	
	Aztreonam	83,3%	18,8%	81,2%	
	Ceftazidima	27,0%	72,7%	27,3%	
	Piperacilina/tazobactam	39,7%		100,0%	
	Imipenem	100,0%	33,3%	66,7%	
	Meropenem	88,0%			100,0%
	Ciprofloxacino	41,3%	77,8%	22,2%	
	Levofloxacino	41,7%		100,0%	
UCI (324 AB)[d]	Amikacina	62,8%	100,0%		
	Tobramicina	69,2%	90,0%	10,0%	
	Aztreonam	80,0%		100,0%	
	Ceftazidima	14,3%	100,0%		
	Piperacilina/tazobactam	40,0%		100,0%	
	Imipenem	60,0%	60,0%	40,0%	
	Meropenem	53,2%			100,0%
	Ciprofloxacino	26,1%	16,7%	83,3%	
	Levofloxacino	41,2%		100,0%	

AB = Antibiótico; UCI = Unidad de Cuidados Intensivos

[a]Motivo de no ajuste por dosis, referido a que se han utilizado dosis más bajas a las recomendadas: aminoglucósidos no ajustados por peso, aztreonam y ceftazidima 1g en vez de 2g, imipenem/cilastina 0,5g en vez de 1g y ciprofloxacino vía oral 0,5g en vez de 0,75g.

[b]Motivo de no ajuste por secuencia horaria, referido a intervalos terapéuticos más amplios que lo recomendado: aminoglucósidos cada 48h en vez de cada 24h, aztreonam, piperacilina/tazobactam e imipenem/cilastina cada 8h en vez de cada 6h, ceftazidima y ciprofloxacino intravenoso cada 12h en vez de cada 8h y levofloxacino intravenoso cada 24h en vez de cada 12h.

[c]Modo de administración referido a meropenem, administrado en infusión intravenosa directa en vez de en una perfusión continúa de 3 horas.

[d]El número de antibióticos prescritos duplica al número de aislados, esta circunstancia se puede deber a varios motivos: solo se detalla un aislado por persona, la utilización de biterapias, y el hecho de que se hayan incluido antibióticos posteriores (es decir, a partir del 2º aislado que no se computa, pero el antibiótico si se tiene en cuenta para el análisis de la inadecuación).

como en UCI) han sido prescritas de forma que se garantizase la exposición (cada 6h en vez de cada 8h). Problema similar nos encontramos con P/T, aún que en este caso con tasas mejores de prescripción (entorno al 60,0%), pero es un AB para el cual ha desaparecido la categoría "S" en PA, lo que acentúa la necesidad de optimizar el intervalo terapéutico.

Sin embargo, los β-lactámicos NC con recomendación de incremento de dosis (ceftazidima y cefepima) el grado de adecuación si ha sido favorable.

Un concepto muy poco integrado en nuestro hospital es el uso de la PE en los β-lactámicos NC. En el estudio de Valero et al. [6], en el que reinterpretaban los datos de susceptibilidad basándose en el análisis PK/PD de AB antipseudomónicos según criterios EUCAST 2021, se demostró que para los β-lactámicos (concretamente cefepima, ceftazidima y P/T) a dosis altas usadas en UCI, la probabilidad de logro del objetivo >90% solo se alcanzaba si se administraban en PE.

Existe poca bibliografía acerca de cómo ha impactado esta nueva clasificación en la práctica clínica real. El estudio de Munting et al. [7] demostró que habían incrementado significativamente en un 10% las prescripciones de meropenem respecto al año 2019 y lo asociaron a que el meropenem es uno de pocos β-lactámicos que se sigue clasificando como "S", así como a la falta de adaptación de los prescriptores a esta nueva clasificación.

En nuestro estudio, analizando el uso de meropenem, se ha encontrado que en el 37,1% de los tratamientos dirigidos con un β-lactámico (incluyendo los carbapenémicos) en UCI

se había utilizado meropenem cuando en el informe de sensibilidad aparecían otras opciones como cefepima, ceftazidima y P/T como "EI". Aunque no se ha evaluado otros condicionantes del paciente que pueden justificar la decisión y asumiendo que meropenem ha sido tradicionalmente un antibiótico muy utilizado de forma empírica en infecciones graves en UCI, si es relevante, que en el análisis de consumos de antipseudomónicos en nuestro centro (expresado en DDD/100 estancias), los únicos para los que se incrementaron las cifras de consumo fueron meropenem (un 11,8 % de mayor consumo en 2021 frente a 2020 en plantas y un 19,0 % en UCI), y en mucha menor medida colistina. El resto de antipseudomónicos reflejaba cifras de consumo inferiores en 2021 frente a 2020 tanto en plantas como en UCI.

En cuanto a las resistencias, el 65,0% de los pacientes de UCI que habían desarrollado resistencias durante el tratamiento recibieron previamente AB de forma no ajustada a la guía de recomendación (se debe tener en cuenta que no se realizó una prueba de tipado molecular para corroborar que era la misma cepa PA); Valero et al. [6], establecían que se podían dar más fallos en el tratamiento si estaba basado únicamente en las tasas de susceptibilidad que cuando se consideraba la exposición del antibiótico. Con los datos epidemiológicos de nuestro país, afirmaban que C/A y C/T eran los antibióticos con mayor probabilidad de alcanzar altas probabilidad de supresión de resistencias.

Existen diversos estudios que analizan el impacto del tratamiento inadecuado con variaciones en su definición. Micek et al. [8], definieron la TI de una bacteriemia por PA, como la documentación microbiológica de la infección que no se trató de manera efectiva en el momento en que se conocía el microorganismo causante y su susceptibilidad a los antibióticos, definición consensuada para fines de investigación clínica por autores como Koffef [9]. Con estos criterios indicaron una mayor tasa de mortalidad hospitalaria en el grupo de terapia inicial inadecuada (30,7% vs 17,8% p=0,018) con un OR: 2,04 (IC 95% 1,42-2,92), datos muy similares a los obtenidos en nuestro estudio para la TI global en planta (OR: 2,34; IC 95% 1,14-4,82), así como para el análisis del subgrupo de tratamientos empíricos inadecuados en planta (OR: 3,64; IC 95% 1,01-13,13). Los autores concluían que el uso empírico del tratamiento combinado contra bacterias gram negativas se asociaba con un mayor porcentaje de adecuación final del tratamiento; sus datos de sensibilidad para PA eran notablemente mejores que las de nuestro medio, por lo que el criterio de recomendación de inicio con tratamiento combinado parece aún más recomendable con nuestra situación.

Otro estudio, en el cual la definición difiere más pero que tiene en cuenta la adecuación de la pauta posológica prescrita como en nuestro caso, es el estudio de Morata et al. [10], donde analizaron la TEI asociada a la bacteriemia por PA MDR, indicando que era adecuado cuando el paciente recibía al menos un AB activo *in vitro* antes de disponer de las pruebas de sensibilidad y si la dosificación era de acuerdo a las normas vigentes. Encontraron que la tasa de mortalidad a los 30 días en el grupo de TEI era del doble respecto a los que recibieron un tratamiento adecuado (39,2% vs 20,8%), tasas que se correlacionan con la TEI en planta de nuestro estudio (22,4% vs 7,3%, p=0,04). Estos datos nos remarcan la relevancia de la optimización de la terapia antipseudomónica tanto en el uso empírico como en la adecuación posológica.

No obstante, se debe tener en cuenta que, la mortalidad atribuible a la dosificación es un concepto difícil de demostrar con certeza, ya que un desenlace desfavorable está influenciado por un conjunto de variables, aparte de la inadecuada prescripción de antibióticos, que influyen significativamente y que en nuestro caso no se realizó un análisis multivariante para descartar otras posibles causas.

Este estudio está limitado por su carácter retrospectivo y monocéntrico, lo que puede cuestionar la validez externa de sus resultados, así como por la falta de información comparativa previa a la implementación de los cambios EUCAST y la coincidencia con un período de tiempo en el que aún había una alta incidencia de pacientes SARS-Cov-2 en UCI.

A pesar de que ya existían referencias sobre la asociación entre una terapia antibiótica inadecuada y mayor mortalidad [8,10], la situación actual con una redefinición de la interpretación del antibiograma que condiciona el modo de administración de los antimicrobianos hace necesarios estudios como este, que reflejan la práctica clínica habitual, y que pueden servir de punto de partida a los equipos PROA para orientar en el análisis de cómo se están manejando los AB antipseudomónicos en cada centro.

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CONFLICTO DE INTERÉS

Los autores declaran no tener ningún conflicto de interés.

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Programa de optimización del uso de antimicrobianos en un Servicio de Medicina Intensiva: análisis retrospectivo observacional de los resultados 15 meses después de su implementación

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RESUMEN

Objetivo. Determinar el grado de aceptación de un Programa de Optimización del Uso de Antimicrobianos (PROA) en un Servicio de Medicina Intensiva (SMI), y evaluar su efecto sobre el consumo de antibióticos, indicadores de calidad y resultados clínicos.

Pacientes y métodos. Descripción retrospectiva de las intervenciones propuestas por un PROA. Comparación de uso de antimicrobianos, indicadores de calidad y seguridad frente a un periodo sin PROA. Se realizó en un SMI polivalente de un Hospital Universitario mediano (600 camas). Se estudió a pacientes ingresados por cualquier causa en el SMI durante el periodo PROA en los que se hubiera obtenido una muestra dirigida al diagnóstico de una potencial infección, o se hubieran iniciado antimicrobianos. Se elaboraron recomendaciones no impositivas para mejorar la prescripción antimicrobiana (estructura *audit and feedback*) y se procedió a su registro durante periodo PROA (15 meses, octubre 2018–diciembre 2019). Comparación de indicadores en un periodo con PROA (abril–junio 2019) y sin PROA (abril–junio 2018).

Resultados. Se emitieron 241 recomendaciones sobre 117 pacientes, el 67% de ellas de tipo desescalada terapéutica. La aceptación de las recomendaciones fue elevada (96.3%). En el periodo PROA se redujo el número medio de antibióticos por paciente (3.3±4.1 *vs* 2.4±1.7, p=0.04) y los días de tratamiento (155 DOT/100 PD *vs* 94 DOT/100 PD, p <0.01). La implementación del PROA no comprometió la seguridad de los pacientes ni produjo cambios en los resultados clínicos.

Conclusión. La implementación de un PROA es ampliamente aceptada en un SMI, disminuyendo el consumo de antimicrobianos, sin comprometer la seguridad de los pacientes.

Palabras clave: PROA, exposición a antibióticos, resistencia antibiótica, optimización antibiótica, optimización antimicrobiana, programa de optimización de antibióticos, audit and feedback, medicina intensiva, cuidados críticos

Antimicrobial stewardship program in an Intensive Care Unit: A retrospective observational analysis of the results 15 months after its implementation

ABSTRACT

Objective. We aim to evaluate the adherence rate to an Antimicrobial Stewardship Program (ASP) in an Intensive Care Unit (ICU), and to assess its effect on the use of antibiotics, quality indicators and clinical outcomes.

Patients and methods. Retrospective description of the interventions proposed by the ASP. We compared antimicrobial use, quality and safety indicators in an ASP *versus* a non-ASP period. The study was performed in a polyvalent ICU of a medium-size University Hospital (600 beds). We studied patients admitted to the ICU for any cause during the ASP period, provided that a microbiological sample aiming to diagnose a potential infection has been drawn, or antibiotics have

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been started. We elaborated and registered of non-mandatory recommendations to improve antimicrobial prescription (*audit and feedback* structure) and its registry during the ASP period (15 months, October 2018-December 2019). We compared indicators in a period with ASP (April-June 2019) and without ASP (April-June 2018).

Results. We issued 241 recommendations on 117 patients, 67% of them classified as de-escalation type. The rate of adherence to the recommendations was high (96.3%). In the ASP period, the mean number of antibiotics per patient (3.3±4.1 *vs* 2.4±1.7, p=0.04) and the days of treatment (155 DOT/100 PD *vs* 94 DOT/100 PD, p <0.01) were reduced. The implementation of the ASP did not compromise patient safety or produce changes in clinical outcomes.

Conclusion. The implementation of an ASP is widely accepted in the ICU, reducing the consumption of antimicrobials, without compromising patient safety.

Keywords: ASP, antibiotic exposure, antibiotic resistance, antibiotic stewardship, antimicrobial stewardship, antimicrobial stewardship program, audit and feedback, intensive care, critical care

INTRODUCCIÓN

Los mecanismos de resistencia a los antimicrobianos hacen que ciertos microorganismos sean cada vez más difíciles de tratar, lo que incrementa la estancia hospitalaria, los costes económicos y sociales, y la morbimortalidad [1,2]. Uno de los objetivos estratégicos del "Plan de acción global para abordar la resistencia a los antimicrobianos" de la Organización Mundial de la Salud consiste en optimizar el uso de los fármacos antimicrobianos, tanto en uso humano como animal [2]. Los Programas de Optimización del uso de Antimicrobianos (PROA) constituyen una estrategia de las organizaciones sanitarias para promover el uso adecuado de los antimicrobianos a través de intervenciones basadas en la evidencia. Los PROA constituyen uno de los pilares de enfoque integrado para el fortalecimiento de los sistemas de salud, junto con las políticas de prevención y control de la infección, y la seguridad del paciente [3]. En España, en 2012, varias sociedades científicas elaboraron un documento de consenso recomendando la creación de estas estructuras [4] y, en 2014, el Plan nacional de Resistencia a ANtibióticos (PRAN) estableció como prioridad la puesta en marcha de programas de promoción de uso prudente de antibióticos en hospitales y atención primaria [5]. Para ello, constituyó un grupo de trabajo que elaboró un documento con los objetivos, marco institucional, cartera de servicios, estructura y composición para la implementación de los PROA a nivel nacional [6].

Los Servicios de Medicina Intensiva (SMI) representan una de las unidades prioritarias en las que implementar un PROA, por su elevado consumo de antimicrobianos, su impacto sobre las resistencias, el beneficio potencial de la optimización del tratamiento a nivel individual y colectivo, y la trascendencia de estas intervenciones más allá de la unidad [3,7]. Sin embargo, existen diferentes barreras para su implementación, entre las que se encuentran: 1) La elevada complejidad clínica de los pacientes que requieren ingreso en estas unidades y la baja tolerancia a la incertidumbre ante su situación de gravedad; y 2) La necesidad de optimización del diagnóstico etiológico, siendo imprescindible una comunicación fluida, ágil y bidireccional con el Microbiólogo Clínico [1,3,8]. Varios trabajos recientes revisan la evidencia y exponen posibles soluciones a estas dificultades [1,8–12]. A pesar de todo, algunos centros de nuestro país han implementado con éxito un PROA en su SMI, consiguiendo excelentes resultados [13,14].

Este estudio pretende determinar si la implementación de un PROA en un SMI es una estrategia aceptada por el personal sanitario, si tiene impacto sobre el consumo de antibióticos de relevancia ecológica, y si las recomendaciones emitidas mejoran los indicadores de calidad sin repercutir sobre los resultados clínicos.

PACIENTES Y MÉTODOS

Contexto y diseño del estudio. Realizamos un estudio de cohorte retrospectivo observacional en el Servicio de Medicina Intensiva (SMI) de 19 camas de un hospital universitario de tercer nivel con capacidad para 600 pacientes, referencia para patología neuroquirúrgica, traumatológica, coronaria, trasplante hepático y quemados, y con capacidad para proporcionar soporte respiratorio avanzado con oxigenación mediante membrana extracorpórea (ECMO). El Servicio participa anualmente en el Registro ENVIN-HELICS [15] y se encuentra adherido a los Proyectos Zero [16–18].

En octubre de 2018 se constituyó en el centro un grupo de trabajo multidisciplinar PROA, integrado por médicos especialistas y en formación de Medicina Intensiva, Microbiología, Medicina Preventiva, Farmacia Hospitalaria, así como enfermería con experiencia en el control de infecciones. El grupo se reunió a diario para evaluar la necesidad teórica de cada prescripción antibiótica en los pacientes del SMI, cada vez que un nuevo resultado microbiológico se encontraba disponible. Para ello, se tuvo en cuenta el contexto clínico, el síndrome infeccioso, el microorganismo aislado y la farmacología de los antimicrobianos. Tras cada reunión, se emitieron recomendaciones no impositivas para optimizar el tratamiento antimicrobiano, que fueron comunicadas al médico responsable del paciente (estructura tipo *audit and feedback*). Estas recomendaciones y la tasa de adherencia a las mismas se documentaron en el Registro PROA Hospitalario.

Este estudio describe las recomendaciones documentadas durante los primeros 15 meses de funcionamiento (octubre de 2018 a diciembre de 2019), dado que el programa fue interrumpido en el primer trimestre de 2020 por el avance de la pandemia de enfermedad por coronavirus (COVID-19). Se describe también la tasa de aceptación de las recomendaciones propuestas. Se comparan indicadores de consumo de antimicrobianos e indicadores de seguridad en dos periodos: 1) Periodo no PROA, de abril a junio de 2018 (año previo a la implementación del PROA); y 2) Periodo PROA, de abril a junio de 2019. Los periodos seleccionados corresponden al "ENVIN

completo", en que se registran todas las infecciones y los antimicrobianos que reciben los pacientes ingresados en el SMI.

El estudio se realizó de acuerdo con los estándares nacionales e institucionales, tras la aprobación por parte del Comité de Ética de la Investigación del Área de Salud de Valladolid Oeste que, por la naturaleza del estudio, no requirió consentimiento informado por parte de los pacientes.

Participantes. Se evaluaron todos los pacientes ingresados por cualquier causa en el SMI durante el periodo PROA, siempre que se hubiera obtenido una muestra dirigida al diagnóstico microbiológico de una potencial infección, o se hubiera iniciado un tratamiento antimicrobiano.

Variables. Las recomendaciones emitidas tras cada reunión del equipo PROA se registraron de forma sistemática en un formulario electrónico.

El grupo PROA emitió recomendaciones agrupadas bajo definiciones propias, que se elaboraron a partir de varios trabajos [3,6,7,19], y se describen en la Tabla 1.

El consumo de antimicrobianos se expresó como dosis diaria definida (DDD), tal como define el *WHO Collaborating Centre for Drug Statistics and Methodology* [20]. Se utilizaron también los días de tratamiento (DOT, *days of therapy*), definidos como el número de días de utilización de cada antimicrobiano, independientemente de la dosis y número de dosis administradas cada día [3]. Ambos indicadores se normalizaron por cada 100 pacientes-día (PD).

Se analizaron varios indicadores de seguridad, expresados como incidencia de complicaciones infecciosas durante la estancia en el SMI, así como la mortalidad. La colonización o infección por microorganismos multirresistentes se definió como la identificación de un microorganismo multirresistente en una muestra clínica (hemocultivos, aspirado traqueal, lavado broncoalveolar o urocultivo) o en un cultivo de vigilancia epidemiológica, que se realiza con una frecuencia semanal a todos los pacientes en nuestro SMI. La infección por *Clostridioides difficile* se definió de acuerdo con las recomendaciones de la *European Society of Clinical Microbiology and Infectious Diseases* [21]. Las infecciones relacionadas con la asistencia sanitaria se definieron según el Manual de Definiciones y Términos ENVIN-HELICS 2018 [22].

Análisis estadístico. Las variables cuantitativas se expresaron como media ± desviación estándar (DE). Las variables cualitativas se expresaron como frecuencias absolutas o relativas (%). Para realizar comparaciones entre variables cuantitativas se aplicó la prueba de T de Student. Para comparar variables cualitativas se utilizó la prueba de Chi-cuadrado. Se estableció el nivel de significación estadística en <0.05. Dado que el análisis estadístico se llevó a cabo sobre una base de datos de tipo registro, y con carácter retrospectivo, no se consideró necesario calcular el tamaño muestral [23].

RESULTADOS

Durante el periodo PROA ingresaron un total de 1.413 pacientes en el SMI (62,1% varones, edad 63,7±17 años): 555 patología médica, 525 patología coronaria, 163 cirugías programadas, 122 politraumatismos, 27 cirugías urgentes y 21 grandes quemados. En este periodo se realizaron un total de 300 reuniones, en las que se emitieron un total de 241 recomendaciones sobre 117 pacientes (59,8% varones, edad 63,3±15,1 años).

Descripción de las recomendaciones emitidas por el PROA en el SMI

Descripción de las infecciones sobre las que se propusieron recomendaciones. Las muestras que desencadenaron

Tabla 1 Definición de las categorías de intervenciones propuestas por el PROA.

Modalidad de intervención	Definición
Reducción del espectro	Desescalada dirigida a disminuir el espectro de acción del antimicrobiano en función del antibiograma (tratamiento dirigido).
Retirada por resultado microbiológico	Desescalada consistente en la retirada de tratamiento iniciado de forma empírica, que ya no resulta necesario de acuerdo con el microorganismo aislado o por ausencia de datos de infección.
Secuenciación oral	Optimización consistente en la transición a vía oral de un antimicrobiano con elevada biodisponibilidad oral.
Ajuste de posología	Optimización consistente en el ajuste de dosis según niveles farmacológicos, función renal, síndrome infeccioso o parámetros pK/pD.
Revisión de la duración	Optimización consistente en la evaluación de la necesidad de continuar tratamiento antimicrobiano más allá del tiempo recomendado en las guías de práctica clínica para el síndrome infeccioso que presenta el paciente.
Inicio o cambio por resultado microbiológico	Adecuación del tratamiento consistente en iniciar un nuevo tratamiento para un microorganismo que no se encontraba adecuadamente cubierto con el tratamiento antimicrobiano prescrito (tratamiento dirigido) o modificar el antimicrobiano por uno de espectro similar de acuerdo con las características del microorganismo aislado (tratamiento dirigido).
Escalada terapéutica	Aumentar el espectro de acción del antimicrobiano en función del antibiograma (tratamiento dirigido).

Tabla 2 **Intervenciones propuestas por el PROA sobre cada grupo de antimicrobianos.**

Grupo antimicrobiano	RE	RRM	SO	AP	RD	I/C	ET	Total
J01A Tetraciclinas	0	2	0	0	1	0	0	3
J01C Penicilinas	7	10	0	1	4	4	2	28
J01D Cefalosporinas	1	7	0	0	3	1	1	13
J01DH Carbapenémicos	24	14	0	1	6	1	0	46
J01EE Cotrimoxazol	0	2	0	0	1	0	0	3
J01F Macrólidos	0	1	0	0	0	1	0	2
J01G Aminoglucósidos	0	2	0	0	2	0	0	4
J01M Quinolonas	1	11	0	0	1	4	1	18
J01XA Glucopéptidos	1	8	0	0	1	1	0	11
J01XB Polimixinas	0	1	0	0	1	0	0	2
J01XD Imidazólicos	1	1	0	0	0	0	0	2
J01XX Otros antibióticos[a]	5	35	4	0	2	4	0	50
J02AA Anfotericina B	1	2	0	0	0	0	0	3
J02AC Triazoles	0	6	0	1	0	0	6	13
J02AX Equinocandinas	5	4	0	0	1	0	1	11
J05AB Antivirales	0	2	0	0	0	0	0	2
Otros antibióticos	0	3	0	0	0	0	0	3
Otros antifúngicos	1	0	0	0	1	0	0	2
Otros antivirales	0	4	0	0	0	0	0	4
Ninguno	0	0	0	0	0	21	0	21
Total	47	115	4	3	24	35	13	241

RE=Reducción del espectro, RRM=Retirada por resultado microbiológico, SO=Secuenciación oral, AP=Ajuste de posología, RD=Revisión de la duración, I/C=Inicio o cambio por resultado microbiológico, ET=Escalada terapéutica. [a]La categoría J01XX Otros antibióticos incluyó únicamente linezolid.

con mayor frecuencia la emisión de una recomendación por parte del PROA fueron los hemocultivos (46,5%), seguidas de muestras respiratorias profundas (29,1%), urocultivo (7,1%), cultivo de LCR (5%) y muestras de otros orígenes (12,3%).

Las recomendaciones se propusieron mayoritariamente sobre infecciones respiratorias (44,8%), seguidas por infecciones intraabdominales (17,4%), urinarias (15,4%), del sistema nervioso central (7,9%), bacteriemia primaria sin otro foco sospechado (6,6%) y otras infecciones (7,9%).

La mayoría de recomendaciones se emitieron ante la identificación de microorganismos Gram-negativos (42,3%) y, con menor frecuencia, ante la identificación de Gram-positivos (30,3%), hongos (10,4%) o ausencia de aislamientos en los cultivos (17%). La mayoría de recomendaciones dieron respuesta a infecciones comunitarias (48,1%), seguido de infecciones nosocomiales (39,4%), con un bajo porcentaje de pacientes en el que no se confirmó infección (12,5%).

Descripción de los tipos de recomendaciones. Las recomendaciones más frecuentemente proporcionadas al médico prescriptor se englobaron dentro de las medidas de desescalada (67,2%), incluyendo la retirada por resultado microbiológico y la reducción de espectro, correspondientes al 47,7% y 19,5% del total de recomendaciones, respectivamente. Fueron menos frecuentes la adecuación del tratamiento (14,5%), las medidas de optimización (ajuste posológico, ajuste de duración o secuenciación a vía oral) (12,9%) y la escalada (5,4%).

Antibióticos sobre los que se propusieron las recomendaciones. El antibiótico sobre el que más recomendaciones se propuso fue linezolid (20,7%, 50/241). La mayor parte de estas recomendaciones consistieron en la retirada del tratamiento (70%, 35/50). En un porcentaje menor, se realizó desescalada (10%, 5/50), de las cuales la mayoría se realizó hacia las penicilinas (80%, 4/5). El resto de intervenciones se repartieron entre secuenciación oral (8%, 4/50), escalada (8%, 4/50) y ajuste de duración (4%, 2/50).

Los carbapenémicos fueron el segundo grupo de antibióticos en importancia sobre los que se propusieron recomendaciones (19,1%, 46/241). En este caso, la mayoría de las re-

Tabla 3 **Características clínicas y factores de riesgo de infección de los pacientes en un periodo no PROA y en un periodo PROA.**

	No PROA (n=236)	PROA (n=224)	p valor
Edad, años (media±DE)	61,6±17,9	63,7±16,5	0,19
Sexo masculino	54,7%	62,9%	0,07
APACHE-II, puntos (media±DE)	16,3±7,7	16,5±7,7	0,78
Pacientes no coronarios	68,6%	62,1%	0,13
Antibioterapia previa a ingreso en UCI	17,4%	15,6%	0,61
Ventilación mecánica	33,9%	28,1%	0,18
Sonda urinaria	63,1%	65,2%	0,65
Catéter venoso central	52,5%	42,9%	0,04
Técnicas de depuración extrarrenal	3,4%	5,8%	0,21
Nutrición parenteral	5,9%	2,7%	0,08
Cirugía urgente	7,2%	7,1%	0,98
Cirugía previa	23,3%	16,9%	0,09
Ingreso en UCI procedente de comunidad	53,8%	58,9%	0,27

comendaciones correspondieron con la desescalada (52,2%, 24/46), fundamentalmente hacia cefalosporinas (58,3%, 14/24) y, en menor medida, hacia quinolonas (8,3%, 2/24), penicilinas (8,3%, 2/24), tetraciclinas (8,3%, 2/24) y otros antimicrobianos. El resto de intervenciones se repartieron entre retirada del tratamiento (30,3%, 14/46), ajuste de duración (13,1%, 6/46), optimización de posología (2,2%, 1/46) e inicio de nuevo tratamiento (2,2%, 1/46).

Las intervenciones propuestas sobre el resto de grupos de antimicrobianos se resumen en la Tabla 2.

Tasa de aceptación de las recomendaciones emitidas por el PROA. El 96.3% de las recomendaciones emitidas por el equipo PROA fueron ejecutadas por el médico responsable del paciente. En el 3,7% de recomendaciones que no fueron aceptadas, el principal motivo que se argumentó fue la situación clínica del paciente, siendo mínima la negativa del médico responsable (0.8% del total de las recomendaciones).

Comparación de indicadores entre periodo no PROA y periodo PROA. Para determinar si la implementación del PROA modificó los indicadores de consumo de antimicrobianos o comprometió la seguridad de los pacientes, se compararon un periodo no PROA (de abril a junio de 2018) y un periodo PROA (de abril a junio de 2019). Las principales características de los pacientes en ambos periodos se resumen en la Tabla 3.

Comparación de indicadores de consumo de antimicrobianos. La proporción de pacientes que recibió antibióticos no cambió de manera significativa en ambos periodos, representando el 50% de los pacientes en el periodo no PROA frente al 51,8% en el periodo PROA, p=0,70. Sin embargo, se objetivó una reducción en el número medio de antibióticos con el que fue tratado cada paciente que requirió tratamiento antimicrobiano, que se redujo de 3,3±4,1 a 2,4±1,7, p=0,04.

El consumo global de antibióticos fue de 160,2 DDD/100 PD durante el periodo no PROA, frente a 164,6 DDD/100 PD durante el periodo PROA, con una diferencia de +4,4 DDD/100 PD, p=0,98. En cambio, cuando se analizaron los días de tratamiento (DOT), el consumo de antibióticos fue de 155 DOT/100 PD en el periodo no PROA, frente a 94 DOT/100 PD en el periodo PROA, con una diferencia de –61 DOT/100 PD, p <0,01. Por su parte, el consumo de antifúngicos fue de 30 DOT/100 PD en el periodo no PROA, frente a 17 DOT/100 PD en el periodo PROA, p=0.07. Las tendencias en el consumo en varios antimicrobianos de relevancia ecológica se describen en la Tabla 4.

Comparación de indicadores de seguridad. La comparación entre los principales indicadores de seguridad entre ambos periodos se describe en la Tabla 5.

DISCUSIÓN

Hallazgos principales. En este estudio se describen las principales recomendaciones emitidas por un PROA basado en una estrategia *audit and feedback* en un SMI durante un periodo de 15 meses. La mayoría de las recomendaciones se dirigieron a optimizar el tratamiento antimicrobiano mediante estrategias englobadas en el concepto de desescalada terapéutica, contando con una elevada tasa de aceptación. El resultado de los hemocultivos fue el principal determinante para que se emitiera una recomendación, siendo el aislamiento más frecuente

Tabla 4 **Tendencia en el consumo de varios antimicrobianos de relevancia ecológica durante los periodos de estudio.**

Antimicrobiano	No PROA (n=236)	PROA (n=224)	Diferencia	p valor
Todos los antibióticos, DOT/100 PD	**155**	**94**	**–61**	**<0,01**
Amikacina, DOT/100 PD	4,6	1,3	–3,3	<0,01
Amoxicilina-Clavulánico, DOT/100 PD	4,8	8,9	+4,1	<0,01
Azitromicina, DOT/100 PD	0,8	0,7	–0,1	0,87
Cefepima, DOT/100 PD	3,2	2,1	–1,1	0,07
Ceftriaxona/Cefotaxima, DOT/100 PD	9,5	6,7	–2,8	<0,01
Imipenem, DOT/100 PD	62,3	62,3	0	0,99
Levofloxacino, DOT/100 PD	8,8	8,2	–0,6	0,57
Linezolid, DOT/100 PD	17,2	12,5	–4,7	<0,01
Meropenem, DOT/100 PD	13,9	15,7	+1,8	0,18
Piperacilina-Tazobactam, DOT/100 PD	9,3	9,1	–0,2	0,84
Vancomicina, DOT/100 PD	10,9	4,2	–6,7	<0,01
Todos los antifúngicos, DOT/100 PD	**30**	**17**	**–13**	**0,07**
Anidulafungina, DOT/100 PD	4,8	5,4	+0,6	0,46
Fluconazol, DOT/100 PD	7,7	6,1	–1,6	0,09

un gramnegativo en infecciones con sospecha de foco respiratorio. Este hallazgo se alinea con el hecho de que el antibiótico sobre el que más intervenciones se propusieron fue linezolid, con una reducción significativa de los días de tratamiento con este fármaco en el periodo de estudio. La implementación del PROA permitió reducir de forma significativa el número medio de antibióticos que recibió cada paciente y los días de tratamiento (DOT), incrementando los días libres de antibiótico en pacientes con necesidad de tratamiento antimicrobiano, lo que se asoció a una reducción global del consumo de antibióticos. La implementación de las recomendaciones emitidas por el PROA no comprometió la seguridad de los pacientes ni produjo cambios significativos en los resultados clínicos.

Relación de los hallazgos con la literatura previa. Nuestro PROA se ha basado en la estrategia de reevaluación formal de la prescripción antibiótica ante criterios previamente especificados (cada vez que se emitió un resultado microbiológico), lo que supone una estrategia activa. De acuerdo con la revisión de Kaki R et al. [24], este tipo de estrategias se asocian a resultados más favorables que las acciones pasivas. La aceptación de las recomendaciones emitidas por el PROA por parte del personal sanitario del SMI fue elevada (96.3%). De acuerdo con Pickens CI et al. [1] y Ruiz-Ramos J et al. [7], con independencia de quién lidere el PROA, el liderazgo compartido con un intensivista con experiencia en patología infecciosa grave, que actúe como interlocutor entre el PROA y el equipo asistencial es crucial para conseguir implementar con éxito el programa en un SMI. La amplia aceptación de las recomendaciones PROA cuando el intensivista es copartícipe del liderazgo también se ha observado en otros trabajos realizados en nuestro país, como el de Ruiz et al. [13] o Álvarez-Lerma et al. [14], con tasas de aceptación >90%.

La reducción del consumo de antimicrobianos de relevancia ecológica es uno de los objetivos de los PROA [6]. El PROA implementado en nuestro centro emitió recomendaciones no impositivas mediante un mecanismo de retroalimentación activa, dado que las políticas restrictivas sobre el consumo de determinados antibióticos se han asociado a incrementos compensatorios que duplican o triplican la utilización de otros agentes de espectro similar, tal como se recoge en la revisión sistemática de Kaki et al [24]. En este sentido, el estudio de Ruiz J et al. [13], de características similares al nuestro en cuanto a tamaño muestral, duración y carácter no impositivo, consiguió reducciones significativas en el consumo de linezolid (–5,71 DDD/100 PD), cefalosporinas (–7,93 DDD/100 PD), aminoglucósidos (–8,59 DDD/100 PD) y en el consumo global de antibióticos (–85,40 DDD/100 PD), reconociendo como limitación el hecho de no haber utilizado los días de tratamiento (DOT, *days of therapy*) como indicador de consumo. Nuestro estudio no encuentra diferencias en significativas en el consumo cuando se utilizan DDD/100 PD. Consideramos que la optimización posológica en base a parámetros pK/pD puede ser responsable de que no encontremos diferencias entre ambos periodos en las DDD/100 PD (por ejemplo, administración de dosis de carga de betalactámicos, seguida de infusión prolongada a dosis elevadas; o la administración de aminoglucósidos

Tabla 5 **Comparación entre los indicadores de seguridad en ambos periodos.**

Incidencia durante estancia en SMI, No. (%)	No PROA (n=236)	PROA (n=224)	p valor
Colonización o infección por microorganismos multirresistentes	11 (4,7)	11 (4,9)	0,90
Infección *Clostridioides difficile*	5 (2,1)	1 (0,4)	0,11
Infección respiratoria asociada a ventilación mecánica	10 (4,2)	9 (4)	0,90
Bacteriemia asociada a catéter	3 (1,2)	1 (0,4)	0,34
Infección urinaria relacionada con sonda uretral	1 (0,4)	3 (1,3)	0,29
Reingreso a los 30 días	18 (7,6)	18 (8)	0,88
Mortalidad	16 (6,8)	23 (10,3)	0,18

en dosis única diaria elevada). Sin embargo, tal como han descrito recientemente Vallès J et al. [25], los DOT parecen representar de forma más fiel el consumo de antimicrobianos en el paciente crítico, evitando la potencial sobreestimación que podría derivarse de la utilización de las DDD. Utilizando este indicador, encontramos una reducción significativa en el consumo de linezolid (–4,7 DOT/100 PD, p <0,01), cefalosporinas (–2,8 DOT/100 PD, p <0,01) y aminoglucósidos (–3,3 DOT/100 PD, p <0,01), así como en el consumo global de antibióticos (–114 DOT/100 PD, p <0,01). Por su parte, Álvarez-Lerma F et al. [14] realizaron un estudio con un tamaño muestral ampliamente superior al nuestro, comparando un periodo de 4 años sin PROA *vs* un periodo de 5 años con PROA, destacando por presentar los resultados de consumo en DDD/100 PD y DOT/100 PD. La principal limitación de este trabajo, en cambio, radica en que la implementación de los Proyectos Zero durante el periodo de estudio tiene una clara repercusión a la baja en las tasas de infecciones nosocomiales, lo que podría justificar parcialmente el menor consumo de antimicrobianos, que no sería atribuible al PROA, sino a una mejor política de prevención y control de la infección. En nuestro estudio no se implementó ninguna medida adicional al PROA para reducir la incidencia de infecciones, ni para reducir el consumo de antibióticos, puesto que los Proyectos Zero ya se encontraban implementados, lo que elimina este factor como fuente potencial de confusión y confirma la utilidad del PROA para mejorar la prescripción antibiótica incluso en un centro en el que ya se han implementado previamente medidas dirigidas a prevenir y controlar la infección nosocomial. Nuestro PROA identificó un menor consumo de los mismos agentes antimicrobianos que Álvarez-Lerma J et al. [14], en términos de DOT/100 PD, con excepción de los agentes anti-SARM, en los que nuestro PROA consiguió disminuir no solo el consumo de vancomicina (–6,7 DOT/100 PD, p <0,01), sino también el de linezolid (–4,7 DOT/100 PD, p <0,01). Consideramos que el incremento en el consumo de amoxicilina-clavulánico (+4,1 DOT, p <0,01) es atribuible al elevado número de recomendaciones de tipo desescalada.

En cuanto a la seguridad de la implementación de los PROA, la revisión sistemática realizada por el grupo anteriormente citado de la Universidad de Toronto determinó que la reducción en el consumo de antibióticos derivada de la implementación de un PROA no se asociaba a un incremento de las infecciones nosocomiales, estancia o mortalidad en los pacientes críticos [24]. Al igual que ocurrió en el trabajo de Ruiz J et al. [13], la implementación del PROA en nuestro SMI no se asoció a cambios en la mortalidad, estancia, tasa de reingreso a 30 días, adquisición de microorganismos multirresistentes, ni infecciones relacionadas con la asistencia sanitaria. Encontramos una menor frecuencia de infección por *Clostridioides difficile* durante el periodo PROA, sin alcanzar la significación estadística, que podría deberse al menor consumo de cefalosporinas durante dicho periodo. El estudio de Álvarez-Lerma F et al. [14], por su parte, consigue mejorar indicadores como la mortalidad, estancia o tasa de infecciones relacionadas con la asistencia sanitaria. Sin embargo, existen importantes factores que pueden haber producido cambios en estos indicadores en su estudio, como la extensa duración del mismo, las pequeñas modificaciones que se producen a lo largo del tiempo en los estándares de cuidados o la implementación de los Proyectos Zero. Así, una revisión sistemática con meta-análisis reciente realizada por Lindsay PJ et al. [26] no fue capaz de encontrar que los PROA activos basados en evaluación y retroalimentación (*audit and feedback*), como el nuestro, se asocien con cambios de mortalidad en las unidades de críticos, por lo que se pueden considerar una estrategia segura.

Implicaciones de los hallazgos. Este estudio observacional implica que la implementación de un PROA activo basado en la evaluación y retroalimentación en un SMI es ampliamente aceptada, y se asocia a un menor consumo de antimicrobianos, sin producir efectos sobre la mortalidad. Estas estrategias pueden ser especialmente relevantes durante la pandemia por SARS-CoV-2, que han producido un incremento notable del consumo de antibióticos [27]. También implica que la administración de ciclos de tratamiento antibiótico más cortos en pacientes graves es segura.

Limitaciones. La contribución que realizamos presenta algunas limitaciones, entre las que cabe señalar que se trata de un estudio unicéntrico retrospectivo, con un bajo número de pacientes y un corto periodo de tiempo, lo que limita la generalización de los resultados. En segundo lugar, nuestro estudio no evalúa la tasa de adecuación del tratamiento antibiótico empírico, que puede resultar clave para una desescalada terapéutica exitosa. En tercer lugar, no se ha evaluado el impacto de otras intervenciones que podrían haber mejorado los resultados en el uso de antimicrobianos en el SMI [28], como las sesiones clínicas y la implementación de pruebas de diagnóstico rápido. Por último, no se ha evaluado el impacto de la reducción del uso de antimicrobianos sobre las muestras de vigilancia epidemiológica o sobre perfiles de resistencia concretos.

CONCLUSIONES

La implementación de un Programa de Optimización del uso de Antimicrobianos es ampliamente aceptada en un Servicio de Medicina Intensiva, permitiendo disminuir el consumo de antimicrobianos de relevancia ecológica, sin comprometer la seguridad de los pacientes.

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CONFLICTO DE INTERESES

Los autores declaran no tener ningún conflicto de intereses.

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Programa de optimización de antibioterapia en infección urinaria por cepas multirresistentes en el servicio de urgencias

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RESUMEN

Introducción. Las infecciones urinarias (ITU) son un motivo frecuente de asistencia a los servicios de urgencias hospitalarias (SU), siendo cada vez más frecuente el aislamiento de cepas multirresistentes. El presente trabajo pretende evaluar el impacto de un programa multidisciplinar de optimización de antibioterapia en pacientes con ITU causada por bacterias multirresistentes atendidas desde el SU.

Material y métodos. Estudio descriptivo de la puesta en marcha de un programa en el que participaron los servicios de urgencias, microbiología y farmacia. El tratamiento antibiótico de los pacientes que consultaron urgencias con urinocultivos positivos para bacterias multirresistentes fue revisado al alta por el equipo multidisciplinar. En aquellos pacientes con tratamiento inapropiado se contactó con los médicos y/o farmacéuticos del siguiente nivel asistencial o con los propios pacientes en el caso de alta a domicilio. Se evaluó el impacto del programa sobre las nuevas consultas a urgencias a 30 días en comparación con los resultados obtenidos de la práctica habitual en tres meses previos a la intervención.

Resultados. Durante el año de implantación se revisaron 2.474 urinocultivos de pacientes con ITU, 537 (21,7%) causadas por bacterias multirresistentes. El tratamiento empírico al alta de urgencias fue inapropiado en 287 (53,4%) pacientes, realizando modificaciones del tratamiento en 232 de ellos. 73 pacientes (19,3%) reconsultaron el SU a los 30 días del alta, siendo este porcentaje inferior a los resultados obtenidos en los tres meses previos a la intervención (27,9%; p=0,031), sin encontrar diferencias significativas en el porcentaje de nuevas visitas asociadas a infecciones urinarias.

Conclusión. La implantación de un programa multidisciplinar centrado en la revisión de urinocultivos por cepas multirresistentes al alta de urgencias consigue corregir la antibioterapia en un elevado número de pacientes, siendo una herramienta con potencial utilidad para reducir el número de nuevas visitas a urgencias.

Palabras Clave: Urgencias, Infección Urinaria, Antibióticos, Programas de optimización de antimicrobianos, resistencia bacteriana

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Antimicrobial stewardship program in urinary tract infections due to multi resistant strains in the emergency department

ABSTRACT

Introduction. Urinary tract infections (UTI) are a frequent reason for attendance at emergency department (ED). The present study evaluates the impact of a multidisciplinary program for the optimization of antibiotic therapy in patients with UTI caused by multi-drug resistant bacteria treated from the hospital ED.

Material and methods. Descriptive study of the implementation of a program in which emergency, microbiology and pharmacy departments participated. Antibiotic treatment of the patients who consulted the ED with positive urine cultures caused by multidrug-resistant bacteria was reviewed upon discharge. In those patients with inappropriate treatment, doctors and/or pharmacists of the next level of healthcare or patients in the case of home discharge were contacted. The impact of the program was evaluated based on new visits to the ED at 30 days after discharge, compared with the results obtained from the usual practice three months prior the intervention.

Results. During the first year, 2,474 urine cultures of patients with UTI were reviewed, 533 (21.7%) were caused by multidrug-resistant bacteria. Empirical treatment was inap-

propriate in 287 (53.4%), making treatment modifications in 243 of them. 73 (19.3%) patients returned to the ED 30 days after discharge, being lower than the results obtained in the three months prior intervention (27.9%; p=0.031), without significant differences in new visits associated with UTI.

Conclusion. The implementation of a multidisciplinary program focused on multidrug resistant UTI at discharge form ED correct antibiotic therapy in a large number of patients, being a potentially tool to reduce the number of new ED visits.

Keywords: Emergency care; Urinary tract infection; Anti-Bacterial Agents; Antimicrobial stewardship; Drug resistance

INTRODUCCIÓN

Las infecciones de tracto urinario (ITU) constituyen una de las principales causas de asistencia a los servicios de urgencias hospitalarios (SU). Estas unidades son entornos de gran complejidad para la prescripción de antibióticos, en los que se unen la incertidumbre diagnóstica por la falta de resultados microbiológicos definitivos con una elevada carga asistencial y presión por acortar el tiempo de estancia de los pacientes [1]. Por otro lado, durante los últimos años se ha observado un incremento progresivo en el aislamiento de gérmenes multirresistentes en las muestras de los pacientes con infecciones atendidas en los SU, especialmente en las ITU, en donde múltiples registros muestran una incidencia creciente de infección causadas tanto por cepas resistentes a quinolonas como por Enterobacterales productoras de β-lactamasas de espectro extendido (BLEE) [2-5]. Este hecho supone una dificultad añadida en el tratamiento empírico de los pacientes atendidos en estas unidades.

Ante la dificultad para iniciar un tratamiento empírico desde los SU en pacientes, especialmente los ancianos y/o con factores de riesgo de multirresistencia, surge la necesidad de generar circuitos que permitan una rápida corrección del tratamiento antibiótico en aquellos pacientes atendidos en el SU pendiente de cultivo y antibiograma. Pese a que varios estudios han investigado la inadecuación del tratamiento antibiótico en los servicios de urgencias [6,7], las experiencias descritas en la literatura relativas a programas de ajuste de antibioterapia tras el alta del SU y su impacto sobre los pacientes son limitadas. Es por ello que planteamos este estudio, con el objetivo de describir los resultados de un programa de optimización de la antibioterapia sobre ITU causadas por gérmenes multirresistentes en los SU, así como describir su impacto en términos de reconsultas a la unidad.

MATERIAL Y MÉTODOS

Se diseñó un estudio cuasiexperimental antes-después de la puesta en marcha de un programa de optimización de antibioterapia en pacientes adultos (>18 años) que consultaron un SU con ITU causadas por cepas multirresistentes en el período entre octubre 2021 y septiembre de 2022. El estudio se llevó cabo en un SU de un hospital terciario de 644 camas que atiende a cerca de 160.000 urgencias al año, en un área de salud con una población de referencia de 410.000 personas, siendo el 24,1% mayor a 65 años [8].

El programa incluyó la participación de tres servicios: urgencias, microbiología y farmacia. Diariamente, el servicio de microbiología seleccionó los urinocultivos positivos por bacterias multirresistentes obtenidos en el SU en las 48h previas. Las bacterias consideradas como tales fueron: *Staphylococcus aureus* resistente a meticilina, *Enterococcus faecium*, *Pseudomonas aeruginosa* multirresistente (resistencia a al menos un antibiótico de tres o más familias) [9] y Enterobacterales productores de BLEE, β-lactamasas AmpC (hiperproducción/plasmídica) y carbapenemasas. Todos los pacientes atendidos en el SU con aislamiento de bacterias multirresistentes en el cultivo de orina identificados por el servicio de microbiología fueron anotados en la agenda para su evaluación por parte del equipo revisor. Este equipo revisor estaba constituido por un urgenciólogo y un farmacéutico hospitalario, que revisaban cada caso y el tratamiento antibiótico prescrito al alta del SU en este grupo de pacientes. En aquellos pacientes con tratamiento inapropiado, definido como no activo de acuerdo a la sensibilidad del antibiograma, se contactó bien con el propio paciente o su centro residencial en caso de alta a domicilio, realizando los cambios pertinentes de tratamiento en la receta electrónica y/o incluyendo a los pacientes en el programa de hospitalización domiciliaria cuando no existía opción de tratamiento antibiótico vía oral. En el caso de alta a un centro sociosanitario u otro centro hospitalario o ingreso en el propio centro, se contactó vía telefónica o mediante correo electrónico con médicos o farmacéuticos del centro, enviando el antibiograma y sugiriendo una nueva pauta de tratamiento.

Para evaluar el impacto del programa sobre la evolución de los pacientes, se comparó la frecuencia de reconsultas a 30 días al SU totales y por ITU durante el periodo de intervención con el de los tres meses previos a la intervención mediante el test estadístico de Ji-cuadrado (Stata v.13.0) en aquellos pacientes dados de alta desde el SU. Los pacientes del periodo pre-intervención incluyeron todos los pacientes adultos de dicho periodo atendidos en el SU con aislamiento de bacterias multirresistentes en el cultivo de orina dados de alta desde la unidad. El programa contó con la aprobación del comité de bioética del Hospital (Nº Referencia: IIBSP-OAM-2022-86).

RESULTADOS

Durante el periodo de estudio se obtuvieron un total de 2474 urinocultivos positivos en el SU, de los cuales 537 (21,7%) presentaron aislamiento de bacterias multirresistentes, siendo éstos los casos evaluados por el equipo revisor. Las características de los pacientes con aislamiento de estas cepas, así como los del periodo previo a la intervención se encuentran reflejadas en la Tabla 1. El destino principal al alta fue en primer lugar el domicilio (179; 33,2%), seguido de otro centro hospitalario o centro de atención intermedia para convalecencia (172; 31,9%) e ingreso en el propio centro (159; 29,2%).

Tabla 1 **Características de los pacientes con infección urinaria por gérmenes multirresistentes en el periodo pre y post intervención**

	Pre-intervención (n=125)	Intervención (n=537)	P-valor
Edad (Media, DE)	82,4 (11,1)	77.7 (16,0)	0,001
Mujer (%)	65 (52,0)	322 (59,7)	0,120
Comorbilidades (%)			
Insuficiencia cardíaca crónica	35 (28,1)	130 (24,1)	0,351
Diabetes Insulina-dependiente	16 (12,8)	52 (9,6)	0,413
Enfermedad renal Crónica III-V	23 (18,4)	83 (15,4)	0,429
Sonda Vesical	22 (17,6)	69 (12,8)	0,075
Demencia	58 (46,4)	222 (41,1)	0,300
Ingreso 3 meses previos	41 (32,8)	160 (29,7)	0,497
> 1 Episodio ITU año previo	19 (15,2)	69 (12,8)	0,476
Origen			
Domicilio	73 (58,4)	358 (66,4)	0,092
Centro Sociosanitario/Residencia	52 (41,6)	155 (28,8)	0,063
Destino			
Domicilio	39 (31,2)	179 (33,2)	0,668
Centro Sociosanitario	41 (32,8)	172 (31,9)	0,846
Ingreso hospitalario	39 (31,2)	157 (29,2)	0,659
Otros hospitales	6 (4,8)	29 (5,4)	0,787

ITU: Infección del tracto urinario

En la Figura 1 se muestran las bacterias multirresistentes responsables de los episodios atendidos en la unidad en el periodo de intervención. *Escherichia coli* fue la bacteria más común causante de ITU, siendo responsable de 361 (67,0%) episodios, seguida de *Klebsiella pneumoniae* con 104 (19,3%). Un total de 73 (13,5%) pacientes presentaron bacteriemia asociada al episodio de ITU durante el periodo de intervención.

El antibiótico más frecuentemente prescrito como tratamiento empírico en los pacientes evaluados fue ceftriaxona (n=121; 22,4%), seguido de ertapenem (109 (20,2%), amoxicilina/clavulánico (56; 10,3%), meropenem (51; 9,5%) y cefuroxima (43; 7,8%), siendo 305 (56,5%) tratamientos intravenosos. De los 539 episodios de ITUs por cepas multirresistentes, 287 (53,3%) presentaban un tratamiento inapropiado según antibiograma, realizándose una intervención con rectificación de la antibioterapia en 232 (80,8%) de ellos. Los antibióticos con mayor frecuencia de tratamientos inapropiados fueron ciprofloxacino (9 tratamientos inapropiados; 50,0%), amoxicilina/clavulánico (24; 42,8%) y cefuroxima (10; 22,8%).

De los 380 pacientes revisados y dados de alta desde urgencias (incluyendo a domicilio, centro sociosanitario u otros hospitales), 73 (19,3%) consultaron de nuevo el SU a los 30 días por cualquier causa, siendo inferior al porcentaje de nuevas consultas del periodo previo a la intervención (27,8%; OR: 0,481 (IC95% 0,291-0,735), p=0,031). No se encontraron diferencias significativas en el porcentaje de nuevas consultas relacionadas con episodios de ITU (8,7%) respecto a periodo previo a la intervención (12,0%; OR: 0,640 (0,327-1,247), p=0,253).

DISCUSIÓN

De acuerdo con los resultados de nuestro estudio, más de un 40% de los pacientes con ITU causadas por cepas multirresistentes pueden recibir un tratamiento antibiótico empírico inapropiado al alta de urgencias. Los motivos son diversos, incluyendo la dificultad en la valoración de los factores de riesgo asociados a multirresistencia en una población de edad avanzada y alto grado de comorbilidad, la necesidad de minimizar el uso de antibióticos de amplio espectro, y la aparición de ITU por bacterias multirresistentes en pacientes sin factores de riesgo. La implantación de un programa multidisciplinar de revisión de urinocultivos es capaz de detectar y corregir en un corto periodo de tiempo estos tratamientos inapropiados, estando asociado a un menor número de nuevas visitas al SU por cualquier causa, sin encontrar diferencias significativas en la reducción de consultas relacionadas con la ITU. Varios estudios han publicado que el porcentaje de prescripciones inapropiadas de antibióticos en este tipo de unidades puede ser superior al 20% [6,7,11,12]. Sin embargo, pese a que durante

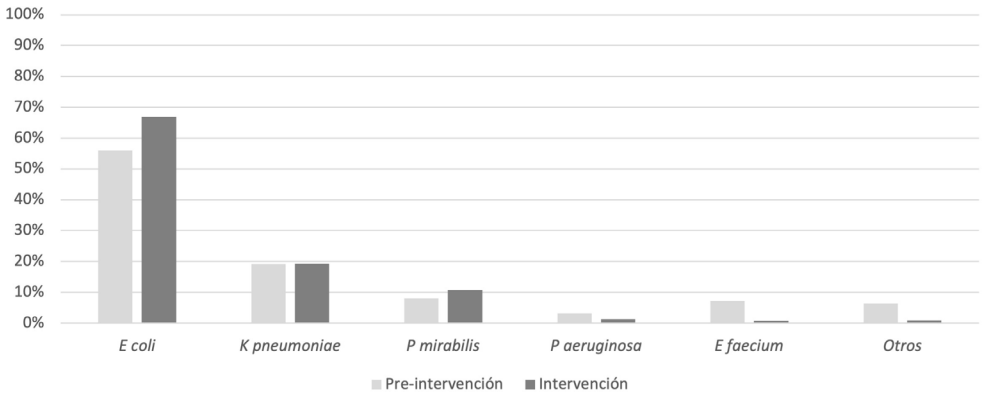

Figura 1 **Bacterias multirresistentes responsables de los episodios evaluados durante el periodo pre y post intervención**

los últimos años las experiencias descritas sobre programas de optimización de uso de antimicrobianos (PROA) en el ámbito hospitalario se han incrementado de forma notable, los datos referidos al impacto clínico de la adecuación del tratamiento antibiótico en los pacientes tratados en los SU son reducidos [10]. Nuestro trabajo tiene el valor de identificar que un sistema de revisión al alta es capaz de reducir nuevas consultas al sistema sanitario.

Existen diferentes experiencias descritas sobre la adecuación del tratamiento antibiótico en pacientes con ITU en los SU. Fagan et al [13] mediante un programa de restricción de formulario obtuvieron una reducción en la prescripción de ciprofloxacino en pacientes con ITU. Otros autores, incluyendo programas formativos a prescriptores dentro del SU, así como algoritmos de manejo de ITU en base al perfil local de resistencias, han logrado una mejor adherencia a las guías y una reducción en el uso de quinolonas [14,15]. Nuestro programa ha evaluado el impacto más allá del consumo de antimicrobianos, incluyendo el análisis de nuevas consultas al SU. Los resultados han mostrado que la implantación del programa consigue reducir el global de nuevas consultas a urgencias más allá de nuevos episodios de ITU. Pese a que el estudio no ha sido diseñado para explorar este fenómeno, la rápida corrección del episodio infeccioso podría haber contribuido a evitar la descompensación de otras patologías de base en una población con alto grado de comorbilidad.

Cabe destacar la alta frecuencia de cepas multirresistentes aisladas en nuestra población, muchas de ellos sin una gran presión antibiótica previa, así como el elevado porcentaje de reconsultas, siendo superior al 25%, por encima de los resultados obtenidos en anteriores estudios publicados [16]. Este fenómeno se puede atribuir a la alta edad media y comorbilidades de la población incluida, pudiéndose considerar una población de alta complejidad. La experiencia descrita en nuestro centro parece indicar que la implantación de este programa de seguimiento de ITUs por bacterias multirresistentes consigue reducir el número de episodios de reconsultas a los SU, siendo una herramienta de valor para reducir el consumo de recursos sanitarios y la saturación de estas unidades. Estos datos muestran la importancia de la optimización precoz del tratamiento empírico, así como el establecimiento de un programa de revisión de cultivos al alta y el rápido contacto con los centros de referencia para la modificación de la cobertura antibiótica. Dada la dificultad para predecir el riesgo de multirresistencia en estos pacientes con alto grado de comorbilidad, futuros estudios deberán evaluar nuevos factores asociados a tratamientos empíricos inapropiados en los pacientes atendidos en los SU. El desarrollo de nuevos modelos de análisis de datos y la incorporación de la inteligencia artificial para mejorar la adecuación en el tratamiento antibiótico al alta de estas unidades son posibles líneas a explorar en los próximos años.

Es relevante señalar que, pese al alto porcentaje de tratamientos inapropiados observado en la población de nuestro estudio, la prescripción de carbapenémicos, especialmente de ertapenem ha sido elevada. El uso de ertapenem se ha incrementado en las altas a residencias y centros sociosanitarios dado su amplio espectro de acción, así como a la posibilidad de administración en dosis única diaria. No obstante, varios autores han documentado una reducción de la sensibilidad a este fármaco debido al incremento en la presencia β-lactamasas tipo AmpC, carbapenemasas y alteraciones en las porinas [17,18]. Es por ello que se ha recomendado reservar su uso para aquellos pacientes con aislamiento o alta sospecha de infección por enterobacterias multirresistentes [19], lo que refuerza la necesidad de programas de seguimiento al alta para corregir aquellos tratamientos inapropiados prescritos en ITUs por cepas multirresistentes en pacientes con pocos factores de riesgo.

Entre las limitaciones de nuestro estudio se encuentra su carácter unicéntrico, que impide generalizar los resultados a otros centros con diferentes perfiles de poblaciones atendidas, perfiles de resistencias y flujos de pacientes. Por otro lado, es conocido que la adecuación en la prescripción de antibióticos no solo se refiere a un adecuado espectro, si no a

otros factores tales como a su dosificación o el recambio de la sonda en pacientes portadores [20]. La inadecuación en el manejo de estas variables podría haber influido en el grado de nuevas consultas al SU. No obstante, no hubo diferencias en los protocolos de manejo en el centro en los periodos previo e intervención. Las características del grupo control, con una población de edad más avanzada y un análisis de tres meses, con posible sesgo asociado a la estacionalidad de la actividad y el perfil de infecciones en el SU podrían haber afectado a los resultados. Además, dado que se trata de un estudio descriptivo de la puesta en marcha de un programa de intervención sobre ITU, el estudio no ha sido diseñado teniendo en cuenta el tamaño muestral necesario para evaluar diferencias entre el periodo previo y de intervención, aspecto que puede haber influenciado en la obtención de una reducción no significativa de nuevos episodios de ITU. Por último, no ha sido posible conocer y evaluar la duración total del tratamiento antibiótico en el periodo de intervención más allá del propio centro, siendo este un elemento de gran relevancia para conocer el impacto en la selección de nuevas cepas multirresistentes, teniendo en cuenta que un alto porcentaje de los pacientes tratados son dados de alta a centros sociosanitarios o residencias.

En resumen, la implantación de un programa multidisciplinar de revisión de urinocultivos positivos a cepas multirresistentes consigue corregir un elevado número de prescripciones, con una posible reducción del número de nuevas consultas a los SU.

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CONFLICTO DE INTERESES

Los autores declaran no tener conflicto de intereses.

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Análisis de la incidencia y epidemiología de las infecciones por micobacterias no tuberculosas en el área de salud III de la comunidad autónoma de Aragón

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RESUMEN

Objetivo. Conocer la incidencia y epidemiología de micobacterias no tuberculosas (MNT) en nuestra área y la prevalencia de comorbilidades en pacientes con infección por MNT. Como objetivos secundarios, estudiamos la distribución por especies de MNT, las formas de enfermedad objetivadas y el tipo de muestra empleada para su diagnóstico.

Material y métodos. Estudio retrospectivo en el que se incluyeron todos los aislamientos de micobacterias realizados por el Laboratorio de Microbiología del Hospital Clínico Universitario Lozano Blesa de Zaragoza durante el periodo comprendido entre el 1 de enero de 2011 y el 31 de diciembre de 2018.

Resultados. Se aislaron un total de 533 micobacterias, de las cuales 295 (55,35%) eran micobacterias tuberculosas (MTB) y 238 (44,65%) MNT. Del total de aislamientos de MNT, el 15,54% fueron considerados clínicamente significativos. Se identificaron 21 especies y las más frecuentes fueron: *M. gordonae* (26,89%), *M. fortuitum* (19,75%) y *M. avium* (16,39%). El 32,72% de los aislamientos de MNT se realizaron en mayores de 70 años.

Conclusiones. Podemos confirmar que el número de aislamientos de MNT en nuestra área está siendo mayor que en periodos previos. La infección por MNT es más frecuente en varones y mayores de 70 años. La epidemiología, especialmente los factores de riesgo, de la enfermedad por MNT está cambiando.

Palabras clave: micobacterias no tuberculosas, MNT, epidemiología.

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Analysis of the incidence and epidemiology of non-tuberculous mycobacterial infections in the health area III of Aragón

ABSTRACT

Objectives. The main objective of our investigation was to know the incidence and epidemiology of non-tuberculous mycobacteria (NTM) in our area and the prevalence of comorbidities in patients with MNT infection. As secondary objectives, we studied the distribution by species of MNT, the forms of disease and the type of sample used for its diagnosis.

Material and methods. A retrospective study was carried out in which all the isolates of mycobacteria carried out by the microbiology laboratory of the Hospital Clínico Universitario Lozano Blesa of Zaragoza during the period between January 1, 2011 and December 31, 2018 were included.

Results. A total of 533 mycobacteria were isolated, of which 295 (55.35%) were tuberculosis (MTB) and 238 (44.65%) were MNT. Of the whole MNT isolates, only 15.54% were considered clinically significant. Twenty-one species were identified being the most frequent: *M. gordonae* (26.89%), *M. fortuitum* (19.75%) and *M. avium* (16.39%). 32.72% of the MNT isolates were found in people over 70 years of age.

Conclusions. We can confirm that the reported number of MNT isolates in our area is higher than in previous periods. MNT infection is more common in men and those older than 70 years. The epidemiology, especially the risk factors, of MNT disease is changing.

Keywords: nontuberculous mycobacteria, MNT, epidemiology.

INTRODUCCIÓN

En las últimas décadas la incidencia de infecciones y enfermedad por micobacterias no tuberculosas (MNT) está incrementándose a nivel global [1,2]. Las MNT son un grupo hete-

rogéneo de más de 190 especies de bacterias, ubicuas en el medio ambiente, y que prácticamente podemos encontrar en casi cualquier localización: suelo, ríos, agua superficial, calderas, animales, alimentos... Los motivos de este aumento de incidencia no son bien conocidos. Aunque la mejora de las técnicas diagnósticas ha incrementado la detección de las MNT, no justifica por sí sola este aumento de la incidencia [1]. Otros factores como el envejecimiento poblacional, las cada vez más frecuentes enfermedades que cursan con alteraciones estructurales del árbol bronquial y el pulmón, así como defectos genéticos, tratamientos y enfermedades que alteran la función del sistema inmunitario, parecen guardar también relación con este fenómeno [1-3].

Intentar hacer una estimación realista sobre la epidemiología de las infecciones por MNT es prácticamente imposible. El hecho de que las micobacteriosis no se consideren enfermedades de declaración obligatoria (EDO), que no existan registros en cada país que recojan los aislamientos de MNT y que haya diferente distribución de especies en cada zona geográfica, se traduce en que los datos disponibles son escasos y provienen de estudios independientes realizados en distintas áreas del mundo. Esta falta de consenso la encontramos, incluso aún mayor, al acercar el foco al territorio español. Si bien comunidades autónomas como Madrid y Asturias han objetivado un incremento en la incidencia de infecciones por MNT en las últimas décadas, lo contrario se ha observado en País Vasco [4-6].

Respecto a la distribución por grupos de edad y sexo, existe consenso en que son infecciones más frecuentes en pacientes de edad media y edad avanzada [2,3]. Pero los datos sobre tendencias de género difieren según el área de estudio. Mientras que, en Europa, mayoritariamente, parece ser que las infecciones por MNT son más prevalentes en hombres, ocurre lo contrario en Australia, Estados Unidos y Asia [1].

El presente estudio tiene como objetivo conocer la incidencia y prevalencia de MNT en nuestra área, la distribución por especies, las formas de enfermedad objetivadas y el tipo de muestra empleada para su diagnóstico. Otros objetivos del mismo incluían conocer la distribución por grupos de edad y género y las principales comorbilidades de nuestra población de estudio.

MATERIAL Y MÉTODOS

Diseño del estudio. Estudio retrospectivo en el que se incluyeron todos los aislamientos de micobacterias realizados por el Laboratorio de Microbiología del Hospital Clínico Universitario Lozano Blesa de Zaragoza durante el periodo comprendido entre el 1 de enero de 2011 y el 31 de diciembre de 2018. El laboratorio de nuestro centro se encarga de analizar las muestras procedentes de las Áreas de Salud Zaragoza III y Calatayud, que engloba una población aproximada de 355.600 habitantes. Se trata de una población predominantemente urbana, cuya edad media en dicho periodo se situaba en los 43,84 años y que además presentaba unas tasas del 19,96% de individuos mayores de 65 años y del 14,12% de población inmigrante [7].

De la información recopilada por el laboratorio para cada aislamiento, se recogieron los siguientes datos: tipo de muestra, método de diagnóstico y especie aislada. Los criterios empleados para considerar un aislamiento como clínicamente significativo fueron los de la American Thorax Society (ATS), la European Respiratory Society (ERS), la European Society of Clinical Microbiology and Infectious Diseases (ESCMID) y la Infectious Diseases Society of America (IDSA) publicados en su guía conjunta de 2019 [8]. En aquellos sujetos que presentaron múltiples aislamientos, simultáneos, de la misma micobacteria, solo se contabilizó el primero de ellos.

La descontaminación de las muestras se realizó por el método de descontaminación con N-Acetilcisteina y posterior concentración de la muestra. A continuación, se sembraban las muestras en medio líquido para sistema automatizado (Bact/ALERT® MP) y en medios sólidos (Coletsos y/o Lowenstein-Jensen). Los cultivos sólidos se mantuvieron en estufa a 37ºC entre un mínimo de 45 días y un máximo de 60 días, mientras que el cultivo en medio líquido se descartó como negativo cuando lo indicaba el sistema prolongándose la incubación, en algunos casos, hasta los 60 días.

La identificación se realizó mediante medios genotípicos (GENOTYPE® AS y CM). Cuando una cepa no era identificada por dicho sistema se remitió al laboratorio de genética de micobacterias de la Facultad de Medicina de la Universidad de Zaragoza, donde se identificaron mediante la técnica de PRA.

Mediante revisión de la historia clínica de los pacientes se recogieron variables demográficas (edad y sexo) y clínicas. Las variables clínicas recogidas incluyeron los antecedentes de tabaquismo, enolismo, virus de la inmunodeficiencia humana (VIH), inmunodepresión (por cualquier causa excepto VIH), neoplasia activa, enfermedad pulmonar obstructiva crónica (EPOC), bronquiectasias, diabetes mellitus (DM), insuficiencia renal crónica, enfermedad autoinmune y pluripatología compleja (definida como pacientes con 3 o más enfermedades crónicas, simultáneas e incurables).

Análisis estadístico. Para el tratamiento estadístico de variables cualitativas se utilizó el Test Binomial Exacto para la comparación de proporciones en variables dicotómicas, el Test Exacto de Fisher en el análisis de tablas de contingencia y el test chi-cuadrado de tendencia en datos temporales. Para variables cuantitativas se emplearon técnicas de regresión gaussiana para la detección de tendencia en series temporales, y para la comparación de distribuciones se utilizaron el test de Shapiro-Wilk de normalidad y el Test de WIlcoxon o el Test de Medianas según el resultado del Test Robusto de Levene para la comparación de varianzas. Se consideraron los p-valores < 0,05 como estadísticamente significativos.

Consideraciones éticas. El estudio fue aprobado por el Comité de Ética de la Investigación de la Comunidad Autónoma de Aragón (CEICA) con número de referencia - C.I. PI19/486.

RESULTADOS

Durante el periodo comprendido en nuestro estudio se aislaron un total de 533 micobacterias, de las cuales 295 (55,35%) eran micobacterias tuberculosas (MTB) y 238 (44,65%) MNT. La distribución de las micobacterias se muestra en la Figura 1. Los 238 aislamientos de MNT procedían de muestras de 217 pacientes diferentes. Las infecciones por MNT fueron más frecuentes en hombres (n=134) que en mujeres (n=83) (61,75% vs. 38,25%, p < 0,001). La ratio hombre/mujer fue de 1,61 (Figura 2). La edad media fue 59,59 años (60,8 años en hombres y 57,64 años en mujeres). Encontramos el mayor número de aislamientos (n=71; 32,72%) en el grupo de mayores de 70 años. La distribución de los aislamientos por rangos de edad se muestra en la Figura 3.

Mientras que las cifras de aislamientos de MTB presentaron una tendencia decreciente (p = 0,00361), las cifras de aislamientos de MNT se mantuvieron relativamente estables. La tasa de incidencia media de infecciones por MNT en el período estudiado fue de 8,215 casos por cada 100.000 personas y año, siendo 2012 con 11,882 casos por cada 100.000 habitantes el año con mayor tasa de incidencia. Del total de aislamientos de MNT, 37 aislamientos (15,52%) cumplieron los criterios de la ATS y la IDSA [8], y fueron considerados clínicamente significativos, mientras que el resto se consideraron como situaciones de colonización. Entre los 37 casos considerados clínicamente significativos, 28 eran hombres (75,68%) y 9 eran mujeres (34,32%), la edad media se situó en los 68,45 años y en todos los casos se detectó algún tipo de comorbilidad (Tabla 1). MAC y *M. kansasii* fueron las especies más habitualmente implicadas en los casos de enfermedad clínicamente significativa.

La tasa de mortalidad media anual en el periodo de nuestro estudio se situó en 1,035 por cada 100.000 personas y, en total, fallecieron 30 pacientes. Por otra parte, la tasa de letalidad media fue de 12,605 muertes por cada 100 casos, alcanzando el pico más alto en el año 2014, cuando fue de 23,33 muertes por cada 100 casos. Cabe destacar que en los pacientes mayores de 70 años la tasa de letalidad aumentó hasta las 24,36 muertes por cada 100 casos.

Las comorbilidades más frecuentes en los pacientes con aislamientos de MNT fueron la presencia de bronquiectasias (67,23%), tabaquismo (56,30%), pluripatología compleja (35,71%) y enfermedad pulmonar obstructiva crónica (EPOC) (33,61%). El virus de la inmunodeficiencia humana (VIH) fue la comorbilidad menos frecuente en nuestra población (4,62%) (tabla 2).

Respecto a los aislamientos de MNT, se identificaron un total de 21 especies y 2 aislamientos en los que la micobacteria no pudo llegar a ser identificada. Las más frecuentes fueron: *M. gordonae* (26,89%), *M. fortuitum* (19,75%), *M. avium* (16,39%), *M. lentiflavum* (8,82%), *M. chelonae* (4,62%) y *M. intracellulare* (4,20%). La tabla 3 muestra todas las especies aisladas en nuestro estudio. Las muestras en las cuales se aislaron las MNT fueron, mayoritariamente, de origen respiratorio (92,02%), siendo la muestra predominante el esputo (86,13%), muy por delante del aspirado bronquial (BAS) (5,04%) y del lavado broncoalveolar (BAL) (0,84%). Las muestras extrapulmonares (7,98%) incluyeron sangre, adenopatías, exudados de abscesos, orina, biopsias cutáneas, jugo gástrico y líquido pleural.

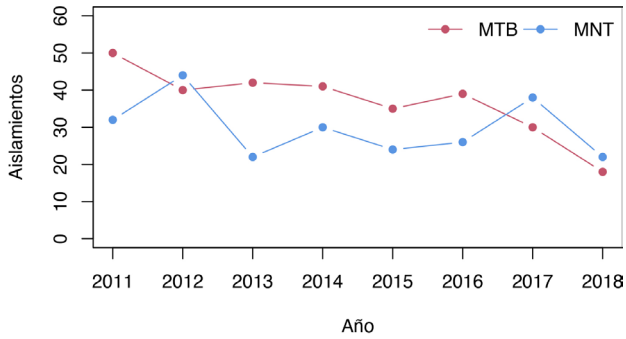

Figura 1 Evolución aislamientos MTB MNT durante el periodo 2011-2018

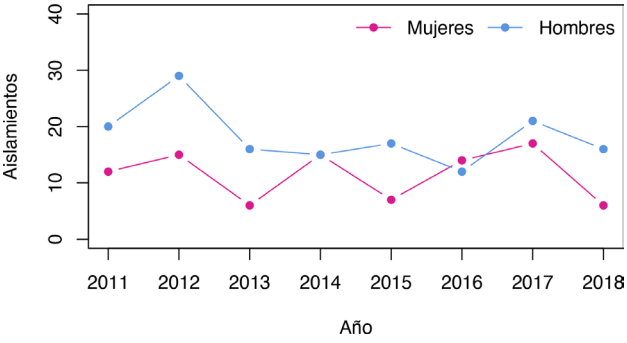

Figura 2 Aislamientos de MNT en mujeres y hombres, distribución por años

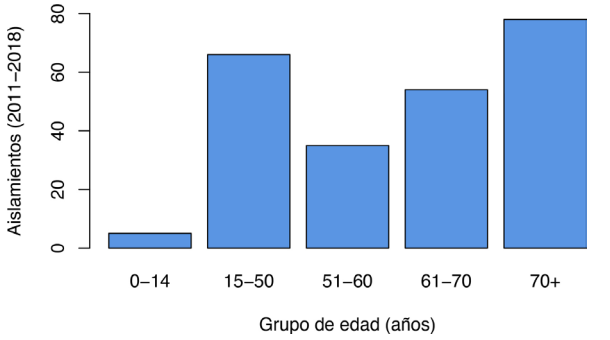

Figura 3 Distribución aislamientos MNT por rangos de edad

Respecto a la distribución de especies por grupos de edad, las especies aisladas con mayor frecuencia en pacientes de edades tempranas (<15 años) fueron *M. avium* (80%) y *M. gor-*

Tabla 1 **Principales comorbilidades en casos de infección por MNT clínicamente significativas.**

Comorbilidad	Valor
Bronquiectasias	30 (81,08%)
Tabaquismo	25 (67,57%)
Pluripatologia compleja*	13 (35,14%)
EPOC	27 (72,97%)
Inmunodepresión (no VIH)	9 (24,32%)
Neoplasia activa	4 (10,81%)
DM	10 (27,03%)
Enolismo	4 (10,81%)
Insuficiencia Renal	5 (13,51%)
Enfermedad Autoinmune	2 (5,41%)
VIH	9 (24,32%)

***Definido como 3, o más, enfermedades crónicas, simultáneas e incurables**
VIH: virus de la inmunodeficiencia humana, EPOC: enfermedad pulmonar obstructiva crónica, DM: diabetes mellitus.

Tabla 2 **Principales comorbilidades en pacientes con aislamiento de MNT**

Comorbilidad	Valor
Bronquiectasias	160 (67,23%)
Tabaquismo	134 (56,30%)
Pluripatologia compleja*	85 (35,71%)
EPOC	80 (33,61%)
Inmunodepresión (no VIH)	70 (29,41%)
Neoplasia activa	41 (17,23%)
DM	40 (16,81%)
Enolismo	36 (15,13%)
Insuficiencia Renal	24 (10,08%)
Enfermedad Autoinmune	19 (7,98%)
VIH	11 (4,62%)

***Definido como 3, o más, enfermedades crónicas, simultáneas e incurables**
VIH: virus de la inmunodeficiencia humana, EPOC: enfermedad pulmonar obstructiva crónica, DM: diabetes mellitus.

donae (20%), mientras que en edades tardías (> 70 años) encontramos mayor diversidad siendo las especies más frecuentes *M. gordonae* (32,05%), *M. avium* (16,67%), *M. fortuitum* (12,82%) y *M. chelonae* (8,97%).

DISCUSIÓN

Nuestro estudio muestra que la incidencia de MNT se mantuvo estable durante el periodo analizado. Por contra, hubo un descenso progresivo, y mantenido, de la incidencia de MTB entre enero de 2011 y diciembre de 2018. Estos datos siguen la tendencia esperada, ya que, tanto en el resto de la comunidad autónoma, como a nivel nacional e internacional, se ha observado el mismo comportamiento [9-11].

Pese a que las cifras de incidencia parecen mantenerse estables en los años analizados, si comparamos nuestros resultados con los de otros trabajos realizados en nuestra misma área poblacional, sí que observamos que las cifras absolutas de aislamientos se han incrementado respecto a las publicadas en investigaciones sobre periodos temporales anteriores [12].

En numerosos trabajos publicados sobre MNT, nacionales e internacionales, se ha constatado un cambio de tendencia en la proporción de aislamientos de MNT respecto a los de MTB [4-6,13]. En nuestra investigación, pese a que parece intuirse que ocurre algo similar, no logramos evidencia estadísticamente significativa para respaldar esta afirmación (p=0,1359). El tamaño poblacional de nuestra área de estudio, pequeño en comparación con los de otros trabajos, creemos que puede ser el motivo por el cual no se corrobora esta tendencia.

Al analizar los datos por grupos de edad y sexo, sí encontramos similitudes con múltiples publicaciones. La infección por MNT se detecta más en personas con edades avanzadas, específicamente en > 70 años, hecho objetivado previamente en múltiples trabajos [1-6,13]. Al poner el foco en el sexo, observamos que se aíslan más MNT en hombres que en mujeres, dato compartido con los de trabajos de otros autores realizados en diferentes áreas geográficas [1,6], pero que contrasta con los de otras zonas [3-5,14].

Respecto a las comorbilidades, las más frecuentes fueron bronquiectasias, tabaquismo, pluripatología compleja, EPOC y situación de inmunodepresión, datos similares a lo reportado por otros autores [1-3,13-15]. Respecto a pacientes con VIH, destacar que solo 11 pacientes presentaban esta comorbilidad. Si bien los primeros diagnósticos de enfermedad por MNT, que datan de las últimas décadas del siglo pasado, se realizaron en este grupo poblacional, observamos que cada vez los pacientes con VIH representan un menor porcentaje en los trabajos realizados sobre MNT (únicamente el 4,62% en nuestra serie) [15,16]. Por tanto, y dado que las tasas de nuevos diagnósticos de VIH se mantienen bastante estables, parece que la instauración de tratamientos antirretrovirales eficaces está siendo la responsable del descenso de aislamientos de MNT en pacientes con VIH [17]. El hecho de que las comorbilidades más observadas sean principalmente enfermedades crónicas, muy habituales en individuos de edades avanzadas, parece ir de la mano con el hecho de que las infecciones por MNT son también más frecuentes en este grupo de edad [2,3].

La especie de MNT más aislada en nuestro trabajo fue *M. gordonae*, lo que ya ha sido descrito previamente, no solo en trabajos de otros países europeos, sino también en otros trabajos españoles de áreas que, como la nuestra, se sitúan en la zona norte del país [5,13]. Tras esta especie, encontramos *Mycobacterium avium complex* y *M. fortuitum* como especies

Tabla 3 Especies de MNT aisladas

ESPECIES	n	%
M. gordonae	64	26,89
M. fortuitum	47	19,75
M. avium	39	16,39
M. lentiflavum	21	8,82
M. chelonae	11	4,62
M. intracellulare/ M. chimaera	10	4,20
M. xenopi	9	3,78
M. abscessus	5	2,10
M. kansasii	5	2,10
M. peregrinum	5	2,10
M. mucogenicum	4	1,68
M. celatum	3	1,26
M. simiae	3	1,26
M. neoaerum	2	0,84
M. thermoresistibile	2	0,84
M. porcinum	1	0,42
M. scrofulaceum	1	0,42
M. asiaticum	1	0,42
M. magerintense	1	0,42
M. smegmatis	1	0,42
M. interyectum	1	0,42
Especies no identificadas	2	0,84
Total	238	100

más aisladas. Estos datos son bastante similares a los objetivados a nivel global y en otras áreas de España, en los que MAC es la MNT más frecuente seguida de *M. gordonae* [4,13,14].

El 15,52% de los aislamientos fueron considerados clínicamente significativos, siendo las especies más habitualmente implicadas MAC y *M. kansasii*, datos muy similares todos ellos a lo reportado sobre otras series [4,5].

Por todo ello y, dada la creciente relevancia que están adquiriendo las MNT a nivel global, y por ende las micobacteriosis, creemos necesaria la realización de estudios multicéntricos, nacionales e internacionales, que permitan una mejor comprensión de su microbiología y su comportamiento clínico. Además, consideramos también de vital importancia la creación de registros nacionales de declaración obligatoria de esta patología, tal y como ocurre con la tuberculosis, que permitan conocer su incidencia y prevalencia reales.

En conclusión, si bien no podemos afirmar que exista una tendencia de aumento de incidencia de MNT en nuestra área, sí podemos confirmar que el número de aislamientos está siendo mayor que en periodos previos. Estas infecciones son más frecuentes en hombres y en personas mayores de 70 años.

El VIH, considerado históricamente el factor de riesgo por excelencia para estas infecciones, es una comorbilidad cada vez menos habitual. Actualmente está siendo sustituido por enfermedades crónicas, principalmente broncopulmonares, y hábitos tóxicos, generalmente en individuos de edad avanzada. Por todo ello, se intuye un cambio en la epidemiología de la enfermedad por MNT y la senectud parece que asume el protagonismo principal.

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CONFLICTOS DE INTERESES

Los autores del manuscrito declaran no tener ningún conflicto de intereses.

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On Behalf of Araba University Hospital Group on COVID-19 Diagnostic Tests*

The importance of prevalence and pre-test probability on the microbiological diagnosis of SARS-CoV-2: the case of Spain in 2020

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ABSTRACT

Objectives. The aim of this work was to estimate the conditioned probability for the diagnosis of SARS-CoV-2 infection with reverse transcription polymerase chain reaction (RT-PCR), viral antigen rapid diagnostic tests (Ag-RDT), and antibody detection tests depending on the prevalence in the specific healthcare settings in Spain in 2020, and on the pre-test probability (PTP) according to the clinical situation, age and unknown or close contacts of the patient.

Material and methods. Performance parameters of tests were obtained from literature. Prevalence data and PTP were obtained from Spanish sources and a survey, respectively. The post-test probability is the positive predictive value (PPV) when test is positive. For negative result, we also calculated the probability of having the infection (false negatives).

Results. For both RT-PCR and viral Ag-RDT, the lowest PPV values were for the population screenings. This strategy proved to be useful in ruling out infection but generates a high number of false positives. At individual level, both tools provided high PPV (≥ 97%) when the PTP values are over 35%. In seroprevalence studies, though the specificity of IgG alone tests is high, under low seroprevalence, false positives cannot be avoided. Total antibodies tests are useful for diagnosis of COVID-19 in those doubtful cases with RT-PCR or Ag-RDT tests being repeatedly negative.

Conclusions. The interpretating of results depends not only on the accuracy of the test, but also on the prevalence of the infection in different settings, and the PTP associated to the patient before performing the test.

Keywords: SARS-CoV-2; RT-PCR; antigen rapid diagnostic tests; antibody detection; testing strategy

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La importancia de la prevalencia y de la probabilidad pre-test en el diagnóstico microbiológico de SARS-CoV-2: el caso de España en 2020

RESUMEN

Objetivos. En este trabajo estimamos la probabilidad condicionada del diagnóstico de infección por SARS-CoV-2 con RT-PCR, pruebas de antígenos virales (Ag-RDT) y pruebas de detección de anticuerpos, en función de la prevalencia en España en diferentes ámbitos durante 2020, y de la probabilidad pre-test (PPT) según la situación clínica, edad y contactos del paciente.

Material y métodos. Los parámetros de rendimiento de las pruebas se obtuvieron de bibliografía. Los datos de prevalencia y PPT se obtuvieron de fuentes españolas y de una encuesta, respectivamente. La probabilidad post-test es el valor predictivo positivo (VPP) cuando la prueba es positiva. Para el resultado negativo, también calculamos la probabilidad de tener la infección (falsos negativos).

Resultados. Tanto con RT-PCR como con Ag-RDT, los valores más bajos de VPP se detectaron en los cribados poblacionales, que demostraron ser útiles para descartar la infección, pero generan muchos falsos positivos. A nivel individual, ambas pruebas proporcionaron un VPP ≥ 97% cuando los valores de PPT son superiores al 35%. En estudios de seroprevalencia, aunque la especificidad de las pruebas de IgG sola es alta, si la seroprevalencia es baja, no se pueden evitar falsos positivos. Además, las pruebas de anticuerpos totales pueden ayudar al diagnóstico de COVID-19 en aquellos casos dudosos con pruebas de RT-PCR o Ag-RDT repetidamente negativas.

Conclusiones. La interpretación de los resultados depende no sólo del rendimiento de las pruebas, sino también de la prevalencia de la infección en diferentes ámbitos, y de la PPT asociada al paciente antes de realizar la prueba.

Palabras clave: SARS-CoV-2; RT-PCR; pruebas de diagnóstico rápido de antígenos; detección de anticuerpos; estrategia diagnóstica.

INTRODUCTION

The interpretation of a microbiological test result depends both on the performance of the test, as assessed by its intrinsic characteristics of sensitivity and specificity, and on the pre-test probability or estimate of the baseline infection risk of each patient prior to ordering the test [1].

Since SARS-CoV-2 emergence, there has been an unprecedented race to develop diagnostic tests for detection of this virus, both directly (reverse transcription polymerase chain reaction, RT-PCR, and viral antigen rapid diagnostic tests, Ag-RDT) and indirectly (serological antibody detection tests). Due to the urgent need for diagnostic tests, most of the commercialized tests have been granted with emergency use authorisation by regulatory agencies (CE-IVD in Europe and EUA in the USA). This type of authorisation is based exclusively on analytical performance under ideal conditions with positive and negative sample controls [2]. RT-PCR is currently considered as the gold standard test for the diagnosis of COVID-19 by the WHO [3]; however, marketed RT-PCR tests use different extraction reagents and amplify different genomic regions of the virus, which affects the sensitivity of the test and makes results interpretation rather challenging. Moreover, most commercial tests have not adequately estimated the sensitivity and specificity in routine clinical practice [4], and most microbiology laboratories used consecutively or simultaneously the available RT-PCR, Ag-RDT, and antibody detection tests depending on the moment of the pandemic and the availability of viral transport media, reagents and consumables.

On the other hand, as for any laboratory test, the reliability of results obtained with microbiological tests differs depending on the pre-test probability of the patient and/or the prevalence of the disease in the particular setting from which the test is requested. When the pre-test probability and/or the prevalence of disease decrease, false positives are more likely to occur, and when the pre-test probability and/or the prevalence of disease increase, false negatives increase, as well.

The aim of this work was to estimate the conditioned probability for the diagnosis of SARS-CoV-2 infection with RT-PCR, Ag-RDT and antibody detection tests depending on the prevalence in the specific healthcare settings in Spain in 2020 and on the pre-test probability according to the clinical situation, age and unknown or close contacts of the patient during the pandemic.

MATERIAL AND METHODS

Diagnostic performance of the diagnostic tests. Performance parameters of RT-PCR, viral Ag-RDT and antibody detection were obtained from literature. Only systematic reviews were considered.

RT-PCR. Three systematic reviews provide similar sensitivity percentages, ranging from 86 to 89% with overlapping 95% confidence interval (95% CI) [5-7]. Out the three studies, we selected that by Kim et al. [5] to calculate the conditional probabilities because the specificity reported (99%) is in accordance with most authors, who assume a false positive rate <1% [8,9]. The study by Kim et al. is a meta-analysis that included 1,502 patients from 19 studies, with a sensitivity of 89% (95% CI: 81%-94%) and specificity of 99%. The calculated positive and negative likelihood ratios (LR) were 89 and 0.11, respectively.

Viral Ag-RDT. The average sensitivity value of 56% (95%CI: 29.5%-79.8%) and specificity of 99%, (95%CI: 98%-99.9%) from the systematic review by Dinnes et al. [10] were used. The calculated positive and negative LRs were 56 and 0.44, respectively. Although the sensitivity demonstrated in asymptomatic screenings was lower than those in symptomatic case studies and contact tracing studies, the sensitivity was similar in the three subject groups when high viral loads are detected by RT-PCR (threshold cycle value, Ct< 25) [11,12]. Therefore, in order to facilitate simulations, we used the same sensitivity and specificity mean values in all health care settings.

Detection of IgG and total antibodies (IgG and IgM). In seroprevalence surveys to estimate the prevalence of detectable antibodies resulting from infection in a community, IgG assay is recommended because it persists for long time after infection. The estimated sensitivity and specificity of IgG tests were 90% (95%CI: 88.5-91) and 99 (95%CI: 98.6-99.1), respectively [13]. The calculated positive and negative LRs were 90 and 0.1, respectively. On the other hand, total antibodies (IgG and IgM) may help diagnose COVID-19 cases in patients with a high clinical suspicion and repeatedly negative RT-PCR testing. Sensitivity and specificity values of total antibodies assays were obtained from the study carried out by Fox et al. [13]. Due to sensitivity variation along time course of infection [14], sensitivity values at week 3 after onset (91%, 95%CI: 88%-93.2%) and at week 5 after onset (94.3%, CI 95%: 93-95.5%) were selected. The specificity was 99% (95%CI: 99.6%-99.9%). The calculated positive and negative LRs were 455 and 0.09 for week 3, and 471 and 0.06 at week 5 after onset.

Prevalence data. Prevalence data were obtained from Spanish sources. In all cases data were from 2020, and different settings were considered.

1. *Population screening.* Firstly, we selected the screening carried out from October 7th to 10th 2020 in Azkoitia (Guipúzcoa), which included 3,069 subjects aged from 17 to 60 years old; 35 positives were detected (1.14%) [15]. Then we also used the positivity rate of different population screenings in the Basque Country, which was < 2% [15].

2. *Primary care centres.* Data from the study carried out by Albert et al. were used [16]. Between 2nd September and 7th October 2020 this prospective study enrolled 412 patients with clinical suspicion of COVID-19 attending primary care centres of the Clínico-Malvarrosa Health Department in Valencia (Spain). An Ag-RDT performed well as point of care for early diagnosis of COVID-19 in primary healthcare centres and was confirmed by RT-PCR. The prevalence estimated ranged from 5% to 10% at the time of study.

3. Nursing homes. Data from a test-based screening carried out at the Vall d'Hebron Hospital, a tertiary hospital in Catalonia, Spain, were considered. In that study, carried out during April 10th –24th 2020, 69 nursing homes with a total census of 6,714 persons were evaluated (previous laboratory-confirmed cases of COVID-19 were excluded). Overall, 768 (23.9%) residents and 403 (15.2%) staff members tested positive for SARS-CoV-2 [17]. RT-PCR was used as diagnostic test.

4. Hospital Emergency Service. Prevalence data in the Emergency Service of the Araba University Hospital in Vitoria-Gasteiz between 18th – 31th March 2020 were used. Prevalence ranged from 35% to 50% of the patients attended [18]. RT-PCR was used as diagnostic test.

5. Seroprevalence. We used the ENE-COVID study, a nationwide, population-based seroepidemiological study, which was carried out between 27th April and 11th May 2020. Individuals from 50 Spanish provinces and the two autonomous cities were included. A total of 51,958 immunoassay analyses were done. The overall seroprevalence was 4.6%, and the seroprevalence of the health care occupational sector was 10% [19].

Pre-test probability. Pre-test probability was obtained from a survey of healthcare professionals who estimated the probability of SARS-CoV-2 infection based on clinical status [20]. The subjects were classified according to age (20-30 years and 60-70 years) and whether or not they had had close contacts. Clinical signs and symptoms included in the survey were: 1. None, 2. Odynophagia and nasal congestion, 3. Odynophagia, nasal congestion and anosmia/ageusia, and 4. Odynophagia, nasal congestion, anosmia/ageusia, fever and body weakness. In accordance with clinical experience, survey results confirmed that pre-test probability increased with increasing prevalence, patient age, documented exposure to the virus in the medical record and clinical signs and symptoms intensity.

In addition, pre-test probability was also estimated from studies that compared the diagnostic test accuracy of total antibodies (IgG and IgM) among patients with varying degrees of clinical suspicion for COVID-19 and negative RT-PCR throughout the course of their illness [21,22].

Estimation of the post-test probability. From the calculated LRs, the prevalence (pre-test probability) was converted into the post-test probability (probability of the patient having the infection after the diagnostic test) according to a previously reported method [23-25]. This method includes the following steps:

1. Calculation of the pre-test odds: pre-test odds = prevalence / (1 – prevalence)
2. Calculation of the post-test odds: post-test odds = pre-test odds × LR
3. Calculation of the post-test probability: post-test probability = post-test odds / (1 + post-test odds)

The post-test probability is the Positive Predictive Value (PPV) when test is positive, and we also estimated the probability of no infection (1-PPV). When the result is negative, the probability of not having the infection is the Negative Predictive Value (NPV). For negative result, we also calculated the probability of having the infection (1-NPV) and a threshold of 5% has been established, below which it is reasonable to consider the person as uninfected (e.g., permission to visit an elderly relative) [2].

The 95% CIs of the post-test probabilities were calculated by Miettinen's method. When Miettinen's method could not be applied, we used the first-order approximation of Taylor's development [25].

RESULTS

Post-test probability for diagnosing infection was estimated in different settings (population screenings, primary care centres, nursing homes, and hospital emergency service) assigning a corresponding prevalence value to each of them. Table 1 shows the post-test probability calculated from the estimates of accuracy of RT-PCR and Ag-RDTs and from the prevalence values in the different settings. With both test methods, the lowest PPV values were for the population screenings: for prevalence of 1%, the PPV was 47% with RT-PCR and 36% with Ag-RDTs. Confident intervals show that PPV could be actually as low as 8% with RT-PCR, and 4% for Ag-RDTs when the prevalence is 1%. Both methods proved to be useful in ruling out infection in population screenings; however, and according to the confidence intervals, > 90% of positives may be false positives (1-PPV). Results also show the gradual increase of PPV as prevalence values increase, with the highest PPV for the hospital emergency service. Regardless the test method, when prevalence is ≥ 15%, PPV was > 94% for the nursing homes and the hospital emergency service, and therefore, RT-PCR and Ag-RDTs are more useful to confirm infection.

Table 1 also shows the NPV estimation, whose values for both tests decreased as prevalence increased. As an example, when the prevalence is 50% in the hospital emergency service, confident intervals show that the probability of having the infection when the result is negative (1- NPV or false negatives) is 21% with RT-PCR and 42% with Ag-RDTs.

Table 2 features the post-test probability for RT-PCR and Ag-RDTs depending on the pre-test probability estimated considering clinical situation, age, and contacts. Regardless of age, contacts, and pre-test probability, post-test probability was similar for both test methods. PPV was ≥ 97 % in all cases except for asymptomatic with unknown contacts (pre-test probability ≤ 5%). For subjects with close contacts, PPV was always close to 100%. In general, the probability of infection if the result is negative (1-NPV or false negatives) is higher for the Ag-RDTs than for the RT-PCR. Confident intervals indicate that the probability of false negatives is as low as 5% with RT-PCR and 8% for Ag-RDTs for asymptomatic with unknown contacts over 60 years of age (pre-test probability of 5%). False negatives increased as the pre-test probability increased. Moreover, if the result is negative, the probability of infection is higher

Table 1 **Conditional probability for the diagnosis of SARS-CoV-2 infection depending on the prevalence in different settings presuming a sensitivity of 89% and a specificity of 99%, LR +/- 89/0.11 (RT-PCR)[5] and sensitivity of 56% and a specificity of 99%, LR +/- 56/0.44 (Ag-RDT) [10].**

		Prevalence in 2020							
		1%	2%	5%	10%	15%	25%	35%	50%
		Population screenings in the Basque Country [15]		Primary Care Centres in Valencia [16]		Staff members	Residents	Hospital Emergency Service	
						Nursing Homes in Barcelona [17]		HUA Vitoria-Gasteiz [18]	
Sensitivity/ Specificity (%)	If positive (+) result	Post-test probability (%)							
89/99 (RT-PCR)	Infection P (PPV)	47 (8-90)	64 (19-93)	82 (41-97)	91 (60-98)	94 (70-99)	97 (81-99.5)	98 (86-100)	99 (90-99.9)
	No infection P (1-PPV)	53 (10-92)	35 (6-81)	17 (3-59)	9 (1.5-40)	6 (1-30)	3 (0.5-19)	2 (0.3-14)	1 (0.1-10)
56/99 (Ag-RDT)	Infection P (PPV)	36 (4-88)	53 (11-91)	75 (29-95)	86 (48-98)	91 (59-98)	95 (72-99)	97 (79-100)	98 (85-100)
	No infection P (1-PPV)	64 (12-96)	47 (9-89)	25 (4-71)	14 (2-52)	9 (1.5-41)	5 (0.7-28)	2 (0.3-14)	1.8 (0.2-15)
	If negative (-) result	Post-test probability (%)							
89/99 (RT-PCR)	Infection P (1- NPV)	**0.1 (0-4)**	**0.2 (0-4)**	**0.6 (0.1-5)**	**1.2 (0.2-6)**	**1.9 (0.5-7)**	**3.6 (1-10)**	6 (2-14)	10 (4-21)
	No infection P (NPV)	99.9 (96-100)	99.8 (96-100)	99.4 (95-100)	98.8 (94-99.8)	98.1 (92-99.5)	96.4 (90-99)	94 (86-98)	90 (79-95)
56/99 (Ag-RDT)	Infection P (1- NPV)	**0.4 (0-5)**	**0.9 (0.1-5)**	**2.3 (0.7-8)**	**5 (2-11)**	7 (3-14)	13 (7-22)	19 (12-29)	31 (21-42)
	No infection P (NPV)	99.6 (95-100)	99.1 (95-100)	97.7 (92-99)	95 (89-98)	93 (85-96)	87 (78-93)	81 (71-88)	69 (58-79)

P: probability; PPV: positive predictive value; NPV: negative predictive value; LR +/-: Positive/negative likelihood ratio.
The probability of having the infection whether the result is positive or negative is expressed in % (95% CI). In bold, 1-NPV < 5% (threshold for ruling out infection).
HUA: Araba University Hospital, Vitoria-Gasteiz.

if the patient has close contacts than if they have unknown contacts, regardless of age and the test method.

Table 3 displays the post-test probabilities for IgG test based on seroprevalence, and pre-test probability of total antibodies (IgG and IgM) among patients with varying degrees of clinical suspicion for COVID-19 and negative RT-PCR throughout the course of their illness. In seroprevalence studies, although the specificity of IgG alone tests is high (around 99%), when seroprevalence is low, false positives, which tend to overestimate infection numbers, cannot be avoided. With a seroprevalence of 5%, false positives reach 17%, while true negatives account for more than 99% of negative results. On the other hand, the available total antibodies tests can help the diagnosis of COVID-19 in those doubtful cases with RT-PCR or Ag-RDT tests repeatedly negative. For instance, in a patient with a high clinical suspicion (persistent symptoms) and repeatedly negative RT-PCR testing (40% pre-test probability), the probability of having the infection reaches values around 100% when the total antibody test is positive at week 3 after onset, and thus the infection would be confirmed. In a second patient with mild symptoms lasting for more than a month of evolution (low pre-test probability), a negative total antibody test practically rules out the infection, while a positive total antibody test, according to the confidence intervals, could yield false positives (1-PPV) of up to 30%.

DISCUSSION

In this work, we present the estimated conditional probability for RT-PCR, Ag-RDT and antibody detection diagnostic assays, in various setting and clinically relevant real-life situations using real data of SARS-CoV-2 prevalence in Spain in 2020. It is well known that false positive and false negative results cannot be completely avoided, despite different strategies to minimize them [22, 26-27].

In 2020, population screenings were very frequent in Spain, and RT-PCR was the diagnostic test used, which is not a screening test. These screenings generally provided a prevalence less than 1% [15]. For this prevalence value, and according to our results, the probability of not having infection if the result is negative is very high (> 99.8%). However, it is very important to take into account, that this strategy generates a high number of false positives. As an example, assuming 89% sensitivity and 99% specificity of RT-PCR, for every 50,000 people screened, we would detect 940 positive results, 495 of them may be false positives (53%). With a lower sensitivity (56%), Ag-RDT would have detected 775 positives, 64% of them may be false positives. On the one hand, population screenings generate unnecessary quarantines, economic losses associated with people who should not have been isolated and consume enormous human and material resources. On the other hand,

Table 2 **Conditional probability for the diagnosis of SARS-CoV-2 infection depending on pre-test probability by clinical situation, age and unknown or close contact [20], presuming a sensitivity of 89% and a specificity of 99%, LR +/- 89/0.11 (RT-PCR)[5] and a sensitivity of 56% and a specificity of 99%, LR +/- 56/0.44 (Ag-RDT) [10].**

	Asymptomatic		Odynophagia + nasal congestion		Odynophagia + nasal congestion + anosmia/ageusia		Odynophagia + nasal congestion + anosmia/ageusia + fever + body weakness		Asymptomatic		Odynophagia + nasal congestion		Odynophagia + nasal congestion + anosmia/ageusia		Odynophagia + nasal congestion + anosmia/ageusia + fever + body weakness	
Unknown contact	20-30 years old								60-70 years old							
Pre-test probability	3%		35%		80%		85%		5%		50%		80%		90%	
	RT-PCR	Ag-RDT	RT-PCR	Ag-RDT	RT-PCR	Ag-RDT	RT-PCR	Ag-RDT	RT-PCR	Ag-RDT	RT-PCR	Ag-RDT	RT-PCR	Ag-RDT	RT-PCR	Ag-RDT
Infection P (PPV) if positive (+) result	74 (27-95)	63 (17-93)	98 (86-100)	97 (79-100)	99.7 (94-100)	99.6 (91-100)	99.8 (95-100)	99.7 (92-100)	82 (41-97)	75 (29-95)	99 (90-100)	98 (85-100)	99.7 (94-100)	99.6 (91-100)	99.9 (95-100)	99.8 (93-100)
Infection P (1- NPV) if negative (-) result	0.3 (0-4)	1.4 (0.3-6)	6 (2-14)	19 (12-29)	31 (17-49)	64 (51-75)	39 (22-58)	72 (58-82)	0.6 (0.1-5)	2.3 (0.7-8)	10 (4-21)	31 (21-42)	31 (17-49)	64 (51-75)	50 (30-70)	80 (67-89)
Close contact	20-30 years old								60-70 years old							
Pre-test probability	40%		60%		87%		>95%		45%		77%		94%		>95%	
	RT-PCR	Ag-RDT	RT-PCR	Ag-RDT	RT-PCR	Ag-RDT	RT-PCR	Ag-RDT	RT-PCR	Ag-RDT	RT-PCR	Ag-RDT	RT-PCR	Ag-RDT	RT-PCR	Ag-RDT
Infection P (PPV) if positive (+) result	98 (88-100)	97 (81-100)	99 (92-100)	99 (88-100)	99.8 (95-100)	99.7 (92-100)	99.9 (96-100)	99.9 (93-100)	99 (89-100)	98 (83-100)	99.7 (94-100)	99.5 (91-100)	99.9 (95-100)	99.9 (93-100)	99.9 (96-100)	99.9 (93-100)
Infection P (1- NPV) if negative (-) result	7 (3-16)	23 (15-33)	14 (7-27)	40 (29-52)	43 (25-63)	75 (61-85)	73 (47-89)	91 (80-97)	8 (3-18)	27 (18-38)	27 (15-44)	60 (47-72)	63 (40-82)	87 (75-94)	73 (47-89)	91 (80-97)

P: probability; PPV: positive predictive value; NPV: negative predictive value. LR +/-: Positive/negative likelihood ratio.
Post-test probability is expressed in % (95% CI).

population screenings with molecular tests led to the saturation of microbiology laboratories, hindering the rapid response to the tests requested from settings with high prevalence, such as hospital emergencies, nursing homes, symptomatic patients and exposed and / or vulnerable people. Processing large numbers of samples within a short period impairs the normal workflow of microbiology laboratories.

Based on the fact that diagnostic tests are not perfect and can be quite inaccurate, it is particularly important to determine how well diagnostic tests rule out infection. According to our data, using RT-PCR, the probability of having the infection when the result is negative (1-NPV) is lower than 5%, even if the pre-test probability is as high as 30%, which leads the subject to be considered uninfected. In this case, these results give confidence to both staff and visitors of elderly people in nursing homes. By using Ag-RDT, which have lower sensitivity than the RT-PCR, the post-test probability may remain below the 5% threshold if the prevalence is ≤ 10%. In settings of high prevalence, such as the hospital emergency services during the first pandemic wave, a positive result with either diagnostic tools, would confirm the infection. On the contrary, a negative result, even using the most sensitive test (RT-PCR), would not rule out infection if the pre-test probability is high. In this situation, the clinician should consider it a false negative and the repetition of the test should be proposed.

To know the impact of pre-test probability on the viral Ag-RDT and RT-PCR results, the clinical situation, the age and exposure history of the patient must be considered. As expected, both diagnostic tools provided high PPV (≥ 97%) when the pre-test probability values are higher than 35%; this result indicates that they correctly classify almost infected individuals as positive. Only if the subject is asymptomatic with unknown contact, the PPV is lower, though always ≥ 63%. These results indicate that a high proportion of positive results in asymptomatic patients may be false positives, and the repetition of the test must be done to confirm the infection.

It is important to highlight that a single negative test result may not be informative if the pre-test probability is high. It is estimated that one patient with typical symptoms of COVID-19 (odynophagia, nasal congestion, fever and body weakness) has a pre-test probability of 90%. If they have a negative RT-PCR or Ag-RDT result, the probability of having the infection is 50% or 80%, respectively, depending on the diagnostic test. Even if the patient has two negative test results, there is still a risk of infection of 10% (RT-PCR) and 64% (Ag-RDT), data not shown. In this regard, Arévalo-Rodriguez *et al.* [28] estimated that out of every 100 tested subjects by RT-PCR, and assuming a prevalence of 50%, 1 to 27 cases would be misdiagnosed and, therefore, adequate clinical management would not be applied; repeated testing during hospitalization or additional testing for other diagnoses would be required. Our results agree with those of Arévalo-Rodriguez *et al.* In fact, considering the confident intervals, the probability of false negatives we estimated ranges from 4 to 21% with RT-PCR when the pre-test probability is 50%. Most authors consider RT-PCR as imperfect reference

Table 3 **Conditional probability of diagnosis of SARS-CoV-2 infection with assays targeting IgG depending on seroprevalence (sensitivity of 90% and a specificity of 99%, LR +/- 90/0.1) [13] or pre-test probability of total antibodies (IgG and IgM) among patients with varying degrees of clinical suspicion for COVID-19 and either negative RT-PCR throughout the course of their illness, presuming a sensitivity of 91% and a specificity of 99.8%, LR +/- 455/0.09 at week 3 after onset and a sensitivity of 94.3% and a specificity of 99.8%, LR +/- 471/0.06 at week 5 after onset [13].**

	Seroprevalence [19]		Pre-test probability [22]	
	5%	10%	40%	10%
	Seroprevalence study ENE-COVID, 27 April - 11 May 2020		Unvaccinated old patient with diabetes presents with low-grade fever and mild cough 15 days prior, beginning 5 days after attending a family reunion	Young patient previously healthy and vaccinated presents with 5 weeks of debilitating fatigue and difficulty concentrating. The patient informs 2 days of a mild sore throat shortly before the onset of current symptoms.
If positive (+) result	Assays targeting IgG alone sensitivity 90%, specificity 99%		Total antibodies, sensitivity 91%, specificity 99.8% (week 3 after onset)	Total antibodies, sensitivity 94.3%, specificity 99.8% (week 5 after onset)
Infection P (PPV)	83 (41-97)	91 (60-98.5)	99.7 (90-100)	98.1 (69-100)
No infection P (1-PPV)	17 (3-59)	9 (1.5-39)	0.3 (0-10)	1.9 (0.1-31)
If negative (-) result				
Infection P (1- NPV)	0.5 (0.1-5)	1 (0.2-6)	6 (2-14)	0.6 (0.1-5)
No infection P (NPV)	99.5 (95-100)	99 (94-100)	94 (86-98)	99.4 (95-100)

P: probability; PPV: positive predictive value; NPV: negative predictive value. LR +/-: Positive/negative likelihood ratio.
The probability of having the infection whether the result is positive, or negative is expressed in % (95% CI).

standard [27,29], even when used repeatedly, because it tends to underestimate the false negatives (RT-PCR is not done for all patients). Although clinical history, epidemiological data and imaging tests are considered jointly with the RT-PCR as a composite standard, bias are not avoided because the assessed test is part of the comparison standard. Therefore, there is a tendency to overestimate sensitivity. False negative cases have important implications for isolation and transmission risk of infected people, and a single negative test should not be used as a rule-out in patients with typical symptoms of COVID-19.

At the population level, antibody tests can be useful in estimating the proportion of people who have serum antibodies to SARS-CoV-2 as a result of a previous infection. However, the uncertainties of seroprevalence studies limit their usefulness for assessing the impact of both non-pharmacological interventions and vaccination campaigns [30]. It is known that protection against COVID-19 induced by infections and vaccines decreases over time. In addition, when many people are sampled, a large number of false positives will be detected if the prevalence is low, even if the test used has a high specificity. The prevalence estimated is not useful to distinguish a high percentage of asymptomatic people from a high level of false positives. In the latter case, the degree of prior infection will be overestimated, which may lead to the relaxation of control measures. It is generally accepted that the estimates provided by seroprevalence studies should be interpreted in conjunction with further information, such as confirmed cases, deaths and infectious disease models, to better understand the disease [31].

At the individual level, antibodies to SARS-CoV-2 are detected in almost all patients after the second week of symptom onset, and they may be useful when RT-PCR or Ag-RDT tests are negative in patients with clinically suspected COVID-19. In this work, we describe two cases with different pre-test probability, presented as clinical examples by the IDSA Diagnostics Committee [22]. In the first case, the patient with potential exposure and symptoms suggestive of COVID-19, presented a high risk of evolution to severe infection due to age, diabetes and not being vaccinated (high pre-test probability). This clinical presentation suggests cytokine release syndrome (CRS), which occurs 1-2 weeks after acute infection and where RT-PCR negative tests have been described with some frequency [32]. A positive SARS-CoV-2 anti-N result would confirm the diagnosis in these patients, who could benefit from the establishment of early treatment with immunomodulators.

The second case involves patients with mild COVID-19 who did not undergo diagnostic tests and experienced sequelae several weeks after a paucisymptomatic infection (low pre-test probability) and had negative RT-PCR results at the time of consultation with the doctor. This presentation suggests post-acute sequelae of SARS-CoV-2 (PASC), which can deteriorate the quality of life of these patients. In addition to a positive anti-S SARS-CoV-2 antibody result due to vaccination, a posi-

tive or negative anti-N at week 5 after onset could confirm or rule out the diagnosis of PASC.

The study has several limitations. First, prevalence reported in the different settings was during the first pandemic waves in 2020, and it should be noted that when the prevalence of COVID-19 changes, the predictive values of the tests will also change. Second, Omicron variant is currently the global-dominated strain with multiple subvariants which demands a continuous evaluation of current detection methods. A lower sensitivity of Ag-RDT for the Omicron variant has been reported [33,34], although similar sensitivity with high viral loads (Ct < 25) between symptomatic and asymptomatic cases have been detected [35]. WHO recommends that Ag-RDT should be prioritized for use in symptomatic individuals meeting the case definition for COVID-19, and to test asymptomatic individuals at high risk of infection, including contacts and health workers, particularly in settings where RT-PCR testing capacity is limited [36]. However, some authors consider that a rapid, highly-specific but modestly-sensitive test for SARS-CoV-2 (sensitivity around 50%) such as Ag-RDT, still allows to identify a large proportion of infected individuals and at the same time reduce the isolation of uninfected contacts [37]. Third, the heterogeneity observed in the studies included in the different meta-analyses may affect the diagnostic performance indicators of the tests used for the diagnosis of SARS-CoV-2 infection. Several factors can alter these indicators, including disease prevalence, sample type (saliva, nasal swabs, nasopharyngeal swabs, pooled nose and throat swabs), study setting, symptom status, etc. However, regarding RT-PCR, Tsang *et al.* [38] in a meta-analysis subsequent to those used in this work, compared the diagnostic performance of different clinical samples collection methods and provided similar values of sensitivity (86%, 95%CI: 77%-93%) and specificity (99%, 95%CI: 96%-100%) for nasopharyngeal and nasal samples among individuals presenting in ambulatory care. Fourth, thresholds for ruling out infection, established in this study at 5%, may vary depending on the sensitivity of the test used and on the clinical-epidemiological needs (for instance, it should be lower in case of visits to hospitalized immunocompromised relatives).

In conclusion, by analyzing Spain prevalence and seroprevalence data during the first waves in 2020, and the estimation of the pre-test probability from epidemiological and clinical data, we have confirmed that interpretating the result of a COVID-19 test depends not only on the accuracy of the test, but also on the prevalence of the infection in different settings, and the pre-test probability associated to the patient before performing the test.

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CONFLICT OF INTEREST

The authors declare no conflict of interest

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The PHH-1V HIPRA vaccine: a new tool in the vaccination strategy against COVID-19

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ABSTRACT

Objectives. Vaccination against SARS-CoV-2 is essential to mitigate the personal, social and global impact of the coronavirus disease (COVID-19) as we move from a pandemic to an endemic phase. Vaccines are now required that offer broad, long-lasting immunological protection from infection in addition to protection from severe illness and hospitalisation. Here we present a review of the evidence base for a new COVID-19 vaccine, PHH-1V (Bimervax®; HIPRA HUMAN HEALTH S.L.U), and the results of an expert consensus.

Materials and methods. The expert committee consisted of Spanish experts in medicine, family medicine, paediatrics, immunology, microbiology, nursing, and veterinary medicine. Consensus was achieved using a 4-phase process consisting of a face-to-face meeting during which the scientific evidence base was reviewed, an online questionnaire to elicit opinions on the value of PHH-1V, a second face-to-face update meeting to discuss the evolution of the epidemiological situation, vaccine programmes and the scientific evidence for PHH-1V and a final face-to-face meeting at which consensus was achieved.

Results. The experts agreed that PHH-1V constitutes a valuable novel vaccine for the development of vaccination programmes aimed towards protecting the population from SARS-CoV-2 infection and disease. Consensus was based on evidence of broad-spectrum efficacy against established and emerging SARS-CoV-2 variants, a potent immunological response, and a good safety profile. The physicochemical properties of the PHH-1V formulation facilitate handling and storage appropriate for global uptake.

Conclusions- The physicochemical properties, formulation, immunogenicity and low reactogenic profile of PHH-1V confirm the appropriateness of this new COVID-19 vaccine.

Keywords: COVID-19, immunogenicity; recombinant protein vaccine

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La vacuna PHH-1V de HIPRA: una nueva herramienta en la estrategia contra la COVID-19

Objetivos. La vacunación frente al SARS-CoV-2 es fundamental para mitigar el impacto personal, social y global de la enfermedad por coronavirus (COVID-19) a medida que pasamos de una fase pandémica a una endémica. Actualmente se requieren vacunas que ofrezcan una protección inmunológica amplia y duradera contra la infección, además de proteger de la enfermedad grave y la hospitalización. En este artículo se presenta una revisión de la evidencia científica para una nueva vacuna COVID-19, PHH-1V (Bimervax®; HIPRA HUMAN HEALTH S.L.U) y los resultados de un consenso de expertos.

Material y métodos. El comité de expertos incluyó expertos españoles en medicina, medicina de familia, pediatría, inmunología, microbiología, enfermería y veterinaria. El consenso se logró mediante un proceso de 4 fases que constó de una reunión presencial durante la cual se revisó la evidencia científica, un cuestionario en remoto para obtener opiniones

sobre el valor de PHH-1V, una segunda reunión presencial de actualización y discusión sobre la evolución de la situación epidemiológica, los programas de vacunas y la evidencia científica para PHH-1V y una última reunión presencial en la que se obtuvo el consenso.

Resultados. Los expertos coincidieron en que PHH-1V constituye una vacuna novedosa y valiosa para el desarrollo de programas de vacunación destinados a proteger a la población de la infección y enfermedad por SARS-CoV-2. El consenso se basó en la evidencia del amplio espectro de eficacia contra las variantes establecidas y emergentes del SARS-CoV-2, una respuesta inmunológica potente y un buen perfil de seguridad. Las propiedades fisicoquímicas de la formulación de PHH-1V facilitan la manipulación y el almacenamiento apropiados para la absorción global.

Conclusiones. Las propiedades fisicoquímicas, formulación, inmunogenicidad y bajo perfil reactogénico de PHH-1V confirman la idoneidad de esta nueva vacuna COVID-19.

Palabras clave: COVID-19, inmunogenicidad; vacuna proteína recombinante

INTRODUCTION

Coronavirus disease (COVID-19) is a highly transmissible infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The virus was first detected as a human pathogen in China in late 2019 [2]. On 30th January 2020 the World Health Organization (WHO) defined that the outbreak of the novel coronavirus constituted a Public Health Emergency of International Concern and declared it as a pandemic on 11th March 2020. On 14th March 2020, the Spanish Government approved Royal Decree 463/2020 declaring a State of Alarm, with drastic measures to protect the health of citizens, contain the spread of SARS-CoV-2 and reinforce the National Health System. Among these measures were the limitation of mobility and free movement of people, home confinement and the closure of various economic activities.

As of March 2023, over 13.7 million confirmed SARS-CoV-2 cases have been reported in Spain. The burden of this pandemic has fallen disproportionately on older and vulnerable adults [3]. Of the 13.5 million confirmed cases in Spain by November 2022, 2.9 million (21%) were among people aged >60 years. Moreover, the risk for severe illness following SARS-CoV-2 infection increases with age and the presence of underlying medical conditions. Currently, the incidence of severe cases of COVID-19 and the number of hospitalisations due to this disease have fallen or stabilised in most countries. This is due, in large part, to active immunisation campaigns using existing vaccines which have proven to be highly effective in reducing hospitalizations due to severe COVID-19-related illness and COVID-19-related deaths. However, the precise case fatality rate remains obscured as it is calculated based on confirmed cases and is therefore influenced by the ability of the system to detect and quantify deaths due to COVID-19 illness and by the ability to confirm and detect all cases of the disease, including asymptomatic cases [4].

Vaccination against SARS-CoV-2 is essential to mitigate the personal, social and global impact of this disease as we move from a pandemic to an endemic phase [1,5,6]. The aim of the national, European and global vaccination strategy has been to reduce the incidence of severe COVID-19-related illness and the associated hospitalisations and deaths, thereby reducing the health and socio-economic impact of this disease. Many national vaccination strategies have prioritised members of the population with the greatest risk for severe illness and death – those of older age and with underlying health conditions. However, the emergence and circulation of different SARS-CoV-2 variants with different mutations affecting the transmissibility of the virus, has impacted the efficacy of currently available vaccines. Additionally, there is evidence of a poor immune response among individuals who are already immunocompromised [7]. Although primary vaccination offers high protection against severe disease, national and international studies using mRNA COVID-19 vaccines show a reduction in effectiveness in adults from 3–6 months post-vaccination, especially in terms of infection rates [8]. Consequently, most national vaccine strategies include additional booster doses with either the same vaccine class (homologous booster) or a different vaccine class (heterologous booster) as both approaches have proven to provide appropriate immunogenicity [9,10]. The benefit of a booster dose against severe disease is most evident among people aged ≥60 years and those younger with underlying diseases, while among those aged <60 years the benefit is most apparent in terms of the rate of symptomatic infection [11].

To date, the most widely used vaccine technology for primary and booster vaccination programmes against SARS-CoV-2 has been mRNA-based, particularly in Europe, with adenoviral vector-based vaccines also used in some countries [4]. These technologies offered a rapid route to vaccine development and manufacture to address the urgent need for immunological protection against the severe illness and death caused by a pandemic virus. The focus is now beginning to move beyond these immediate needs to the development of vaccines that also offer broad and long-lasting immunological protection from infection using established vaccine development technologies. One such established technology is adjuvanted recombinant protein vaccines, a technology used safely and effectively for vaccination against hepatitis B, human papilloma virus and influenza [12].

The SARS-CoV-2 pandemic also highlighted the importance of National-level vaccine development to complement international efforts and ensure country-level preparedness for future health crises. The vaccination strategy against COVID-19 in Spain has been modified as vaccines have been authorised and become available for use, in accordance with advances in scientific knowledge and epidemiological changes as the pandemic has evolved. On 30th March 2023, the European Medicines Agency (EMA) recommended approval of Bimervax® (PHH-1V) from HIPRA HUMAN HEALTH S.L.U as a COVID-19 booster vaccine [13,14]. PHH-1V is an adjuvanted recombinant protein vaccine based on the receptor binding domain (RBD) sequences of the Beta and Alpha variants of SARS-CoV-2 [13].

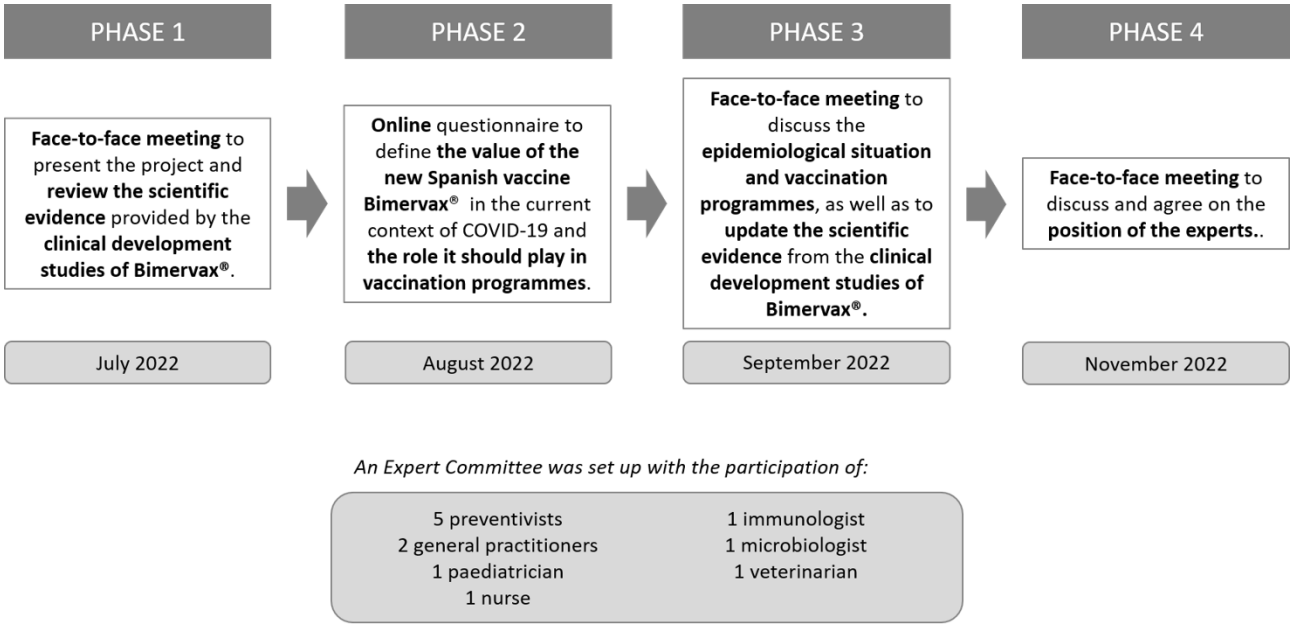

Figure 1 | **Four-phase process for review of the scientific evidence and consensus development**

The aim of this work was to present a review of the evidence base for PHH-1V and the consensus among vaccine experts on the utility of the new vaccine PHH-1V in the current context of COVID-19 illness prevention, and the role that this new vaccine should play in the implementation of booster vaccination programmes.

MATERIAL AND METHODS

An expert committee was convened consisting of Spanish experts in preventive medicine (n=5), family medicine (n=2), paediatrics (n=1), immunology (n=1), microbiology (n=1), nursing (n=1) and veterinary medicine (n=1). Consensus was achieved using a 4-phase process (Figure 1). Phase 1 consisted of a face-to-face meeting during which the scientific evidence base, consisting of the clinical development studies of PHH-1V, was reviewed. Phase 2 consisted of an online questionnaire to elicit opinions on the value of PHH-1V in the current context of the COVID-19 pandemic from the perspective of vaccine formulation, efficacy, safety and storage characteristics, and the role it should play in vaccination programmes. Phase 3 was a face-to-face update meeting to discuss the evolution of the epidemiological situation, vaccine programmes and the scientific evidence for PHH-1V. Consensus was achieved during a final face-to-face meeting.

RESULTS

Vaccine formulation. PHH-1V is formulated as an emulsion for intramuscular injection [15]. The active substance is a fusion heterodimer based on the SARS-CoV-2 RBD, which includes the B.1.351 (Beta) and B.1.1.7 (Alpha) variants fused into a single peptide via recombinant DNA technology (Figure 2a) [13]. The peptide is expressed in a Chinese Hamster Ovary (CHO) cell line. Each individual dose consists of 0.5 mL of vaccine containing 40 µg of the active substance in phosphate buffered saline supplemented with a squalene (SQBA) adjuvant consisting of an inner oil phase of squalene and an outer aqueous phase of sodium citrate-citric acid buffer.

Expert consensus: The PHH-1V dimer includes key mutations (K417N, E484K and N501Y) which were present in the latest Variants Of Concern (VOC) [16–19] and may play a role in cross-neutralization (Figure 2b). The adjuvant has the role to enhance and induce an earlier, more robust and long-lasting immune response against the recombinant RBD. The ready-to-use formulation without the need for reconstitution prior to use will be of benefit for vaccination programmes.

Clinical evaluation of PHH-1V. The safety and immunogenicity of PHH-1V has been evaluated in a double-blind, Phase 2b randomised, controlled, non-inferiority clinical trial (NCT05142553) as a heterologous booster to subjects who had previously received the complete course of the mRNA-based COVID-19 monovalent vaccine BNT162b2 (Cominarty®; Pfizer-BioNTech) at least 182 days prior to the booster dose [20]. The control arm of the study consisted of a homologous booster dose. The study was conducted at multiple centres in Spain and included 782 healthy adults (≥18 years of age) who were randomised either to receive PHH-1V or the mRNA vaccine. The primary outcome measures were immunogenicity against

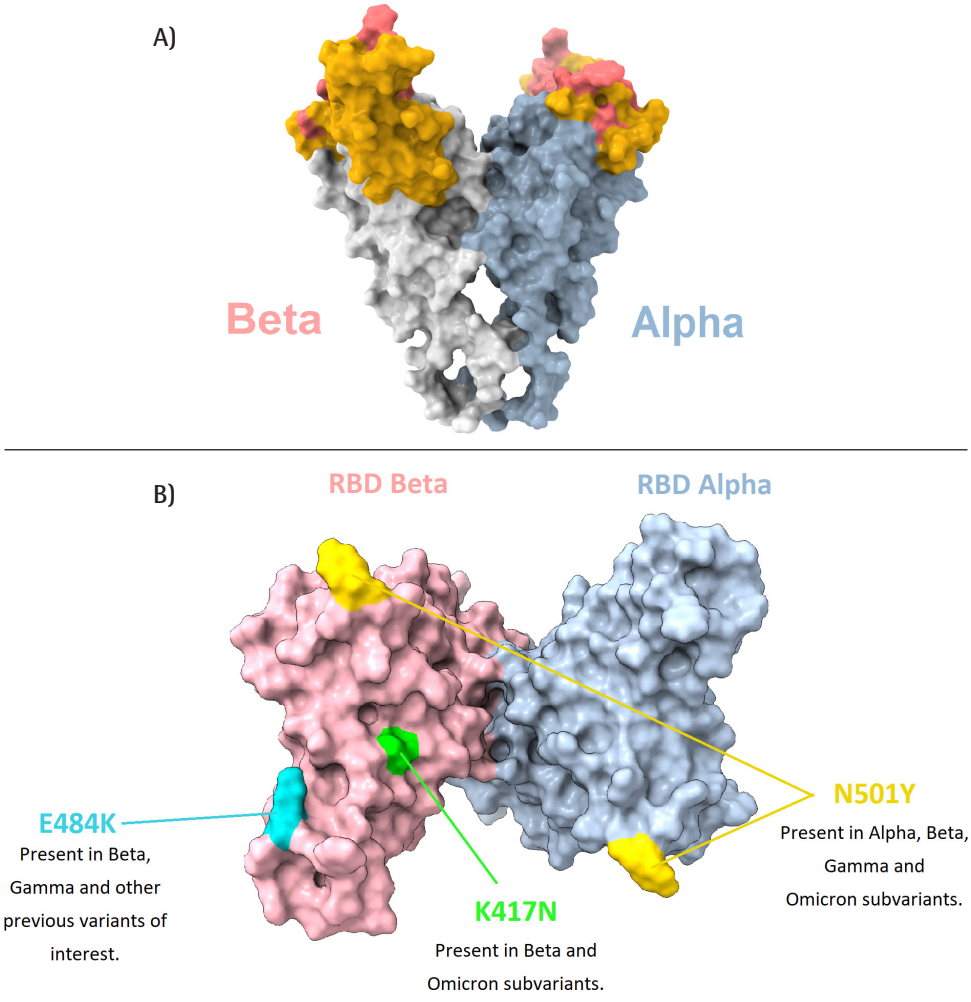

Figure 2 | **a) PHH-1V antigen: recombinant protein based on the receptor binding domain (RBD) sequences of the Beta and Alpha variants of SARS-CoV-2. b) Top view of the PHH-1V antigen and locations of key mutation that are present in most relevant VOC at present. Adapted from iScience [13]**

the Wuhan-Hu-1 strain of SARS-CoV-2 (neutralisation titre measured as the individual inhibitor concentration [IC_{50}] and geometric mean titre [GMT] from baseline to Day 14) and tolerability. Secondary endpoints included immunogenicity against additional SARS-CoV-2 variants of concern (Beta, Delta and Omicron BA.1) and the T-cell response towards the spike glycoprotein of SARS-CoV-2. The study has been recently completed and interim data are available for 782 subjects, 522 of whom received PHH-1V and 260 who received BNT162b2, with follow-up to Day 182 (6 months) [15]. The safety evaluation consisted of adverse event monitoring (safety population n=765 [PHH-1V n=513, BNT162b2 n=252]). The majority of subjects in both vaccine groups reported at least one adverse event (PHH-1V 89.3% of subjects, BNT162b2 94.4% of subjects). The most frequently reported adverse events to Day 28 in both vaccine groups were injection site pain (79.7% and 89.3%, respectively), fatigue (27.5% and 42.1%, respectively) and headache (31.2% and 40.1%, respectively). The overall frequency of adverse events was statistically significantly lower among subjects who received PHH-1V than among those who received BNT162b2 (Table 1) [20]. The majority of adverse events in both groups were mild. A non-inferior neutralising antibody response against the original Wuhan-Hu-1 strain was achieved for PHH-1V compared with BNT162b2 at Day 98 and superiority at Day 182 after immunisation [15,20]. PHH-1V achieved statistically significantly superior neutralising antibody responses at Days 14, 28, 98 and 182 against the Beta and Omicron BA.1 variants and at Days 98 and 182 against the Delta variant compared to BNT162b2 [15,20]. A robust T cell response was observed on Day 14 with a significant increase in interferon-gamma (IFN-γ) expression by CD4+ and CD8+ T cells [20]. A Phase 3 study is also ongoing (NCT05246137) in which 2,646 subjects aged ≥16 years received

Table 1 Frequency of Adverse Events by Treatment Group among the safety population

	PHH-1V (N=513)	BNT162b2 (N=252)	OR (95% CI)	p value*
Total Adverse Events	1581; 458 (89.3)	1061; 238 (94.4)	0.49 [0.26, 0.91]	**0.0219**
Injection site pain	748; 409 (79.7)	466; 225 (89.3)	0.47 [0·30, 0.75]	**0.0010**
Headache	193; 160 (31.2)	122; 101 (40.1)	0.68 [0.49, 0.94]	**0.0190**
Fatigue	166; 141 (27.5)	115; 106 (42.1)	0.52 [0.38, 0.72]	**0.0001**
Myalgia	107; 100 (19.5)	93; 86 (34.1)	0.47 [0.33, 0.66]	**0.0001**
Injection site induration	45; 44 (8.6)	44; 43 (17.1)	0.46 [0.29, 0.72]	**0.001**
Injection site erythema	33; 33 (6.4)	37; 36 (14.3)	0.41 [0.25, 0.70]	**0.0007**
Intensity				
Mild	1382; 342 (66)	885; 146 (57.9)	1.45 [1.06, 1.98]	**0.02**
Moderate	187;108 (21)	165; 85 (33.7)	0.52 [0.37, 0.74]	**0.0002**
Severe	12; 8 (1)	11; 7 (2.8)	0.55 [0.20, 1.74]	0.27
Serious Adverse Events (SAEs)	1; 1 (0)	0; 0 (0.0)	∞ [0.03, ∞]	1
Treatment-related Adverse Events	1384; 434 (84)	975; 231 (91.7)	0.5 [0.29, 0.83]	**0.0061**
COVID-19 cases ≥ 14 days post-booster	52; 52 (10)	31; 30 (11.9)	0.83 [0.51, 1.36]	0.45

Data are shown as the "total number of events; total number of subjects (percentage)". For the total adverse events, only those events with a frequency ≥ 10% of treated patients are shown. OR=Odds ratio and p-value of Fisher's exact test are shown to compare between groups. In bold, statistically significant differences. Adapted from Lancet Regional Health- Europe [20]

PHH-1V as a booster vaccination following primary immunisation with either an mRNA or an adenovirus-based vaccine. In the preliminary results of that Phase 3 study, PHH-1V induced a strong humoral response at Day 14 after immunization independently of the previous vaccination (BNT162b2, ChAdOx1-S [Vaxzevria®, AstraZeneca, UK], mRNA 1273 [SPIKEVAX®, Moderna Biotech, Spain], Ad26.COV2-S [Jcovden®, Jannsen-Cilag International NV]), with no differences in safety profile [15,21]. Serum samples from individuals vaccinated with PHH-1V are being further evaluated for neutralising antibody responses against the Omicron BA.4 and BA.5 sub-variants. Those preliminary results indicate potent immunogenic responses against these sub-variants 14 days after the booster vaccination [22].

Expert consensus: The data from the Phase 2b study indicate a potent humoral response of PHH-1V from Day 14 up to 6 months after immunisation when administered as a booster vaccine in individuals previously vaccinated with BNT162b2 [15,20]. The safety data from the Phase 2b trial support an acceptable safety profile for PHH-1V with statistically fewer adverse events reported by subjects compared with BNT162b2 [20]. Together, the clinical trial results available to date indicate a robust humoral response against all variants studied (Wuhan-Hu-1, Beta, Delta and Omicron BA.1) at 6 months and against Omicron BA.4 and BA.5 variants at Day 14 [15,20]. The robust T cells responses observed following booster vaccination with PHH-1V are encouraging as such responses are critical to confer protection against severe COVID-19 disease as cell-mediated immunity specifically destroys virus-infected cells [23].

Storage characteristics. PHH-1V must be stored at 2ºC to 8ºC with a shelf-life of 12 months [15].

Expert consensus: PHH-1V does not require freezing or deep-freezing during distribution or onsite storage. The one-year shelf-life at temperatures of 2ºC to 8ºC facilitates storage and distribution within different logistical and healthcare situations and reduces costs compared with vaccines requiring freezing/deep freezing during storage and distribution. The logistical advantages are particularly important for any vaccination programme and specially for developing countries and geographic areas that are difficult to access.

Indication. PHH-1V has been approved by EMA for its use in people aged >16 years as a booster vaccination against COVID-19 [15]. Future studies will evaluate the potential for PHH-1V as a primary vaccination and in people aged <16 years. Also, additional evidence in pregnant women and immunocompromised individuals will be assessed.

Expert consensus: No further limitations of use are expected from other evaluation bodies.

Finally, Table 2 summarises the main characteristics of the PHH-1V vaccine.

Table 2 Characteristics of the PHH-1V vaccine (Bimervax®; HIPRA Scientific, S.L.U. and Laboratorios HIPRA, S.A., Spain) [15]

Formulation	Emulsion for intramuscular injection Recombinant protein adjuvanted vaccine based on the receptor binding domain (RBD) sequences of the Beta and Alpha variants of SARS-CoV-2
Handling	Ready-to-use preparation, no requirement for reconstitution prior to use
Storage	Must be stored between 2ºC and 8ºC
Shelf-life	12 months when stored between 2ºC and 8ºC
Dosing	Single-dose
Safety	Low reactogenicity
Effectiveness	Long duration of immunity demonstrated in clinical trials. At 6 months, individuals who received a booster dose of PHH-1V had significantly higher neutralising antibody titres than those who received the BNT162b2 mRNA vaccine against all variants tested (Wuhan, Beta, Delta and Omicron BA.1)
Protection against new variants	Broad spectrum protection against all variants studied to date (Wuhan, Beta, Delta. Omicron BA.1 and Omicron BA.4/5)
Authorisation	Initial license is for use as a booster dose in people aged ≥16 years previously vaccinated with a mRNA vaccine

DISCUSSION

Mass vaccination programmes against SARS-CoV-2 have drastically reduced the global mortality and morbidity associated with the pandemic [1]. However, the current epidemiological situation at a global or European level cannot be considered completely under control. Since the beginning of the pandemic more than 1,850 SARS-CoV-2 lineages have been identified worldwide, with 9 variants of the virus and their descendant lineages considered of concern [16]. The ancestral Wuhan strain was followed by the Alpha, Beta, Gamma, and Delta variants, and, more recently, by the Omicron variants. The Omicron variant has given rise to a number of highly transmissible sub-variants able to evade natural or vaccine-induced immunity to varying degrees [24,25]. For this reason, second-generation vaccines are now required that generate neutralising immune responses against a wider range of variants to minimize the potential immune escape capability of potential future variants and with longer duration of humoral immunity. In addition to demonstrating robust immune responses in previously unvaccinated individuals, future vaccine candidates must also demonstrate immunogenicity in individuals previously vaccinated with the same type of vaccine (homologous booster) or a different type (heterologous booster). A previous study demonstrated a highly immunogenic response following real-world heterologous booster vaccination with the mRNA-based BNT162b2 vaccine and the adenoviral vector-based ChAd-BNT (AstraZeneca, UK) vaccine [26]. Indeed, data are emerging to suggest a more robust immune response may be elicited through heterologous booster vaccination [27–29]. But a recent Cochrane report points out the complexity to stablish comparisons between studies with different vaccination schedules, vaccines, and time endpoints, concluding that further studies on heterologous vaccination are needed. A favourable reactogenicity profile and prolonged duration of action are also beneficial to support coverage and compliance with national vaccination programs. Storage and shelf-life characteristics are also important features of future SARS-CoV-2 vaccines to enable distribution within different national and supply chain situations [30].

PHH-1V is based on a fusion heterodimer protein consisting of the RBD of two SARS-CoV-2 variants, Beta and Alpha, that elicits high and long-lasting levels of neutralising antibodies against all studied variants, as well as a strong cellular immunity response, when used as heterologous booster in previously vaccinated individuals with mRNA and vector vaccines [15,20,22]. These features along with a favourable reactogenicity profile, ready- to-use formulation without the need for reconstitution, storage at 2ºC to 8ºC and a prolonged shelf-life mean that PHH-1V is a suitable, next generation vaccine option for either annual, seasonal, or targeted immunisation programmes against SARS-CoV-2 to improve the protection of high-risk groups. The favourable reactogenicity profile for PHH-1V may be of relevance in the context of the slowing of the uptake of SARS-CoV-2 booster vaccinations reported in many countries worldwide [31,32].

Two other recombinant protein SARS-CoV-2 vaccines have been also approved for use, NVX-CoV2373 (Novavax) and MV B.1.351 (Sanofi-GSK). Both vaccines have demonstrated robust immunogenicity against common variants, including B.1.1.7, and acceptable safety profiles [33,34]. MV B.1.351 has demonstrated robust immunogenicity when given as a heterologous booster vaccination in individuals previously vaccinated with the mRNA-based BNT162b2 vaccine [34]. Subtle difference in terms of the mechanisms by which the different vaccine classes (mRNA-, adenoviral vector- and recombinant protein-based) elicit immune response have emerged [35]. Studies are now needed to determine whether these sub-

tle differences have implications for the ways in which these vaccines are deployed, for example, whether individuals who are immunocompromised might benefit preferentially from an adjuvanted vaccine. Adjuvanted vaccines induce high levels of protective antibodies, long-lasting immune response of memory cells and a higher degree of cross-immunisation than do non-adjuvanted [36–41]. The improved amplitude of the response achieved with adjuvanted versus non-adjuvanted vaccines may offer an advantage in the face of antigenic drift such as is being observed for the SARS-CoV-2 virus.

In summary, PHH-1V is a bivalent, adjuvanted vaccine based on an established technology, with a broad-spectrum efficacy against established and emerging SARS-CoV-2 variants and elicits a prolonged neutralising antibody response. The physicochemical properties of the PHH-1V formulation facilitate handling and storage appropriate for global uptake. As such, PHH-1V constitutes a valuable novel vaccine for the development of national vaccination programmes aimed towards protecting the population from SARS-CoV-2 infection and disease.

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CONFLICTS OF INTERESTS

- Gloria Mirada Masip: has received honoraria from Pfizer, GSK, MSD, Sanofi and HIPRA for educational activities and advise.
- Ángel Gil de Miguel has received honoraria for conferences and consultancy services from Sanofi, MSD, GSK, Seqirus, Moderna, HIPRA, AstraZeneca and Pfizer.
- María Fernández-Prada has received honoraria from Pfizer, GSK, Seqirus, MSD, HIPRA, Sanofi and Sanofi-Genzyme as member of advisory boards and speaker in educational activities.
- Carmen Cámara Hijón has received honoraria from Pfizer and HIPRA as advisor.
- Fernando Moraga-Llop has received honoraria from Pfizer, GSK, MSD and HIPRA as advisor and speaker in educational activities.
- Jorge Vázquez is full-time employee at VINCES consultancy working for HIPRA as advisor.
- Joan Puig-Barberá has received honoraria from CSL, Novavax, Sanofi and HIPRA as advisor and speaker in educational activities.
- Júlia Vergara-Alert has received institutional grants and/or financial support from Grifols, HIPRA, Rokote laboratories, Dentaid, and PharmaMar.
- Cristina Borralleras and Salomé de Cambra are employees of HIPRA.
- Daniel Ocaña Rodríguez has received honoraria from Pfizer, GSK, Seqirus, MSD, HIPRA, Sanofi and Sanofi-Genzyme as member of advisory boards and speaker in educational activities.
- Pilar Arrazola has received honoraria from HIPRA as advisor.
- Javier Castrodeza Sanz has received honoraria from Pfizer, GSK, AstraZeneca, Seqirus, Sanofi and HIPRA as scientific advisor and speaker in educational activities.
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Brief report

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Role of Hologic® Panther Aptima™ SARS-CoV-2 assay in the detection of SARS-CoV-2: screening or diagnostic technique?

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ABSTRACT

During the multiple waves of COVID-19 suffered all over the world, having a rapid and sensitive diagnostic test has become a priority for microbiology laboratories. The AptimaTM SARS-CoV-2 transcription-mediated amplification (TMA) assay running on the Panther system (Hologic) was presented as a very good option to cover this need. To evaluate this system, 570 respiratory samples were included in the study and were processed both by the Panther (Hologic) system and by qRT-PCR (Thermo Fisher Science, Waltham, USA), current assay for the diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A high number of false positives (n=76) was obtained with Panther system (Hologic), but the number of false positives decreases as the relative light units (RLU) value increases. These results show that this technique can be a good option for sample screening but checking for positive results should be mandatory, especially those with low RLU values.

Keywords: SARS-CoV-2; COVID-19; RT-qPCR; Panther; TMA.

Papel del ensayo Hologic® Panther Aptima™ SARS-CoV-2 en la detección del SARS-CoV-2: ¿técnica de cribado o de diagnóstico?

RESUMEN

Durante las múltiples oleadas de COVID-19 sufridas en todo el mundo, disponer de una prueba diagnóstica rápida y sensible se ha convertido en una prioridad para los laboratorios de microbiología. El ensayo de amplificación mediada por transcripción (TMA) AptimaTM SARS-CoV-2 que se ejecuta en el sistema Panther (Hologic) se presentó como una muy buena opción para cubrir esta necesidad. Para evaluar este sistema, se incluyeron en el estudio 570 muestras respiratorias y se procesaron tanto por el sistema Panther (Hologic) como por qRT-PCR (Thermo Fisher Science, Waltham, EE. UU.), técnica utilizada actualmente para el diagnóstico del síndrome respiratorio agudo severo por coronavirus 2 (SARS-CoV-2). Se obtuvo un alto número de falsos positivos (n=76) con el sistema Panther (Hologic), pero el número de falsos positivos disminuye a medida que aumenta el valor de las unidades relativas de luz (RLU). Estos resultados muestran que esta técnica puede ser una buena opción como técnica de *screening*, pero la verificación de resultados positivos debería ser obligatoria, especialmente aquellos con valores bajos de RLU.

Palabras clave: SARS-CoV-2; COVID-19; RT-qPCR; Panther; TMA

INTRODUCTION

The multiple waves of the covid pandemic have highlighted the need for an automatic, fast and reliable technique for positive detection [1].

Current tests for the diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) relies on real-time polymerase chain reaction (qRT-PCR) diagnostic assays [2, 3]. Although this technique has many advantages, it does not allow for continuous automated random-access testing or the possibility to perform on-demand testing avoiding run series. In this sense, the Hologic Aptima transcription-mediated amplification (TMA) assay running on the Panther system (Hologic) was presented as a very good option since, in addition to having this characteristic of continuous loading of reagents and specimens during the process, it is also easy to use and fast, being able to perform a high number of determinations in one day (up to 60 per hour), which is a limiting factor for other diagnostic techniques [4].

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However, TMA tests have the disadvantage of not providing any type of semiquantitative result since there is no evidence of any relationship between the viral load of the samples and the units of measurement of the system (RLU). As healthcare workers often require an estimate of viral load to decide on patient management, samples with a positive result by this system (TMA) were retested by qRT-PCR in order to obtain Ct value and use it for clinical decision making. Some negative ones were also retested by qRT-PCR.

The results obtained were analyzed to determine the sensitivity of the Panther device and to check if any type of correlation could be established between the Ct obtained by qRT-PCR and the units of measure used by the Panther (RLU).

MATERIAL AND METHODS

Five hundred and seventy respiratory samples collected in a virus transport medium (VTM) were included in the study. Five hundred positive and 70 negative samples by Panther (Hologic) were re-analyzed by the TaqPath COVID-19 RT-PCR kit (Thermo Fisher Science, Waltham, USA) in order to determine the Ct. In addition, some of these samples with discordant result, were repeated by both techniques and 50 positive (10%) and 5 negative (7%) were verified by Cepheid Xpert Xpress SARS-CoV-2.

Both assays were performed following the manufacturer's instructions.

Samples were always handled in a biosafety hood and taking extreme precautions to avoid contamination and filter tips were used throughout the process.

Positive samples were selected from those with negative samples around them to ensure there was no cross contamination.

RESULTS

TaqPath COVID-19 RT-PCR confirmed the negative results in all samples detected as negative by Panther Hologic (n= 70). The results obtained with the 500 positive samples are shown in Table 1.

Of the total positive samples, four hundred twenty-four (84,8%) confirmed the result by qPCR. The remaining 76 samples (15.2%) were clearly negative by qPCR. Some of the non-concordant results (16 of 76) were repeated again by both techniques obtaining in all cases the same result as initially, and all samples retested by Cepheid Xpert Xpress SARS-CoV-2, showed 100% agreement with the qRT-PCR.

When the positive samples were divided according to the Panther RLUs, it can be seen that the percentage of false positives decreased as RLUs increased as well as the positive percent agreement (PPA) increase. The percentage of false positives goes from 80,55%, in the range >500- <1000 RLUs, to only 8,85% when the RLU value is greater than 1200.

The sensitivity was very high, 100% in all RLU ranges, but the global specificity was very low, 47,9%. However, since the number of negative samples included is much lower than the number of positives, this last data may be biased.

Although there was not a clear correlation between the RLU and Ct values, since there were high Ct values (Ct >40) in all RLU ranges, it can be seen that the lowest RLU values were associated with higher Ct ranges.

DISCUSSION

This study evaluated the usefulness of the Aptima assay for the diagnosis of SARS-CoV-2 compared to the TaqPath COVID-19 RT-PCR kit as the reference gold standard [2, 3].

Several studies have previously evaluated Hologic Panther Aptima assay ability for SARS-CoV-2 detection in comparison to different qPCR commercial kits [5, 6, 7, 8, 9]. The efficacy of the technique has already been demonstrated, although it is true that a previous study by our group [10] showed that the sensitivity of Hologic Panther Aptima assay is lower than TaqPath COVID-19 RT-PCR.

However, in all these previous studies samples were selected by qPCR results and later on analysed by Aptima assay. The approach of the present study was just the opposite and the selection of specimens' was made based on the results of Aptima to later perform the analysis by qPCR.

The results showed and excellent sensitivity and negative

Table 1 Relationship between results obtained by qRT-PCR y TMA in panther positive samples

	N	Positive qRT-PCR	Negative qRT-PCR	Ct range	False positives (%)	PPA
Panther RLU >500	500	424	76	10->40	15.2%	84.8%
Panther RLU >500- <1000	36	7	29	34->40	80.55%	19.45%
Panther RLU >1000-<1200	12	5	7	25->40	58.33%	41.67%
Panther RLU >1200	452	412	40	10->40	8.85%	91.15%

Ct (cycle threshold); PPA (positive percent agreement); RLU (relative light units)

percent agreement (100%), an acceptable positive percent agreement (84,8%), but a very low specificity (47,9%) when all samples were considered. However, the specificity improved when samples with the lowest RLU values were discarded.

Other comparator studies showed similar values of sensitivity but higher PPA values [7, 8, 9]. The differences are probably due to the dissimilar way of sample selection. The inclusion in the comparative studies of only positive samples by qPCR does not allow the detection of false positives by Hologic since all specimens are true positives.

Some of the false positives corresponded to samples from patients with previous positives who had recently become negative. So, there is a possibility that what the Hologic system detected is some viral residue with no clinical value. Nevertheless, since this was not the case in all samples, there must be other factors responsible for the false positives detected.

In conclusion, analytical validation of this study shows that the Aptima assay can be a very good tool for screening samples. This system is fast, easy to use and get ability to continuously load reagents and samples during the process; it is also able to discriminate true negative samples. However it would be recommendable to check positive results by a different technique, especially those with RLU values below 1000.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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Original breve

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Otitis media tuberculosa: Presentación de un caso y revisión de la literatura europea

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RESUMEN

La otitis media tuberculosa (OMT) es una afectación rara en nuestro medio que supone un reto en su diagnóstico debido a los síntomas inespecíficos que suele presentar. Este trabajo presenta nuestra experiencia en el diagnóstico de un caso de OMT en una mujer de 66 años con pérdida auditiva y otorrea crónica de más de 6 meses de evolución, que no respondía a los tratamientos convencionales. Además, se realiza una revisión de los casos publicados en los últimos 20 años (2000-2022) en países de la Unión Europea (EU). Se incluyeron un total de 25 artículos con datos sobre 43 pacientes diagnosticados de OMT. Las edades se situaron en un rango de: 3 meses - 87 años con un mayor porcentaje de mujeres (n=30; 69,77%). El tiempo medio de diagnóstico fue de 13,6 meses (rango, 1-72 meses). Los síntomas más comunes fueron otorrea (n=43; 100%), pérdida auditiva (n=37; 86,05%), perforación timpánica (n=19; 44,18%), parálisis facial (n=12, 27,91%) y otalgia (n=13; 30,23%). La muestra empleada en mayor porcentaje para el diagnóstico fue la biopsia obtenida por mastoidectomía (n=34; 79,06%). Todos los pacientes fueron tratados con antituberculosos con una media de duración de 8,11 meses (rango, 6-12 meses). La secuela más frecuente fue la pérdida auditiva (n=28; 65,12%). La OMT debe incluirse en el diagnóstico diferencial de las otitis supurativas crónicas ya que el diagnóstico y tratamiento precoz disminuyen la probabilidad de sufrir secuelas irreversibles.

Palabras Clave: otitis media, *M. tuberculosis*, antituberculosos.

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Tuberculous otitis media: A case presentation and review of european literature

ABSTRACT

Tuberculous otitis media (TOM) is a rare affectation in our environment that represents a challenge in its diagnosis due to the non-specific symptoms that it usually presents. This paper presents our experience in the diagnosis of a case of TOM in a 66-year-old woman with hearing loss and chronic otorrhea of more than 6 months of evolution that did not respond to conventional treatments. In addition, a review of the cases published in the last 20 years (2000-2022) in countries of the European Union (EU) is carried out. The most common symptoms were otorrhea (n=43; 100%), hearing loss (n=37; 86.05%), eardrum perforation (n=19; 44.18%), facial paralysis (n=12, 27,91%) and ear pain (n=13; 30,23%). The most used sample for diagnosis was the biopsy obtained by mastoidectomy (n=34; 79.06%). All patients were given antituberculous therapy for a mean duration of 8.11 months (range, 6-12 months). The most frequent aftereffect was hearing loss (n=28; 65.12%). TOM should be included in the differential diagnosis of chronic suppurative otitis, since early diagnosis and treatment reduce the probability of suffering irreversible sequelae.

Keywords: otitis media; chronic otitis media; *Mycobacterium tuberculosis*; antituberculous therapy

INTRODUCCIÓN

Cada año diez millones de personas enferman de tuberculosis. A pesar de ser una enfermedad prevenible y curable, 1,5 millones de personas mueren de tuberculosis al año, lo que la convierte en una de las principales causas de muerte en todo el mundo [1].

La infección puede afectar a cualquier órgano, aunque su localización preferencial es el pulmón. En el 2020 se noti-

ficaron un 17% de casos de tuberculosis extrapulmonar en la Región Europea de la OMS [1], siendo la afectación del oído medio una forma excepcional de la enfermedad que supone menos del 0,1% de todos los casos de tuberculosis [2].

En los países desarrollados, la otitis media tuberculosa (OMT) es una afectación rara que representa entre el 0,05% y 0,9% de los casos de infección crónica de oído medio [3]. La patogénesis de la OMT implica tres mecanismos principales: la diseminación hemática desde otros focos, principalmente pulmonar u otros órganos distantes, la propagación por contigüidad a través de la trompa de Eustaquio o la implantación directa a través del conducto auditivo externo por perforación timpánica [4]. La presentación clínica se caracteriza por la triada clásica de otorrea no dolorosa de larga duración, múltiples perforaciones timpánicas y en algunos casos parálisis facial.

Estos síntomas poco específicos, pueden confundirse fácilmente con otras causas más comunes de otitis crónica, llevando a retrasos en el diagnóstico y tratamiento [4].

El objetivo de nuestro trabajo ha sido presentar un caso de OMT diagnosticado en el área sanitaria de Granada y realizar una revisión de los casos publicados en los últimos 22 años (2000-2022) en países de la EU.

PRESENTACIÓN DEL CASO

Mujer de 66 años, de nacionalidad argentina, pero residente en España desde hace más de 10 años y sin antecedentes de interés, que en diciembre de 2021 acude a su médico de atención primaria refiriendo otorrea, otalgia, hipoacusia y sensación de taponamiento en oído izquierdo tras sufrir un resfriado 2 meses y medio antes.

En consulta se le realizó una otoscopía donde se observó un oído derecho normal y un oído izquierdo con cierta inflamación en la zona atical y eritema junto al mango del martillo.

Se derivó al servicio de otorrinolaringología donde se realizó un TAC en el que no se apreció la presencia de un colesteatoma pero sí ocupación de la mastoides preservando el scutum y las celdillas mastoideas.

Se decidió realizar una miringotomía con la que se consiguió drenar una gran cantidad de líquido y se le pautó tratamiento con antibiótico y corticoides durante 20 días.

En la revisión la paciente describe falta de mejoría a pesar del tratamiento, y se le realizó un segundo TAC de control donde se visualiza extensa ocupación inflamatoria del oído medio y mastoides rodeando ampliamente la cadena osicular sin evidencia de erosión de scutum. Dada la situación se plantea la posibilidad de realizar una mastoidectomía del oído izquierdo que la paciente aprueba.

En la intervención se observó material inflamatorio en el conducto auditivo externo y se procedió a la toma de múltiples biopsias para analizar.

El estudio anatomo-patológico describió fragmentos de necrosis fibrinoide con tejido inflamatorio con focos pseudocalcificados compatibles con un colesteatoma de larga evolución.

A nivel microbiológico se realizó un cultivo de bacterias y micobacterias, siendo el cultivo bacteriano negativo a los 5 días. Para el estudio de micobacterias se realizó una tinción auramina-rodamina en la que no se observaron bacilos ácido-alcohol resistentes, sin embargo, la PCR (Anyplex™ MTB/NTM Real-Time Detection. Seegene) mostró un resultado positivo para *Mycobacterium tuberculosis complex* sobre muestra directa. A continuación, se le realizó una segunda PCR (Anyplex™ MTB/MDR/XDR Detection. Seegene) donde no se detectaron mutaciones en los genes de resistencias para los fármacos de primera y segunda línea. El cultivo fue positivo a los 14 días de incubación no presentando tampoco resistencias a nivel fenotípico para los antibióticos estudiados: estreptomicina, isoniazida, rifampicina, etambutol y pirazinamida, realizándose en BACTEC™ MGIT™ 960 de BD.

La paciente diagnosticada de otomastoiditis tuberculosa se derivó al servicio de enfermedades infecciosas donde se le pautó tratamiento antituberculoso con isoniazida, rifampicina y pirazinamida durante 2 meses y tras finalizarlos otros 10 meses con rifampicina e isoniazida. En una segunda consulta al servicio de enfermedades infecciosas se le realizó un test de Mantoux y se le solicitó estudio con QuantiFERON® - TB Gold in Tube (QFT-GIT) obteniendo en ambos un resultado positivo. También se le realizó una RX de tórax en la que no se observaron lesiones compatibles con infección pulmonar y se le solicitó cultivo de muestras respiratorias, pero estas no llegaron a enviarse al servicio de microbiología. Aunque la paciente no ha completado aún los 6 meses de tratamiento, la evolución está siendo favorable.

MATERIAL Y MÉTODOS

Se realizó una búsqueda bibliográfica en la base de datos de PubMed utilizando "tuberculous otitis media" y "tuberculous otomastoiditis" como palabras clave. Se seleccionaron artículos publicados en el período de 2000-2022 que incluyesen informes de casos diagnosticados de OMT en países de la EU.

De cada uno de los artículos se obtuvo la siguiente información: datos demográficos, edad, signos y síntomas clínicos, hallazgos de laboratorio, diagnóstico, tratamiento empleado y evolución.

La limitación principal de esta revisión ha sido la alta heterogeneidad de los artículos consultados. Muchos de los estudios incluidos no mencionaban variables de interés como la historia clínica de los pacientes, datos demográficos, hallazgos de laboratorio, estudios anatomopatológicos, tratamiento utilizado y duración del mismo, lo que ha podido influir en los datos finales analizados.

RESULTADOS

Se seleccionaron un total de 25 artículos, de los cuales 7 corresponden a series de casos [3,5,12-14,16,26] y 18 a casos

Tabla 1 **Pacientes y sintomatología de la otitis media.**

	N	%
Pacientes n=43; 1-10 pacientes por artículo		
Rango edad: 3 meses – 87 años		
Sexo		
Femenino	30	69,76%
Masculino	13	30,23%
Pacientes con TBC en otras localizaciones [10,11,17,20,24]	7	16,28%
Contactos de casos confirmados de TBC [12,15,23,24,27]	5	11,63%
Tiempo medio hasta diagnóstico de OMT (rango: 1-72 meses)	13,6 meses	
Oído(s) afectado(s)		
Unilateral [2,4,6,8-13,15,16,22-24,27,28]	33	76,74%
Bilateral [3,8,15,18-22,26,27]	10	23,25%
Síntomas		
Otorrea	43	100%
Pérdida de audición [2,3,5,6,8,10-15,17-22,24,25]	37	86,05%
Perforación timpánica [3,5,7,8,13-15,17,21,22,24,26]	19	44,19%
Parálisis facial [3,13-16,19,21-23,25,26]	12	27,91%
Otalgia [2,3,7,8,14,16,21,22,24-27]	13	30,23%
Tinnitus [14,15,18,19]	4	9,30%
Vértigo [14,15,18,19]	4	9,30%
Síntomas constitucionales (fiebre, pérdida de peso, sudores nocturnos, cefalea) [7,10,11,17,19,23]	6	13,95%

[2,6-11,15,16,18-25,27], todos ellos retrospectivos. El total de pacientes fue de 43 con edades comprendidas en el rango: 3 meses-87 años, siendo en su mayoría mujeres (n=30, 69,76%) (Tabla 1). El área geográfica de los artículos seleccionados incluye los países: Alemania (8%) [5,6], Croacia (4%) [2], España (20%) [3,7-9,26], Francia (8%) [10,11], Grecia (8%) [12,13], Hungría (4%) [14], Italia (16%) [15-18], Países Bajos (4%) [19], Portugal (4%) [20], Rumania (4%) [21] y UK (20%) [22-25,27].

Para 18 de los 43 pacientes (41,86%) se presentan antecedentes médicos y/o sociales significativos [2,3,5,7,9-12,16-20,23,24,27]. Tres (6,97%) provenían de países de América del Sur [5,7], 3 (6,97%) del continente asiático [17,18,24] y 5 (11,62%) del africano [9-11,19,23]. De estos últimos, hay 3 casos de niños menores de 14 años nacidos en Europa, pero cuya familia emigró de países africanos [10,11,23].

En cuanto a los datos clínicos destaca: exposición a casos confirmados de TBC (n=5; 11,63%) [12,15,23,24,27], inmunosupresión (n=2; 4,65%) [2,5], infección VHC (n=1; 2,32%) [17], patología cardiovascular (n=1; 2,2%) [16] y patología respiratoria (n=1; 2,32%) [17]. Además, 4 pacientes presentaron infección previa o concomitante por *M.tuberculosis complex* a nivel pulmonar [10,17,24], 1 nasal [20] y 2 ósea y pulmonar a la vez [10,11].

Según datos del total de los pacientes, el tiempo medio hasta el diagnóstico de la OMT fue de 13,6 meses (rango, 1-72 meses). En cuanto a la afectación, la unilateral fue más frecuente (n=33, 76,74%), aunque 10 presentaron afectación bilateral (23,25%). Respecto a la sintomatología, el síntoma predominante fue la otorrea, presente en el 100% de los casos, seguido de pérdida auditiva (n=37; 86,05%), perforación timpánica (n=19; 44,19%), parálisis facial (N=12; 27,91%) y otalgia (n=13; 30,23%) [2,3,7,8,14,16,21,22,24-27]. Otros síntomas menos comunes fueron tinnitus y vértigos (ambos n=4; 9,30%). La cefalea y los síntomas sistémicos como fiebre, pérdida de peso y sudores nocturnos se dieron en 6 pacientes (13,95%), padeciendo todos ellos infección tuberculosa en otras localizaciones, principalmente pulmonar (n=4; 9,3%) [10,11,17,19] o en menores de 3 años (n=2; 4,65%) [7,23] (Tabla 1).

Las muestras enviadas para el diagnóstico fueron principalmente biopsias (n= 34; 79,07%), exudados óticos (n=8; 18,6%) y jugo gástrico en el caso de niños (n=4; 9,3%) (Tabla 2).

La realización de mastoidectomía se especifica en 24 pacientes (55,81%) [2,3,7,10,12,14,15,17,21,24-26], siendo las muestras obtenidas durante este procedimiento las más utilizadas para el diagnóstico de OMT.

Se obtuvieron cultivos positivos para *M. tuberculosis com-*

Tabla 2 **Tipo de muestras y técnicas empleadas en el diagnóstico microbiológico.**

Pacientes en los que se realizó estudio microbiológico = 39				
Muestras obtenidas				
Tipo de muestra	N	Técnicas	Total	Resultado positivo
Biopsia	34 [2,3,7,10-15,17,19-26]	Tinción	25	11 [3,8,9,12,14,19,21,24,26]
		Cultivo	24	19 [3,5,8,12-14,17,19,23,24,26]
		PCR	16	16 [5,6,8,12-14,20,22,26]
Exudado ótico	8 [3,9,16-18,27]	Tinción	8	3 [3,17]
		Cultivo	8	7 [3,9,17,27]
		PCR	2	2 [16,18]
Jugo gástrico	4 [7,11,18,23]	Tinción	1	1 [11]
		Cultivo	4	3 [7,11,23]
		PCR	0	0
Técnicas empleada				
Prueba cutánea de la tuberculina (Test de Mantoux)				16 [3,10-15,17,18,25,26]
Test IGRA				8 [2,7,8,14,17-20]

plex en 29 (69,44%) pacientes, recuperados 19 (55,19%) a partir de biopsias, 7 (12,28%) de exudados y 3 (6,98%) de jugo gástrico. De ellos, 14 (32,56%) pacientes pusieron de manifiesto a su vez la presencia de bacilos ácido-alcohol resistentes.

Mediante el uso de técnicas de amplificación de ácidos nucleicos (TAAN) se obtuvieron resultados positivos para 18 (41,86%) pacientes, 16 (37,21%) a través de biopsias y 2 (4,65%) de exudados (Tabla 2). De ellos, 12 (27,91%) pacientes tuvieron también cultivos positivos [5,8,12-14,26], para el resto o solo se especifica la realización de TAAN (n=4; 9,3%) [6,15,16,20] o el cultivo fue negativo (n=2; 4,65%) [18,22].

En 4 del total de los artículos revisados [2,3,10,21], debido a que solo mencionan la realización de la tinción de bacilos ácido-alcohol resistentes y no aportan datos de cultivo o antibiograma, presuponemos que el diagnóstico se realizó desde anatomía patológica. Siendo en este caso el único resultado para iniciar el tratamiento antituberculoso, sin intervención por parte de microbiología. Hubo 8 pacientes en los que el tratamiento se inició tras los resultados histopatológicos; en 5 de ellos [9,12,19,24,26] se confirmó posteriormente el diagnóstico por parte del laboratorio de microbiología, ya sea por cultivo o técnicas de NAAT y en 3 [3,25] no se llegó a confirmar.

La prueba cutánea de la tuberculina (test de Mantoux) fue positiva en 16 pacientes (37,21%) y el test IGRA (Interferon gamma release assays) en 8 (18,6%) (Tabla 2). Ambas pruebas fueron positivas en 3 pacientes (6,98%) [14,17,18]. Para el resto de pacientes este dato no está recogido.

En relación al tratamiento aplicado una vez establecido el diagnóstico, a todos los pacientes recogidos en esta revisión se les trató con antituberculosos, principalmente rifampicina, isoniazida, etambutol y pirazinamida. De los 43 casos, solamente se especifica la duración del tratamiento en 25 de ellos (58,14%) con un rango de 6-12 meses dependiendo de la presentación clínica, extensión de la infección y gravedad.

Por último, referente a la evolución se dispone de da-

tos tras iniciar el tratamiento en 38 pacientes (88,37%): 36 (83,72%) consiguieron curarse de la infección [2,3,7,9-11,13-20,22-24,26,27] y 2 (4,65%) continuaron con síntomas a pesar de varios meses con tratamiento antituberculoso lo que llevó al hallazgo de resistencias a isoniazida en un caso, e isoniazida y estreptomicina en el otro [12].

Como secuelas, 28 (65,12%) individuos padecieron hipoacusia [2,3,9-11,13-20,24,26] y 3 (6,98%) parálisis facial permanente [14,22,26]. No hubo ningún fallecimiento.

DISCUSIÓN

La OMT es una afectación rara en nuestro medio que representa solo entre el 0,05% y 0,9% de todos los casos de infección crónica del oído medio [3], siendo la afectación secundaria la más común.

La patogénesis implica tres mecanismos principales: la aspiración a través de la Trompa de Eustaquio, la diseminación hemática desde otros focos tuberculosos y por último la implantación directa a través del conducto auditivo externo [28].

En los artículos revisados son solo 7 los pacientes en los que se confirma enfermedad por MTB en otras localizaciones. Por lo tanto, la implantación directa a través del conducto auditivo externo y la membrana timpánica debe considerarse también como una vía importante de propagación de la OMT.

Las características clínicas clásicas de la OMT fueron descritas por Wallmer en 1953 incluyendo: otorrea indolora, perforaciones múltiples de la membrana timpánica, presencia de granulaciones en el oído medio y mastoides, pérdida auditiva progresiva, parálisis del nervio facial homolateral y necrosis ósea [29].

Todos estos síntomas se han observado en diferente porcentaje en los pacientes incluidos en la revisión, pero curiosamente, aunque la otalgia no está incluida entre los síntomas clásicos de la OMT según Wallmer [29], se han encontrado 13 pacientes (30,23%) que presentaban este síntoma además de la paciente diagnosticada en nuestro caso. La afectación unilaterial fue la más común en nuestra serie de pacientes.

En aquellos casos con historia previa de infección por MTB o contacto estrecho con casos confirmados, puede aumentar la probabilidad de sospecha de esta afectación, pero en el resto de los casos es difícil de diferenciar de otras posibles causas de otitis crónica produciéndose muy frecuentemente retrasos en el diagnóstico y uso de tratamientos inadecuados [28].

Según los resultados de la revisión, la biopsia obtenida por mastoidectomía es la muestra más frecuentemente utilizada para la evaluación de la OMT, siendo el estudio histopatológico y el cultivo o las TAAN fundamentales para el diagnóstico definitivo. Debido a la baja sospecha inicial de OMT en la mayoría de los casos, no se suele solicitar estudio de micobacterias en muestras de exudados óticos, ya que cuando se considera este diagnóstico se ha debido recurrir a muestras más invasivas. En nuestro caso, a la paciente se le realizaron varios cultivos de exudados óticos durante el periodo de estudio obteniendo siempre resultados negativos, y no se solicitó estudio de micobacterias hasta que se tomaron muestras por mastoidectomía.

Los hallazgos histopatológicos más comunes son necrosis caseosa, material inflamatorio con células epitelioides y células gigantes de Langerhans [4]. Esto en el contexto clínico adecuado puede ser suficiente para justificar el inicio del tratamiento antituberculoso, sin embargo, es importante el envío de las muestras al laboratorio de microbiología para que así se realice la confirmación y los estudios de sensibilidad correspondientes.

La combinación de fármacos antituberculosos es el tratamiento de elección para la OMT [28], y han sido utilizados en el total de los casos recogidos en esta revisión. En general, la duración del tratamiento debe ser de al menos 6 meses dividido en dos fases: una primera fase de mayor intensidad que tiene una duración de al menos 2 meses en la que se combinan 4 fármacos (isoniazida, rifampicina, pirazinamida y etambutol) y una segunda fase de mantenimiento con una duración de al menos 4 meses con isoniazida y rifampicina [28]. La duración del tratamiento en los datos recogidos ha variado entre los 6-12 meses. A nuestra paciente se le pautó un tratamiento de 12 meses.

En cuanto a las secuelas según los datos revisados, la pérdida auditiva es el síntoma que más se repite en los pacientes una vez superada la infección (n=28; 65,12%). La parálisis facial permanente se dio en un porcentaje inferior (n=3; 6,98%) pero no despreciable debido a la gravedad del mismo. La probabilidad de sufrir estas consecuencias parece estar estrechamente relacionada con el tiempo hasta el diagnóstico y la instauración de un tratamiento adecuado [4].

CONCLUSIONES

Es importante sospechar la posible implicación de *M. tuberculosis complex* como causante de otitis media crónica, en aquellos pacientes: que presenten historia sugestiva o confirmada de infección respiratoria por este microorganismo, que hayan estado en contacto con casos positivos, y en aquellos pacientes con otitis media supurativa crónica que no respondan a los tratamientos convencionales. Los estudios microbiológicos y anatomopatológicos a menudo ofrecen resultados que pueden ayudar o confirmar la sospecha diagnóstica, y por tanto disminuir el tiempo hasta el inicio del tratamiento, que parece ser aún a día de hoy una limitación a la hora de prevenir secuelas irreversibles en pacientes con esta afectación.

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CONFLICTO DE INTERESES

Los autores declaran no tener ningún conflicto de intereses.

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In vitro assessment of the combined effect of letermovir and sirolimus on cytomegalovirus replication

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ABSTRACT

Introduction. Letermovir (LMV) is used for prophylaxis of cytomegalovirus (CMV) reactivation and end-organ disease in adult CMV-seropositive allogeneic hematopoietic stem cell transplant recipients (allo-HSCT). In turn, sirolimus (SLM) which displays *in vitro* anti-CMV activity, is frequently employed for prophylaxis of Graft vs. Host disease in allo-HSCT. Here, we aimed at assessing whether LMV and SLM used in combination may act synergistically *in vitro* on inhibiting CMV replication.

Material and methods. The antiviral activity of LMV and SLM alone or in combination was evaluated by a checkerboard assay, using ARPE-19 cells infected with CMV strain BADrUL131-Y. LMV and SLM were used at concentrations ranging from 24 nM to 0.38 nM and 16 nM to 0.06 nM, respectively.

Results. The mean EC_{50} for LMV and SLM was 2.44 nM (95% CI, 1.66-3.60) and 1.40 nM (95% CI, 0.41-4.74), respective. LMV and SLM interaction yielded mainly additive effects over the range of concentrations tested.

Conclusion. The additive nature of the combination of LMV and SLM against CMV may have relevant clinical implications in management of CMV infection in allo-HSCT recipients undergoing prophylaxis with LMV.

Keywords: Cytomegalovirus; letermovir; sirolimus.

Evaluación *in vitro* del efecto combinado de letermovir y sirolimus en la replicación de citomegalovirus

RESUMEN

Introducción. Letermovir (LMV) se utiliza para la profilaxis de la reactivación de la infección y de la enfermedad orgánica por citomegalovirus (CMV) en adultos receptores de trasplante alogénico de células madre hematopoyéticas (alo-TPH) en pacientes seropositivos para CMV. A su vez, sirolimus (SLM), que muestra actividad anti-CMV *in vitro*, se usa con frecuencia para la profilaxis de la enfermedad de injerto contra huésped en alo-TPH. Nuestro objetivo fue evaluar si LMV y SLM utilizados en combinación pueden actuar sinérgicamente *in vitro* en inhibir la replicación del CMV.

Material y métodos. La actividad antiviral de LMV y SLM individualmente o en combinación se evaluó mediante un ensayo de tablero de ajedrez, utilizando células ARPE-19 infectadas con la cepa BADrUL131-Y de CMV. Se utilizaron LMV y SLM en concentraciones que variaron entre 24 nM y 0,38 nM y entre 16 nM y 0,06 nM, respectivamente.

Resultados. La EC_{50} media para LMV y SLM fue de 2,44 nM (IC del 95 %, 1,66-3,60) y 1,40 nM (IC del 95 %, 0,41-4,74), respectivamente. La interacción LMV y SLM produjo principalmente efectos aditivos en el rango de concentraciones ensayadas.

Conclusión. La naturaleza aditiva de la combinación de LMV y SLM frente a CMV puede tener implicaciones clínicas relevantes en el tratamiento de la infección por CMV en alo-TPH que reciben profilaxis con LMV.

Palabras clave: actividad in vitro; letermovir; sirolimus; citomegalovirus.

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INTRODUCTION

Cytomegalovirus (CMV) infection remains a significant cause of morbidity and mortality in the allogeneic hematopoietic stem cell transplantation (allo-HSCT) setting [1]. Although preemptive antiviral therapy (PET) has dramatically decreased the incidence of CMV end-organ disease [1], there is growing evidence that CMV DNAemia, especially if requiring PET, may be detrimental by increasing the risk of overall and non-relapse mortality [2-5]. Letermovir (LMV), an antiviral compound that blocks virion maturation by inhibiting the CMV DNA terminase complex [6], has been approved for prophylaxis of CMV reactivation and end-organ disease in adult CMV-seropositive allo-HSCT recipients. LMV efficiently suppresses CMV replication and seemingly increases survival by week 24 after allo-HSCT [7]. Nowadays, sirolimus (SLM), an mTOR inhibitor that inhibits T cell activation specifically by binding the cytosolic protein FKPB-12, is currently in wide use combined with other immunosuppressive agents for prophylaxis of acute graft-versus-host disease (aGvHD) in allo-HSCT. SLM exposure has been shown to dose-dependently decrease the risk of CMV DNAemia in a cohort of allo-HSCT recipients at high risk of CMV end-organ disease [8]. Furthermore, risk of CMV DNAemia requiring PET was shown to fall by 6% for each 1 ng/mL increase in SLM trough concentration [9]. The protective effect of SLM against CMV infection may be mechanistically related to the key role of the mTOR pathway in CMV protein synthesis and replication [10-14] and improvement of CMV-specific T-cell function via modulation of the environmental milieu [15]. The use of LMV and SLM in combination may improve the management of CMV infection in allo-HSCT by increasing clinical efficacy, reducing adverse effects and minimizing the likelihood of emergence of LMV-resistant variants. Evidence partly supporting the assumption that the association of LMV and SLM may reduce the rate of clinically significant CMV infection (CMV DNAemia that requires preemptive antiviral therapy/CMV end-organ disease) was recently provided [16]. A synergistic effect has been shown *in vitro* for maribavir, another anti-CMV drug inhibiting virus DNA replication, and SLM [17]. Here, we evaluated *in vitro* the potential interaction between SLM and LMV regarding its anti-CMV activity.

METHODS

Cells and virus. Human ARPE-19 retinal pigment epithelial cells (ATCC CRL-2302) were cultured in high-glucose Dulbecco's Modified Eagle Medium Nutrient Mixture F-12 (DMEM:F12K) (Gibco, ThermoFisher Scientific, Waltham, Massachusetts, USA), supplemented with 10% FCS (HyClone Laboratories Inc, Cytiva, USA), 10,000 IU penicillin (Gibco, ThermoFisher Scientific, Waltham, Massachusetts, USA), and 10 mg streptomycin (Gibco, ThermoFisher Scientific, Waltham, Massachusetts, USA). The CMV strain BADrUL131-Y4 [18] was kindly provided by Dr Pilar Pérez (ISCIII, Madrid, Spain). This strain is derived from a bacterial artificial chromosome clone of the CMV strain AD169 genome that was modified in *Escherichia coli* to express a functional UL131 protein, which permits replication in ARPE-19 and MRC-5 cells. Viral titers of CMV BADrUL131-Y4 were determined by limiting dilution in 96-well plates using MRC-5 cells.

Antiviral compounds. LMV was kindly provided by Merck, Sharp & Dohme (MSD) and stored as a stock solution of 50 milimolar (mM) in dimethyl sulfoxide (DMSO). A fresh working solution of 50 nanomolar (nM) was prepared in DMEM/F12K medium for each experiment and for medium renewal. SLM was purchased from Sigma Aldrich Merck (Merck KGaA, Darmstadt, Germany) and stored in a stock solution of 11 micromolar (µM) in DMSO. A working solution of 110 nM in in DMEM/F12K medium was prepared for each experiment.

Antiviral assay. The antiviral activity of LMV and SLM alone or in combination was evaluated by a checkerboard assay, as previously described [19]. ARPE-19 cells were seeded in 96-well microtiter plates ($4x10^4$ cells/well) for 24 h at 37ºC and 5% CO_2 and infected with 0.1 MOI of CMV strain BADrUL131-Y for 2 h in DMEM/F-12K medium containing either LMV (two-fold dilutions from 24 nM-14 ng/ml- to 0.38 nM- 0.22 ng/ml-), SLM (two-fold dilutions from 16 nM-15 ng/ml- to 0.06 nM-0.05 ng/ml-), or both drugs. The resulting two-dimensional matrix included all possible combinations of LMV and SLM and individual concentrations of each drug. The range of LMV and SLM concentrations tested in the current study was derived from that used in previous studies addressing the *in vitro* anti-CMV activity of LMV [6,17,20] or the potential synergistic effect between SLM and maribavir [17], respectively. For both drugs, these ranges were centered on the reported EC_{50} against CMV [6,17,20]. Four positive (CMV-infected cells in cell culture medium) and negative (CMV-uninfected cells in cell culture medium) controls were included in each plate. A total of five plates were prepared in three separate experiments. The plates were incubated for 6 days, and the medium (with or without the drugs) was replaced (with and without drugs, as appropriate for each well) every 2-3 days, as half-life for LMV and SLM are approximately of 12 and 60 hours, respectively, according to the corresponding manufacturer. After incubation, cells were washed, fixed with acetone/methanol (1:1), permeabilized with 0.2% Triton-X100 and stained for 1 h with 100 µl/well of a mouse IgG2a monoclonal antibody anti-Cytomegalovirus immediate early 1 (IE1) protein (1:150) (ThermoFisher, Waltham, Massachusetts, USA). A secondary FITC-labelled goat anti-mouse IgG2a cross-adsorbed secondary antibody (ThermoFisher, Waltham, Massachusetts, USA) was added at a dilution of 1:150 and incubated in dark for 1 h. Green-fluorescent nuclei were counted in a fluorescence microscope. Potential drug cytotoxicity was assessed for each experiment using mock-infected cells and matched drug exposure. Cell viability was verified after 6 days of culture for each condition using the alamarBlue cell viability assay (ThermoFisher, Waltham, Massachusetts, USA), following the manufacturer's recommendations.

Table 1 Analysis of the combination of letermovir and sirolimus by checkerboard matrix

Drug A	Max[a] (nM)	EC50[b] (95%CI)	Drug B	Max[c] (nM)	EC50[b] (95%CI)	Mean vol μM²%[d] (95%)		Mean vol μM²%[d] (99%)		Mean vol μM²%[d] (99.9%)	
						Synergy	Antagonism	Synergy	Antagonism	Synergy	Antagonism
Letermovir	24	2.44 (1.66-3.60)	Sirolimus	16	1.40 (0.41-4.74)	0	-172	0	-117	0	-76

95%CI, 95% Confidence Interval; EC50, 50% Effective Concentration; nM, nanoMolar; vol, volume.

[a]A total number of n=7 2-fold dilutions were tested starting from 24nM.

[b]The mean concentration capable of inhibiting Cytomegalovirus infection by 50% (EC50) was calculated by using the individual dose-response curve for each compound (Graphpad Prism software, v.6).

[c]A total number of n=9 2-fold dilutions were tested starting from 16nM.

[d]Volumes (μM²%) of synergy and antagonism were calculated using the MacSynergyII software. Values >50 μM2% were considered moderate and significant in vivo. Volumes at statistical level of confidence of 95%, 99% and 99.9% are shown.

Statistical analysis. EC_{50} was calculated by non-linear regression and using the dose-response curve obtained from the average percentage inhibition for each compound alone (GraphPad Prism software). Drug interaction was evaluated using MacSynergy II software, and interpreted as detailed elsewhere [20]. Differences between frequencies were analyzed using the Chi Square test. A *P* value <0.05 was considered statistically significant.

RESULTS

Both LMV and SLM inhibited CMV replication in ARPE-19 cells in a dose-dependent manner. The mean EC_{50} was 2.44 nM [1.40 ng/ml] (95% CI, 1.66-3.60) and 1.40 nM [1.28 ng/ml] (95% CI, 0.41-4.74), respectively (Table 1 and Figure 1 for dose-response curves). Overall synergy/antagonism volumes were 0% for synergy and -117% for antagonism at 99% confidence interval (Table 1). Interaction between the two drugs was concentration-dependent and mainly yielded additive effects (linear isobologram) over the range of concentrations tested (Figure 2), although low-level antagonistic interactions could be found, particularly at low concentrations of LMV (0.75 nM [0.43 ng/ml] and relatively high concentrations of SLM (8 nM [7.31 ng/ml]. Both LMV and SLM induced no cytotoxicity at the concentration ranges used during the incubation time, as revealed by the alamarBlue cell viability assay (not shown).

DISCUSSION

Prophylaxis with combined LMV and SLM is currently common practice in the allo-HSCT setting for prevention of CMV end-organ disease and aGvHD. Since both compounds display anti-CMV activity [6,10-12], we were interested in determining whether their interaction could result in a synergistic anti-CMV effect in epithelial ARPE-19 cells. To address this issue, we employed a conventional checkerboard assay using LMV and SLM concentrations centered around their EC_{50}

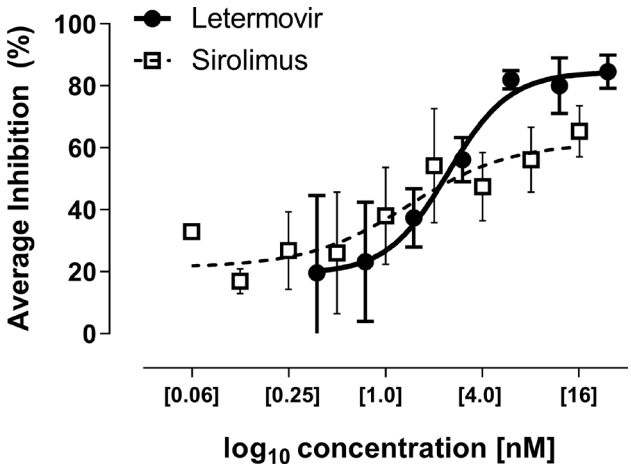

Figure 1 Dose-response curves of letermovir (LMV) and sirolimus (SLM) on CMV strain BADrUL131-Y infection of ARPE-19 cells. The percentage of inhibition represents the mean vaule of 5 experiments

against CMV [6,17,20] and SLM concentrations across the therapeutic range (4-12 ng/ml) [21]. Yet, due to the mechanism of action of both compounds and the choice of IE-1 as the assay read out full inhibition could not be achieved, as expected; in this sense, in the presence of LMV, CMV IE-1 can only be expressed in primarily infected cells (roughly 1/10 cells as an MOI of 0.1 was used); no further rounds of CMV replication ensue, as LMV blocks the generation of virus infectious particles. We obtained inhibition rates for LMV and SLM similar to previous studies [6,17,20], although our data indicated that the combination of LMV and SLM was additive at best. Notably, a low-level antagonistic effect could be observed in certain drug concentration combinations, in particular when

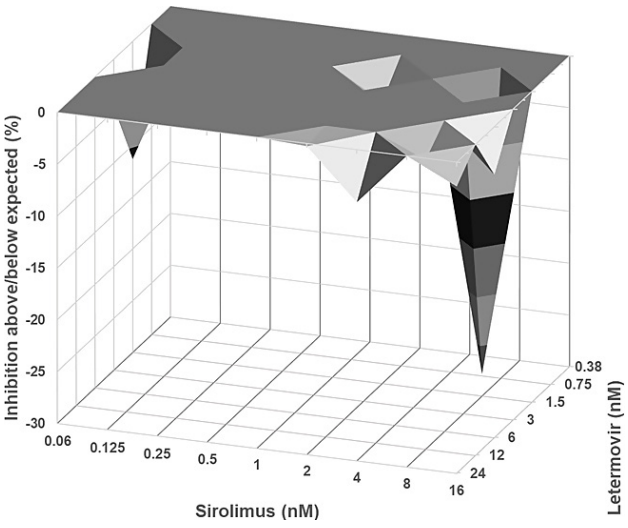

Figure 2 **Dimensional synergy plots for antiviral drug combinations with letermovir and sirolimus. The plots were generated from the results of 5 experiments of selected letermovir and sirolimus combinations against using MacSynergy II software. The difference between the observed viral growth inhibition and the amount expected from an additive effect of the drug concentrations was calculated at 99.9% confidence level.**

we used high concentrations of SLM and low concentrations of LMV. Although speculative, the lack of synergy between the two drugs and the antagonistic interactions documented could be mechanistically related to the ability of SLM to interfere with CAP-dependent translation by inhibiting mTOR kinase [4], which may impair expression of the LMV viral target, the CMV terminase complex. Whether our *in vitro* observations mirror *in vivo* interaction between these drugs is uncertain; in this context, two facts need to be considered; first, peak LMV levels reached during prophylaxis could be 100-fold higher (approximately 5**μ**M) than those used in our experiments [22], and thus CMV replication at mucosal and tissue sites could be drastically reduced *in vivo*, likely to a greater extent than in our *in vitro* model (around 50%); second, coadministration of LMV and SLM resulted in a 3.4-fold increases in area under the plasma concentration–time curve and 2.8-fold increases in maximum plasma concentration, respectively, of SLM [23].

The current study has several limitations. First, clinical CMV isolates were not used in the experiments; yet, given the nature of the recombinant CMV strain used herein (BAD-rUL131-Y4) [18], we do not foresee a straightforward biological reason that would account for LMV and SLM acting differently when employing clinical isolates. This assumption needs confirmation, though. Second, due to logistic reasons infectious virus yields could not be quantitated.

In summary, we have shown the additive nature of LMV and SLM *in vitro* interaction (over most drug concentrations assayed) in terms of anti-CMV activity in epithelial cells. Mechanistically the combination of LMV and SLM in vivo may thus shut off CMV replication *in vivo* at higher level than either drug used individually. Nevertheless, real-life data of the combined use of these drugs is required to gauge the potential clinical relevance of our *in vitro* observations.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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Letter to the Editor

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Turicella otitidis central venous-related bacteremia during pediatric acute lymphoblastic leukemia

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Sir,

We read with great interest the article by De Frutos M *et al.* [1] about 5 cases of otitis media due to *Turicella otiditis*, some of them complicated, as a case of mastoiditis that required surgery.

We agree with the authors [1] that some microorganisms isolated only anecdotally can become relevant pathogens, especially in immunosuppressed patients and therefore it is necessary to update the epidemiological surveillance with the description of new cases [1]. A suggestive report of central venous catheter (CVC)-related *T. otitidis* bacteremia is described and commented on the ground of an updated literature review. *T. otitidis* is a non-fermenting Gram-positive rod isolated almost exclusively from ear exudate fluids, although its clinical significance in both acute and chronic otitis is still controversial [2-5]. Isolated since two decades [2], its genoma has been sequenced [3]. *T. otitidis* habitat seems limited to the ear and surrounding areas, but it has been retrieved as an infrequent cause of bacteremia [2-5], especially in children with hematologic malignancies [2,4]. We discuss a rare case of CVC-related *T. otitidis* bacteremia in a child with acute leukemia, based on the available literature data.

A 11-year old child suffering from acute lymphoblastic leukemia was hospitalized due to fever, in the absence of organ signs of localization, and in particular of acute or chronic otitis, mastoiditis, sinusitis. Laboratory workup at hospital admission showed low hemoglobin of 9 gm% and high leukocyte count of 22.86 × 10^9/L with predominant neutrophil (82%), alanine aminotransferase level of 96 U/L (normal range, 21–72 U/L) and C-reactive protein raised at 158 mg/L.

During the last previous outpatient check-up, seven days before hospital admission, results of laboratory examinations showed a white blood cell count of 11.3 × 10^9/L with neutrophil ratio of 60%, hemoglobin of 11 gm% and a level of C reactive protein of 5 mg/L.

The patient had a temperature of 39.4°C, a heart rate of 123 beats/min, a respiratory rate of 24 breaths/min, a blood pressure of 90/60 mmHg, and a SaO_2 of 94%.

Microbial isolation has been obtained from the CVC blood culture after a 48-hour incubation in a Bactec Ped Plus /aerobes vial (Becton Dickinson Italia s.p.a.). Direct microscopy and Gram stain pointed out pleomorphic, asporigenous Gram-positive bacilli with a palisade appearance. Appropriate culture media (Agar Columbia with 5% mutton blood byBioMerieux Italy s.p.a.) and Agar chocholate PVX (by BioMerieux Italy s.p.a.) mantained in a CO_2 thermostat, allowed the growth of small rounded granular greysh-creamy transparent colonies of a 1.5 mm diameter.The identification was performed by the authomathized system Vitek2-VitekMS (by BioMerieux Italy s.p.a.) while the in vitro antimicrobial susceptibility assay by Kirby-Bauer was carried out on Mueller Hinton agar plus 5% defibrinated horse blood (by BioMerieux Italy s.p.a.). According to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines, the following MIC s were obtained: benzilpenicillin 1.5 mg/L, ciprofloxacin 2mg/L, gentamicin 1.5 mg/L, vancomycin MIC 0.38 mg/L, clindamycin 0.5 mg/L, tetracycline MIC 1.5 mg/L, linezolid MIC 1 mg/L and rifampicin MIC 0.004 mg/L. No other microbiological tests were requested, in addition to peripheral blood cultures, because the boy did not present a precise organic symptomatologist which would have suggested further pertinent microbiological investigations.

Systemic intravenous rifampicin in association with vancomycin CVC lock therapy and the prompt CVC removal, allowed a prompt resolution of local and systemic signs and symptoms of infection, in the absence of complications and rcurrences, as observed in the subsequent, prolonged follow-up. Very few cases of systemic *T. otitidis* infection have

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been reported until now [2-5], usually in cancer patients [1], with only one case described in a child with a malignant hemopathy like ours [4]. Clinicians shold be aware of the opportunistic potential of *T. otitidis*, especially when immunocompromised hosts are of concern. In our experience, a timely CVC removal seemed more effective when compared with systemic-local antibiotic treatment based on the *in vitro* sensitivity testing.

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CONFLICT OF INTEREST

Authors declare no conflict of interest

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Carta al Director

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Neumonía asociada a derrame parapneumónico en paciente inmunocompetente causado por *Bordetella bronchiseptica*

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Estimado Editor: *Bordetella bronchiseptica* es un cocobacilo gramnegativo aerobio obligado perteneciente al género *Bordetella*. *Bordetella pertussis, Bordetella bronchiseptica, Bordetella parapertussis*$_{hu}$, y *Bordetella parapertussis*$_{ov}$ están estrechamente relacionados e infectan a diferentes especies de mamíferos. Mientras que *B. pertussis* y *B. parapertussis*$_{hu}$ infecta humanos de forma exclusiva, *B. bronchiseptica* generalmente coloniza el tracto respiratorio de diferentes animales como perros, caballos o cerdos, causando traqueobronquitis infecciosa en perros o rinitis alérgica en cerdos, entre otros cuadros [1].

Mujer de 85 años de edad con antecedentes de diabetes mellitus en tratamiento oral, que consultó por presentar astenia generalizada, sudoración profusa, tos seca y disnea de dos meses de evolución. A la exploración se evidenció hipoventilación en hemitórax izquierdo y en la analítica de sangre no presentaba elevación de reactantes de fase aguda. En una radiografía de tórax (Figura 1) se observó derrame pleural izquierdo por lo que se ingresó para estudio. Se realizó toracocentesis con extracción de 600 ml de líquido pleural de aspecto claro con 1000 eritrocitos/µL, 474 leucocitos/ µL con 10% de neutrófilos y 90% de mononucleares, glucosa de 157 mg/dL, LDH de 113 U/L y ADA de 20 U/L, obteniéndose además muestras de broncoaspirado y lavado broncoalveolar para cultivo. En tomografía computarizada (TC) torácica (Figura 2) se observaron hallazgos compatibles con neumonía lobar inferior izquierda con derrame metaneumónico y desde ese momento comenzó tratamiento mediante 1000 mg/200 mg de amoxicilina/clavulánico IV. En días posteriores se realizó otro drenaje de 100 ml de líquido pleural cuyas características eran similares al del anterior líquido pleural, con 1000 eritrocitos/µL, 820 leucocitos/µL con 4% de neutrófilos y 96% de mononucleares, glucosa de 81 mg/dL, LDH de 119 U/L y ADA de 18 U/L.

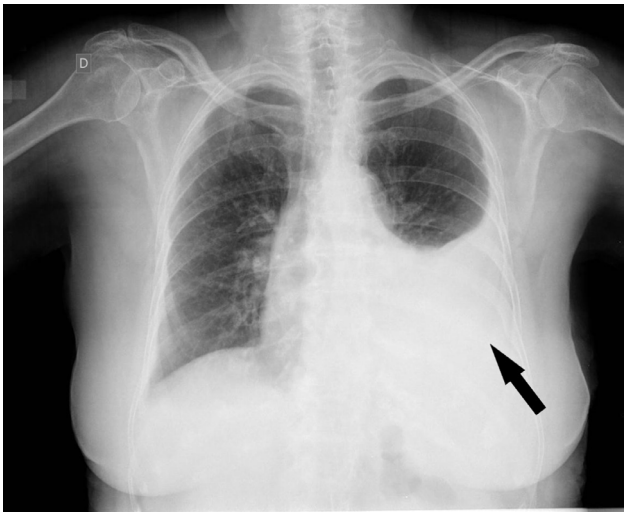

Figura 1 **Radiografía de tórax en proyección anteroposterior, en la que podemos apreciar marcado derrame pleural en hemitórax izquierdo (flecha).**

Las muestras de broncoaspirado y lavado broncoalveolar se sembraron en agares TSA con 5% de sangre de carnero y chocolate en condiciones de aerobiosis con 7,5% de CO_2, en agares McConkey y Columbia (CNA) en condiciones de aerobiosis y en agar Brucella en condiciones de anaerobiosis. En la tinción de Gram se observaron cocobacilos gramnegativos, y en agar McConkey se observaron a las 48 h 10000 UFC/ml de crecimiento lento, oxidasa y catalasa positivas, siendo identificadas mediante el sistema API^{R} 20 NE (Biomerieux, Marcy-l'Étoile, Francia) como *B. bronchiseptica*. El antibiograma se realizó mediante la técnica disco-difusión en agar Mueller-Hinton resultando sensible a piperacilina/tazobactam, ceftazidima, carbapenem, aminoglucósidos, quinolonas y colistina,

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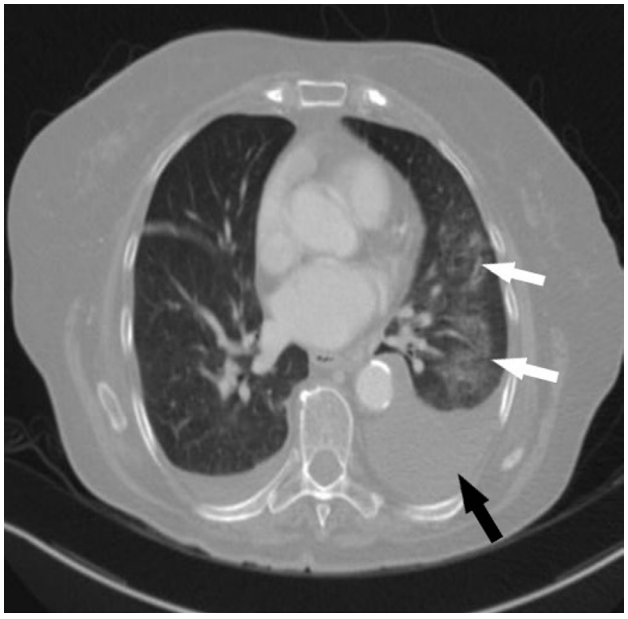

Figura 2 | **TC de tórax tras contraste intravenoso con ventana de pulmón en el que se confirma la presencia de derrame pleural izquierdo (flecha negra) y donde se apreciaban también la presencia de infiltrados alveolares en lóbulo inferior izquierdo (flechas blancas), todo ello sugestivo de neumonía con derrame metaneumónico.**

mientras que resultó resistente a cefepima y cotrimoxazol. Tras reinterrogar a la paciente, esta negó cualquier contacto estrecho con animales domésticos o salvajes, aunque vivía en una zona rural. Tras 1 semana de ingreso y después de conocer el resultado del antibiograma se cambió el tratamiento antibiótico a 500 mg/12 h de levofloxacino oral. Dada la buena evolución clínica y radiológica, manteniéndose afebril, asintomática y con resolución completa del derrame pleural, la paciente fue dada de alta con 1 semana de antibioterapia oral hasta completar 2 semanas en total.

Los factores de virulencia clave en *B. bronchiseptica* incluyen las adhesiones necesarias para la colonización traqueal, los autotransportadores y un sistema de secreción de tipo 3 para inyectar toxinas que incluyen la adenilato ciclasa, la toxina dermonecrótica y la citotoxina traqueal en las células del huésped [2, 3].

B. bronchiseptica también puede causar infecciones humanas, sobre todo en pacientes adultos o en edad pediátrica inmunodeprimidos (mayoritariamente VIH), con comorbilidades respiratorias como fibrosis quística o en contacto estrecho con animales [2,4,5]. Si bien en muchos casos se describe contacto estrecho de los pacientes con animales como en la serie de Woods P et al. (18/26 pacientes reportaron contacto habitual con animales), en otros casos como en la serie de Ducours M et al. (solo 1 paciente reportó contacto con animales) se desconoce la causa [5,6]. Los cuadros respiratorios como la bronquitis, la neumonía o el síndrome pertusoide son los cuadros clínicos más frecuentemente producidos por *B. bronchiseptica*, aunque en otras ocasiones se ha visto asociado a cuadros graves como bacteriemia o meningitis [8,9].

Los pacientes en riesgo con mascotas deben ser conscientes de la posible contaminación de las vías respiratorias por *B. bronchiseptica*. La vacunación de las mascotas puede no conferir beneficios protectores, además de que estos pacientes de riesgo deberían evitar las vacunas vivas por el riesgo de infección de cepas vacunales. Por otro lado, parece que la protección proporcionada por la vacuna contra *B. pertussis* podría ofrecer cierta protección cruzada contra *B. bronchiseptica*. De modo que, en pacientes seleccionados y con mascotas, podría ser útil el uso de vacunas de refuerzo no vivas para evitar el desarrollo de tos ferina y así mitigar el posible riesgo de infección zoonótica de este microorganismo [9].

Normalmente, *B. bronchiseptica* es sensible a penicilinas antipseudomonas, carbapenémicos, tetraciclinas, fluoroquinolonas y aminoglucósidos, pero no a la eritromicina, a diferencia de otras especies de *Bordetella*. Sin embargo, en algunos casos se ha descrito resistencia de algunas cepas a tetraciclinas, trimetoprim-sulfametoxazol o betalactámicos (albergando genes bla_{BOR-1} o bla_{OXA-2}), de modo que es necesario el estudio de la susceptibilidad en cada caso [10].

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CONFLICTO DE INTERESES

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Letter to the Editor

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Multidrug-resistant *Acinetobacter baumannii*: A therapeutic challenge

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Sir,

The World Health Organization (WHO) has classified carbapenem-resistant *Acinetobacter baumannii* (AB) as a priority pathogen whose epidemiological evolution toward multidrug resistance or pan-resistance is a critical threat to global welfare [1]. We present the clinical case of a 49-year-old man with a history of inflammatory bowel disease and human immunodeficiency virus (HIV) infection diagnosed in the 7 months before to admission. He attended the emergency department with acute paraparesis 0/5 in muscle balance and was admitted to neurosurgery where a D7-D10 laminectomy was performed where samples were taken for pathological anatomy. Following the results, a diagnosis of Burkitt's lymphoma was made, and the treatment was started on an inpatient basis in accordance with the BURKIMAB protocol. After 5 days of intensive treatment, the patient was stable and blood cultures (BC) were repeatedly negative; however, he presented occasional febrile peaks that were well tolerated. Given the oscillating clinical manifestations with recurrent signs of infection, and after new BC and catheter cultures pending results, treatment with meropenem was prescribed empirically, adding daptomycin after 48 hours as the tendency to worsen persisted.

Twelve hours after starting daptomycin, the patient developed a rash and it was decided to replace it with teicoplanin. Due to the patient's clinical situation (HIV infection with CD4/CD8 T-cell inversion (29/41), elevated hepatobiliary profile with symptoms suggestive of acute viral/toxic/ischaemic hepatitis and signs of septic shock without a definite primary focus of infection (high fever, tachycardia and a tendency to hypotension), the immunosuppressed state and the high susceptibility to infection by opportunistic pathogens led to admission to the Intensive Care Unit (ICU) under empirical treatment with imipenem, vancomycin, tigecycline, acyclovir and cotrimoxazole. AB producing carbapenemase type IMP and OXA-48, with restricted susceptibility to colistin and cefiderocol, was isolated in the BC. A complete study of antibiotic synergies was carried out according to the evidence, and all combinations were negative. Previous antibiotherapy was replaced by colistin at a loading dose of 9 million international units (MUI) and maintenance dose of 4.5 MUI/12h together with cefiderocol at 2 mg/8h administered over 3 hours, both for 8 days. Despite the vital compromise that our patient had who required close multidisciplinary management and the use of noradrenaline at a dose of 1-1.5 mcg/kg/min; 48 hours after the start of the referred treatment, hemodynamic stability was achieved, with a decrease in procalcitonin and other inflammation parameters, and he could be transferred back to Hematology for the management of his Burkitt's lymphoma.

The choice of a correct empirical treatment is of vital importance to reduce death in patients with sepsis or septic shock, where even with an adequate therapeutic line, mortality can reach 40% if the patient is immunocompromised [2]. We find ourselves in a complex era in which the emergence of multidrug-resistant (MDR) bacteria in nosocomial spaces has increased in recent years, where the therapeutic options available against these pathogens are more limited. This is even more worrying in the case of oncology and HIV+ patients.

Focusing on AB, we know that it is a non-fermenting Gram-negative coccobacillus that mainly affects hospitalized and immunocompromised patients producing nosocomial and opportunistic infections, such as ventilator-associated pneumonias, urinary tract infections, meningitis or sepsis. The main world health authorities, such as ECDC, have warned of the development of resistances that pose a therapeutic challenge and compromise the lives of our patients [3, 4].

In our case we were faced with a AB-MDR resistant to the first lines of treatment (carbapenems, glycylcyclines, aminoglycosides and rifampicin) [4] with an antibiogram that re-

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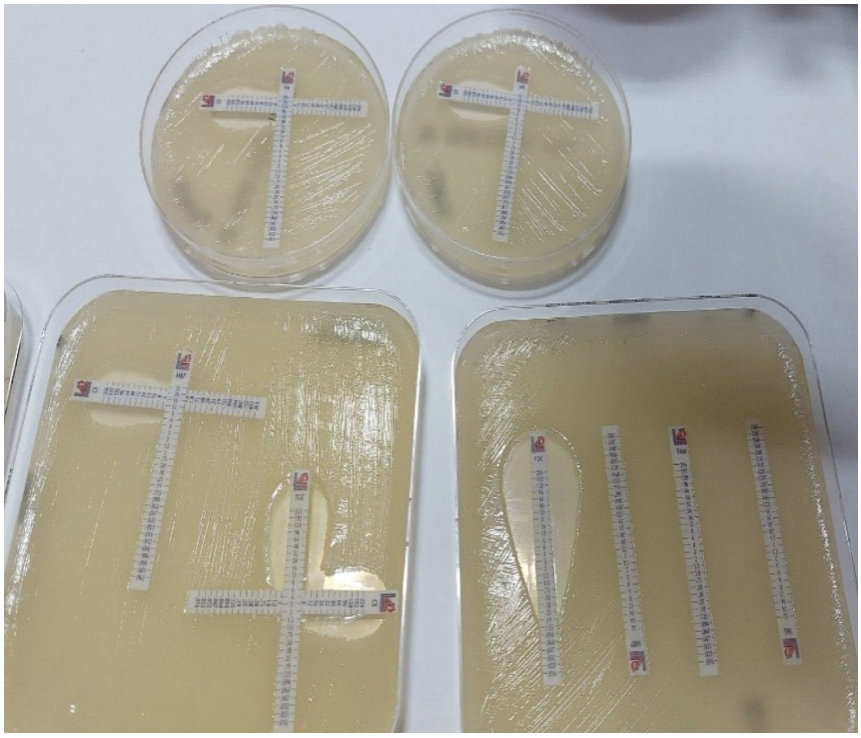

Figure 1 | **Synergy study of multidrug-resistant *Acinetobacter baumannii*.**

flected susceptibility only to colistin with a MIC ≤ 0.5 mg/L and to cefiderocol with MIC ≤ 0.125 mg/L. Hernández-Torres et al. demonstrated in their study that the use of therapeutic combinations such as colistin + tigecycline, colistin + meropenem, colistin + vancomycin or colistin + rifampicin, constituted a positive interaction in which significantly greater activity was obtained than expected in monotherapy in severe infections. Despite this scientific evidence, it was not possible to apply this therapeutic combination, because after its study, it was concluded that our pathogen did not present synergies (Figure 1). Finally, based on the patient's clinical situation and the data obtained, it was decided to prescribe colistin + cefiderocol bitherapy, despite the fact that the clinical practice guidelines of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) [5] and Infectious Diseases Society of America (IDSA) [6] advise against the use of cefiderocol in AB infections due to the results of the phase III CREDIBLE-CR clinical trial in which patients with severe AB infections treated with cefiderocol had higher mortality than those treated the best available therapy at the time. However, our patient responded favorably. In short, cefiderocol is a new siderophore cephalosporin, which differs from the mechanisms of action usually known, making it one of the best therapeutic alternatives in patients with severe AB-MDR infections despite its limited evidence [7].

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest

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Neisseria meningitidis, más allá de la afectación del sistema nervioso central

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Estimado Editor: *Neisseria meningitidis* es una causa importante de infección del sistema nervioso central así como de sepsis a nivel mundial, con alto índice de mortalidad secundaria a su alta patogenicidad [1-2]. Sin embargo, son pocos los casos reportados de neumonía en la literatura, en torno a 344 entre los años 1906 y 2015, a pesar de ser la segunda manifestación orgánica más frecuente [2].

Presentamos un caso de neumonía adquirida en la comunidad por *N. meningitidis*. Se trata de una mujer de 94 años que como antecedentes relevantes presenta una hepatopatía crónica sin hipertensión portal por infección crónica de hepatitis C y Gamapatía monoclonal de significado incierto (GMSI) Kappa. El 10 de noviembre de 2022 acude al Servicio de Urgencias derivada desde su Residencia por episodio de disnea, ruidos respiratorios y fiebre de 38,5ºC. La paciente el día previo al ingreso presentó dos episodios de vómitos alimenticios sin otra clínica abdominal concomitante. A su llegada a Urgencias precisa aporte de oxigenoterapia (O_2) mediante gafas nasales a 4 litros para mantener saturaciones de oxígeno por encima de 92%. A la auscultación destacaba murmullo vesicular disminuido con roncus dispersos. Se solicitan analítica sanguínea que mostraba elevación de reactantes de fase aguda con proteína C reactiva de 9,6 mg/dL y procalcitonina de 1,46 ng/mL junto con leucocitosis de 16.500 con neutrofilia de 14.960; y radiografía de tórax donde se observaban 2 condensaciones en pulmón derecho compatibles con dos focos neumónicos (Figura 1). Para estudio etiológico se extrae frotis nasofaríngeo de virus respiratorios (incluye Virus respiratorio sincitial, Influenza A y B y *SARS CoV2*) y antigenuria de *Legionella* y neumococo con resultado negativo. Ante cuadro compatible con neumonía adquirida en la comunidad se inicia antibioticoterapia empírica con ceftriaxona 2g cada 24h previa extracción de 2 hemocultivos pareados; para cubrir tanto *Streptococcus neumoniae*

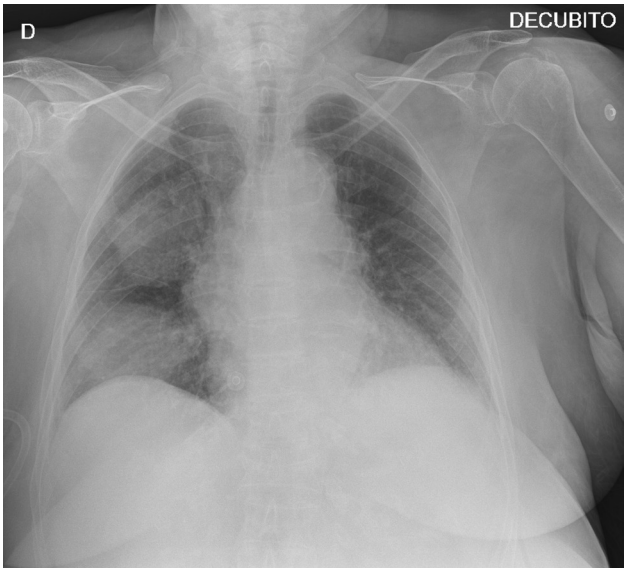

Figura 1 | **Radiografía de tórax anteroposterior realizada el día del ingreso. Se observan 2 condensaciones en pulmón derecho, compatibles con focos neumónicos.**

como *Haemophilus influenzae* como agentes etiológicos más frecuentes y según las sensibilidades de estos microorganismos en nuestro medio. A las 24h de inicio del tratamiento se objetivó aislamiento de *N. meningitidis* sensible a todos los antimicrobianos testados en los 4 frascos de hemocultivos. Aunque en nuestro centro se disponen de técnicas de inmunoensayo para la determinación del serotipo, este procedimiento únicamente es utilizado en investigación y no durante la práctica clínica habitual, dado que no modifica el manejo clínico del paciente. A pesar de mantener O2, antibioticoterapia dirigida y fluidoterapia intensiva la paciente mostró empeoramiento clínico-radiológico (Figura 2) progresivo con mal control sinto-

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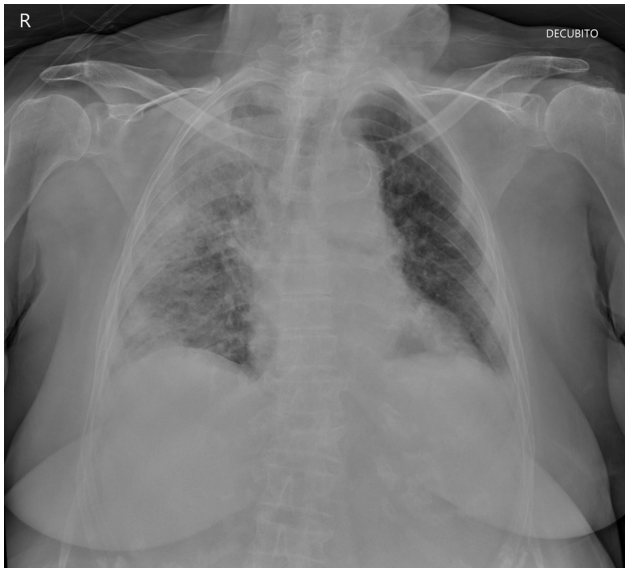

Figura 2 **Radiografía de tórax anteroposterior realizada en día + 7 desde inicio del tratamiento. Se objetiva afectación extensa de todo el hemitórax derecho, empeoramiento en relación a exploración del día del ingreso.**

mático de disnea e inquietud a pesar de midazolam y morfina, precisando sedación terminal. La paciente fallece una semana después de su ingreso en planta.

N. meningitidis es un diplococo gramnegativo, aerobio, inmóvil, capsulado y productor de endotoxinas. Se conocen al menos 13 serogrupos de meningococo identificados según el polisacárido capsular [1-3]. La transmisibilidad, virulencia y la capacidad invasiva varía dependiendo del serotipo. La mayoría de los serogrupos no son capaces de producir enfermedad en pacientes inmunocompetentes. Los tipos B, Y, W-135 son los que se relacionan con mayor frecuencia con neumonías [4]. El único huésped del meningococo es el humano, pudiendo estar presente en la naso-orofaringe hasta en un 10% de la población como portador [5]. Su mecanismo de transmisión es por contacto de persona a persona, por inhalación de gotas respiratorias o por microaspiraciones de secreciones de la orofaringe [4-5]. Pacientes en edades extremas de la vida, inmunocomprometidos (mieloma múltiple, tumores sólidos en tratamiento quimioterápico, VIH...), esplenectomizados, asplenia funcional o aquellos con enfermedades autoinmunes o en tratamiento inmunosupresor son los de mayor riesgo [4-5] para padecer neumonía causada por *N. meningitidis*; tal y como se refleja en nuestro caso (edad avanzada y GMSI).

Las manifestaciones clínicas de la neumonía causada por meningococo no se pueden discernir de las causadas por patógenos comunes, ya que se manifiesta como un cuadro febril con tos, expectoración purulenta y dolor pleurítico [3-4]. El diagnóstico se basa en la identificación del microrganismo en muestras estériles como cultivos de sangre o líquido pleural; ya que el aislamiento en cultivo de esputo no siempre es identificado como patógeno debida a la alta prevalencia de pacientes portadores asintomáticos [3-5]. A nivel radiológico el patrón lobar con afectación de lóbulo inferior derecho es la más frecuente.

El tratamiento empírico de las infecciones causadas por *N. meningitidis* se basa en la administración de cefalosporinas de 3º generación [1-5] como cefotaxima y ceftriaxona; debida a la aparición de resistencias a nivel de las PBP2 (penicillin binding protein 2). También son válidos regimenes de carbapenémicos (en caso de alergia a cefalosporinas), aztreonam o fluoroquinolonas (en caso de alergia a betalactámicos) [3]. Debida a la alta mortalidad la identificación y el tratamiento precoz de las infecciones causadas por este germen son de vital importancia [5].

En conclusión, la neumonía por meningococo es una patología infradiagnosticada en nuestro medio debido a que las manifestaciones clínicas son similares a las neumonías causadas por otros patógenos y el alto porcentaje de portadores asintomáticos. Es por ello, que recomendamos considerar a este patógeno como agente causal de neumonías, sobre todo en aquellos pacientes que presentan factores de riesgo, tal y como se refleja nuestro caso clínico.

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CONFLICTO DE INTERESES

Los autores declaran no tener conflicto de intereses.

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Letter to the editor

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Non-Candida isolates from blood cultures and intra-abdominal samples: data derived from a multicentre prospective study conducted in Madrid

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Sir,

Since most surveillance studies focus on candidaemia, non-Candida species such as *Saccharomyces cerevisiae*, *Cryptococcus* spp, *Trichosporon* spp, *Rhodotorula* spp, or *Magnusiomyces* spp, among others, have received little attention [1]. Emerging non-Candida spp might account for up to 2.8% of fungaemia episodes [2-6] and are characterised by diminished susceptibilities to systemic antifungal agents. We recently reported the epidemiology and antifungal susceptibility of *Candida* spp sourcing from blood cultures and intra-abdominal samples from patients under care at 16 hospitals in Madrid (Spain) from January 2019 to December 2022 (CANDIMAD study) [7]. Here we describe the non-Candida species distribution and their antifungal susceptibility collected in the CANDIMAD study. Isolates, one per species, patient, and compartment, were identified by molecular methods, and subjected to antifungal susceptibility testing to amphotericin B, azoles, echinocandins and ibrexafungerp according to the EUCAST E. Def 7.3.2 method [8].

We detected a total of 25 non-Candida isolates sourcing from blood cultures (n=12) or intra-abdominal samples (n=13; peritoneal samples [n=11], liver samples [n=2]) that represented 1.1% (n=12/1,101) and 1.3% (n=13/1,031) of isolates from blood cultures and intra-abdominal samples, respectively (Figure 1). Non-Candida yeasts were found in 1.3 % (n=25/1,912) of the patients (*Candida* spp were simultaneously found in 8/25 patients). Interestingly, higher species diversity was found in isolates from blood cultures; the species found in intra-abdominal samples were also found in blood culture isolates except for *S. cerevisiae*, which was exclusively found in intra-abdominal samples. Blood-cultured isolates were mainly sourced from patients in medical (42%) or ICU wards (33%), whereas intra-abdominal isolates were mainly sourced from patients in surgery wards (77%). The number of isolates detected per year were 12 in 2019, 8 in 2020, and 5 in 2021.

Antifungal MIC ranges against the isolates were: amphotericin B, 0.125 – 4 mg/L; fluconazole 0.5 - >64 mg/L; voriconazole, 0.008 – 8 mg/L; posaconazole, 0.016 – 2 mg/L; isavuconazole, 0.016 - 2 mg/L; micafungin, 0.03 - >8 mg/L; anidulafungin, 0.016 - >8 mg/L; and ibrexafungerp, 0.25 - >8 mg/L. MIC distributions broken down per species is shown in Table 1. Clinical breakpoints to classify these species as resistant or susceptible according to EUCAST methodology are absent with the exception of amphotericin B against *Cryptococcus neoformans*; ECOFFS are only available for amphotericin B against *Saccharomyces cerevisiae*, and amphotericin B, voriconazole and posaconazole against *Cryptococcus neofor-*

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†In Memoriam

Table 1 **Minimum inhibitory concentration (MIC) distributions of the eight antifungal drugs used against the species tested**

	MIC distributions (no. of isolates at each MIC, in mg/L)													No. isolates (%)	
	≤0.016	0.03	0.06	0.125	0.25	0.5	1	2	4	≥8	16	32	≥64	Non-wild type	Resistant
Saccharomyces cerevisiae (n= 9)															
Amphotericin B	-	-	0	4	3	2	0	0	0	0	-	-	-	0 (0)	ND
Fluconazole	-	-	0	0	0	0	1	2	3	1	1	0	1	ND	ND
Voriconazole	0	1	6	0	1	0	1	0	0	0	-	-	-	ND	ND
Posaconazole	0	0	1	1	4	2	1	0	0	0	-	-	-	ND	ND
Isavuconazole	1	3	3	0	2	0	0	0	0	0	-	-	-	ND	ND
Micafungin	0	1	1	6	1	0	0	0	0	0	-	-	-	ND	ND
Anidulafungin	1	0	2	5	1	0	0	0	0	0	-	-	-	ND	ND
Ibrexafungerp	0	0	0	0	1	6	2	0	0	0	-	-	-	ND	ND
Trichosporon spp (n= 5)															
Amphotericin B	-	-	0	0	0	1	0	2	2	0	-	-	-	ND	ND
Fluconazole	-	-	-	0	0	1	1	0	2	0	0	1	0	ND	ND
Voriconazole	2	1	1	0	0	1	0	0	0	0	-	-	-	ND	ND
Posaconazole	0	0	3	0	0	1	1	0	0	0	-	-	-	ND	ND
Isavuconazole	2	0	1	0	0	0	1	1	0	0	-	-	-	ND	ND
Micafungin	0	0	0	0	0	0	0	0	0	5	-	-	-	ND	ND
Anidulafungin	0	0	0	0	0	0	0	0	0	5	-	-	-	ND	ND
Ibrexafungerp	0	0	0	0	0	1	0	0	3	1	-	-	-	ND	ND
Magnusiomyces capitatus (n= 4)															
Amphotericin B	-	-	0	0	0	2	2	0	0	0	-	-	-	ND	ND
Fluconazole	-	-	-	0	0	0	0	0	1	2	0	1	0	ND	ND
Voriconazole	0	0	0	3	0	1	0	0	0	0	-	-	-	ND	ND
Posaconazole	0	0	0	1	2	1	0	0	0	0	-	-	-	ND	ND
Isavuconazole	0	0	1	0	1	1	0	1	0	0	-	-	-	ND	ND
Micafungin	0	0	0	0	0	0	0	1	0	3	-	-	-	ND	ND
Anidulafungin	0	0	0	0	0	0	0	2	2	0	-	-	-	ND	ND
Ibrexafungerp	0	0	0	0	1	0	1	1	0	1	-	-	-	ND	ND
Rhodotorula mucilaginosa (n= 3)															
Amphotericin B	-	-	0	1	2	0	0	0	0	0	-	-	-	ND	ND
Fluconazole	-	-	-	0	0	0	0	0	0	0	0	0	3	ND	ND
Voriconazole	0	0	0	0	0	0	0	2	0	1	-	-	-	ND	ND
Posaconazole	0	0	0	0	1	0	0	2	0	0	-	-	-	ND	ND
Isavuconazole	0	0	1	0	0	1	1	0	0	0	-	-	-	ND	ND
Micafungin	0	0	0	0	0	0	0	0	0	3	-	-	-	ND	ND
Anidulafungin	0	0	0	0	0	0	0	0	0	3	-	-	-	ND	ND
Ibrexafungerp	0	0	0	0	0	0	0	0	0	3	-	-	-	ND	ND
Cryptococcus neoformans (n= 2)															
Amphotericin B	-	-	0	0	2	0	0	0	0	0	-	-	-	0 (0)	0 (0)
Fluconazole	-	-	-	0	0	1	0	2	0	0	0	0	0	ND	ND
Voriconazole	1	1	0	0	0	0	0	0	0	0	-	-	-	0 (0)	ND
Posaconazole	1	0	1	0	0	0	0	0	0	0	-	-	-	0 (0)	ND
Isavuconazole	0	1	1	0	0	0	0	0	0	0	-	-	-	ND	ND
Micafungin	0	0	0	0	0	0	0	0	0	2	-	-	-	ND	ND
Anidulafungin	0	0	0	0	0	0	0	0	0	2	-	-	-	ND	ND
Ibrexafungerp	0	0	0	0	0	0	0	1	1	0	-	-	-	ND	ND
Kodamaea ohmeri (n= 1)															
Amphotericin B	-	-	0	0	1	0	0	0	0	0	-	-	-	ND	ND
Fluconazole	-	-	-	0	0	0	0	0	1	0	0	0	0	ND	ND
Voriconazole	0	1	0	0	0	0	0	0	0	0	-	-	-	ND	ND
Posaconazole	0	1	0	0	0	0	0	0	0	0	-	-	-	ND	ND
Isavuconazole	0	0	0	1	0	0	0	0	0	0	-	-	-	ND	ND
Micafungin	0	0	0	0	0	1	0	0	0	0	-	-	-	ND	ND
Anidulafungin	0	0	0	0	0	0	0	0	0	1	-	-	-	ND	ND
Ibrexafungerp	0	0	0	0	0	0	1	0	0	0	-	-	-	ND	ND
Exophiala dermatitidis (n= 1)															
Amphotericin B	-	-	0	0	1	0	0	0	0	0	-	-	-	ND	ND
Fluconazole	-	-	-	0	0	0	0	0	1	0	0	0	0	ND	ND
Voriconazole	0	1	0	0	0	0	0	0	0	0	-	-	-	ND	ND
Posaconazole	0	1	0	0	0	0	0	0	0	0	-	-	-	ND	ND
Isavuconazole	0	0	1	0	0	0	0	0	0	0	-	-	-	ND	ND
Micafungin	0	0	1	0	0	0	0	0	0	0	-	-	-	ND	ND
Anidulafungin	0	0	1	0	0	0	0	0	0	0	-	-	-	ND	ND
Ibrexafungerp	0	0	0	0	0	0	0	0	1	0	-	-	-	ND	ND

"-", antifungal concentration not tested. "ND", not determined as either breakpoints or ECOFFs were not available

[a]Underlined values indicate non-wild-type isolates according to ECOFFs, and values in bold indicate resistant isolates [9]

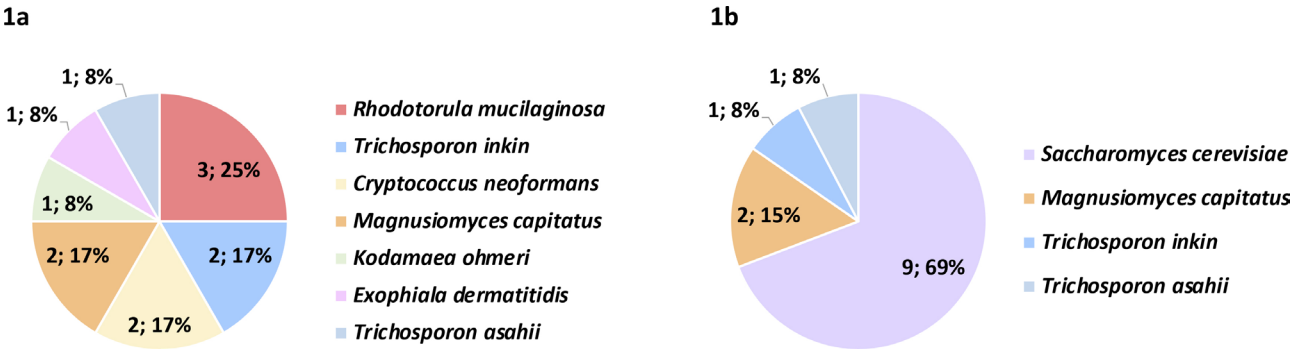

Figure 1 | **Non-Candida species found in blood cultures (1a) or intra-abdominal samples (1b)**

mans [9]. In those cases we did not find any resistant/non-wild type isolate but echinocandins and ibrexafungerp presented high MICs against the *Trichosporon*, *Magnusiomyces*, *Rhodotorula*, and *Cryptococcus* isolates studied (Table 1). If all isolates are considered intrinsically echinocandin-resistant, then the overall echinocandin resistance rate would rise from 0.5% to 1.5% ($P<0.05$) in blood cultures, and from 1.0% to 2.2% ($P<0.05$) in intra-abdominal samples. Likewise, adopting the non-species-specific fluconazole EUCAST breakpoint (resistant >4 mg/L) [10], a total of n=10 isolates should be considered fluconazole-resistant (*Magnusiomyces capitatus* [n=3], *Rhodotorula mucilaginosa* [n=3], *Saccharomyces cerevisiae* [n=3], and *Trichosporon asahii* [n=1]), and the overall fluconazole resistance rate would also rise slightly from 9.1% to 9.5% ($P>0.05$) in blood cultures, and from 8.2% to 8.4% ($P>0.05$) in intra-abdominal samples.

In conclusion, we observed that non-Candida yeasts represented 1.1% and 1.3% of isolates from blood cultures and intra-abdominal samples, respectively. Considering these species as a cause of fungaemia will lead to increased rates of echinocandin resistance given the intrinsically diminished susceptibility of the species to these drugs. The future setting of ECOFF and clinical breakpoints may offer clinicians better guidance in the management of patients with invasive infections caused by non-Candida yeasts.

ETHICAL CONSIDERATIONS

This study was approved by the Ethics Committee of the Gregorio Marañón Hospital (CEim; study no. MICRO.HGUGM.2019-001).

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CONFLICT OF INTEREST

JG has received funds for participating in educational activities organized on behalf of Gilead, Pfizer, Mundipharma, and MSD; he has also received research funds from FIS, Gilead, Scynexis, F2G, Mundipharma, and Cidara, outside the submitted work.

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Letter to the Editor

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Nirmatrelvir/ritonavir as a possible treatment for Long-COVID

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Sir,

It is estimated that about 10% of patients who have been infected with SARS-CoV-2 worldwide suffer from Long-Covid, about 65 million people [1]. Although we are beginning to know its pathophysiology, there is still no evidence on its treatment. We present the case of a patient with persistent prolonged symptoms who had an optimal response to nirmatrelvir/ritonavir 2 years after acute infection.

A 38-year-old woman with a history of psoriasis (untreated and well controlled) who, after receiving the first dose of Pfizer-BioNTech® vaccine on January 13, 2021, presented with headache, fever of 38ºC and myalgias. Given the persistence of symptoms after 48 hours, RT-PCR against SARS-CoV-2 (ARGENE® SARS-COV-2 R-GENE®) was performed and was positive. No antiviral treatment was administered. Anosmia, ageusia and dry cough were added to the referred symptomatology. On February 8, serology was performed, detecting IgG against protein S of SARS-CoV-2 by chemiluminescence technique (CLIA) in automated equipment (Liaison® SARS-CoV-2 S1/S2 IgG). Given the persistence of symptoms, including hyperthermia, corticotherapy was started at medium doses for 3 weeks. She presented better thermal and other symptom control but persisted with afternoon low-grade fever. He was referred to the Post-Covid-19 consultation of the Infectious Diseases Unit.

In a first contact, physical examination was normal and complementary tests were requested in which only elevated values of erythrocyte sedimentation rate [ESR: 20 mm/h (0-10)] and D-dimer [900 ng/mL (0-500)], with autoimmunity, hemogram, proteinogram, acute phase reactants, immunoglobulins, lymphocyte populations, liver enzymes, ions, hormone and vitamin studies were unremarkable. Serology was negative and RT-PCR against SARS-CoV-2 was repeated several times and was always negative. A second course of corticosteroids was started, with no response, persisting with poorly tolerated afternoon low-grade fever with headache, asthenia, myalgia and atypical chest pain. A complete computed axial tomography (CAT) scan was performed, showing adenopathies of non-significant size at the cervical, retroperitoneal and mesenteric levels. A positron emission tomography (PET) scan was requested, which only reported diffuse inflammatory gastric hypermetabolism, so gastroscopy was performed with biopsies that ruled out pathology including infection by *Tropheryma whipplei*. The initial analytical study was repeated 10 months after the onset of the clinical picture, adding tumor markers and extraction of blood cultures, and again the results were irrelevant.

One year after the onset of symptoms and due to the persistence of a poorly tolerated daily afternoon fever, treatment with colchicine was tried as an immunomodulator and a genetic study of autoinflammatory syndrome was requested, which was negative. After starting colchicine, the patient was afebrile and her general symptoms improved. The treatment was maintained for 5 months with good control and after its withdrawal she again presented low-grade fever and worsening of the previous symptoms. Colchicine was reintroduced at the same dose and again she was asymptomatic.

A few weeks later, despite continuing with colchicine, the low-grade fever reappeared and she presented a significant clinical deterioration that did not improve despite increasing the dose. Finally, two years after the onset of symptoms and after the approval by a multidisciplinary committee after the good response described by Peluso et al. of 4 patients with Long-Covid [2], we withdrew colchicine and started antiviral treatment against SARS-CoV-2 (off-label) with nirmatrelvir/ritonavir for 5 days with immediate resolution of symptoms. After 6 weeks of treatment, she has not presented low-grade fever or the symptoms previously mentioned.

Long-Covid has been more frequently associated with ages between 36-50 years, female sex and independently of the

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severity of the acute infection [3]. Multiple hypotheses have been proposed, including the persistence of viral activity from certain reservoirs [4,5]. We suggest that, in the present case, viral persistence would have triggered a persistent inflammatory response, causing the symptomatology. Colchicine would have modulated the inflammatory response, thus explaining the good symptomatic control with its administration and the worsening with withdrawal.

After a literature review, we found only 4 case reports describing a clear improvement after the use of nirmatrelvir/ritonavir in patients with persistent symptoms after acute infection [2]. However, in most of them it was administered a few weeks later and after re-infection and none of them had such a prolonged and disabling evolution as in the referred patient. In addition, a recent preprint shows a decrease in the incidence of Long-Covid with the use of nirmatrelvir/ritonavir in the acute phase, supporting the practice [6].

In conclusion, the persistence of viral activity after acute infection could be a cause of Long-Covid and in this sense, the use of nirmatrelvir/ritonavir is a treatment option. However, the evidence is scarce and there are probably other influencing factors such as immune dysregulation, alteration of the microbiota or vascular microtombosis and endothelial dysfunction [5].

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CONFLICT OF INTEREST

Authors declare no conflict of interest

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Carta al Director

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Detección de co-infección por el virus Herpes simple tipo 1 y tipo 2 en úlceras genitales femeninas

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Estimado Editor:

Las infecciones causadas por el virus herpes simplex (VHS) son una entidad muy frecuente que afecta a la mayoría de la población general. El VHS se subdivide en dos tipos, el herpes simple tipo 1 (VHS-1) y el herpes simple tipo 2 (VHS-2) a partir de consideraciones genéticas, antigénicas, biológicas y epidemiológicas [1]. El VHS-1 es el principal causante de las infecciones que afectan al área craneal y cervical, siendo la gingivoestomatitis la principal manifestación clínica de la primoinfección. La primoinfección se adquiere precozmente en la infancia y las reactivaciones se producen casi siempre en la misma zona anatómica. La infección por el VHS-2 debe considerarse como una enfermedad de trasmisión sexual pues su principal vía de contagio durante la primoinfección es la de tipo sexual (infección genital). Como consecuencia de ello su adquisición es mas tardía y coincide generalmente con el inicio de la actividad sexual; las reactivaciones del VHS-2 ocurren casi exclusivamente en la misma zona anatómica [1]. Varios estudios han demostrado que el VHS-1 también es capaz de provocar infecciones genitourinarias en un porcentaje que puede oscilar entre el 10-35%. Además se ha observado un importante incremento de las mismas en los últimos años debido al aumento de las prácticas sexuales orogenitales [1,2]. La co-infección genital entre ambos herpesvirus es una entidad poco descrita y por ello nos ha parecido interesante presentar este caso clínico.

Mujer africana de 21 años que acudió a urgencias por prurito y dolor genital y vaginal múltiple y difuso de 4 días de evolución sin fiebre. Había tenido dos días antes sangrado y flujo vaginal espeso. En los genitales externos se observó amplias zonas eritematosas perianales y vulvares con lesiones vesiculares y ulcerosas múltiples en introito vaginal y labios mayores y menores. No se detectaron adenopatías inguinales. La exploración general fue normal y la prueba frente VIH fue negativa. Se tomaron muestras de las lesiones genitales que fueron remitidas para su diagnóstico microbiológico. La paciente fue diagnosticada de herpes genital múltiple y fue dada de alta con tratamiento de aciclovir 400 mg/8 horas/día durante 10 días y una crema anestésica con lidocaína.

Para el cultivo bacteriano y fúngico, que fueron negativos, se siguieron las recomendaciones de la SEIMC [3]. La detección de *Neisseria gonorrhoeae*, *Chlamydia trachomatis* y *Mycoplasma* spp. se realizó mediante una PCR múltiple (STI Assay; Alinity-m, Abbott). En la PCR realizada frente a los herpesvirus (Allplex Neurotropic Viruses; Seegen) se detectó de forma simultánea la presencia de VHS-1 y VHS-2. Se repitió la determinación y el resultado confirmó el primer diagnóstico. No se realizó cultivo celular por no disponer de esta metodología y no se realizó serología frente a los herpesvirus por el antecedente previo de otro episodio de herpes genital.

Tal y como se ha mencionado las co-infecciones genitales por los dos tipos herpéticos parecen una entidad poco frecuente. Este dato se confirmó por Obisesan et al. [4] en Sudáfrica al comunicar que sólo el 2,3% de los hombres y el 4,5% de las mujeres con úlceras genitales herpéticas estaban coinfectados por ambos tipos detectados mediante PCR específica. Sin embargo, las coinfecciones entre el VHS-2/VIH eran del 13,6% en hombres y del 54,5% en mujeres y entre el VHS-1/VIH del 2,3% y 4,5% respectivamente. Las mujeres presentan el doble de infecciones genitales por el VHS-2 o mixtas que los hombres [1,4].

Los estudios de seroprevalencia en adultos de 18-49 años descritos por Beydoun et al. [5] en Estados Unidos demuestran que en los pacientes con úlceras genitales herpéticas, el 21,6% eran positivos frente al VHS-1, el 34,8% frente al VHS-2 y el 39,2% frente a ambos virus (co-infección). Los porcentajes detectados entre la población sin herpes genital reconocido se estimó que el 48,4% presentaban anticuerpos frente al VHS-1, el 7,4% frente al VHS-2 y el 11,8% frente ambos virus, observándose diferencias significativas. Sin embargo debe tenerse en

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cuenta que la seroprevalencia frente a estos herpesvirus varía ampliamente dependiendo de la edad, sexo, étnia, área geográfica, actividad sexual y situación socioeconómica y sanitaria [1,4,5]. Así en el Reino Unido la seroprevalencia frente al VHS-2 es del 4% pero en Bulgaria del 24% [6].

Las infecciones herpéticas mixtas VHS-1/2 no parecen presentar una mayor gravedad, aunque si parecen afectar a zonas mas amplias que las causadas por el VHS-2 en solitario, como en nuestro caso [2]. Se ha postulado que los anticuerpos frente al VHS-1 podrían aportar cierto grado de protección cruzada frente al VHS2, pero no existen datos concluyentes [4]. El tratamiento debe ser aciclovir independientemente del tipo herpético implicado, ya que ambos se han mostrado sensibles a este antiviral.

Aunque el diagnóstico de la mayoría de las infecciones genitales herpéticas se realiza en la exploración clínica, es muy importante la toma de muestras para llegar a un diagnóstico etiológico definitivo que permita obtener resultados sorprendentes como el de este caso.

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CONFLICTO DE INTERESES

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Letter to the Editor

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Do face masks increase the rate of the *Staphylococcus aureus* nasal carriers?

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Sir,

Staphylococcus aureus is a Gram-positive bacteria relevant in clinical practice. This microorganism can be part of the skin and mucosal microbiota, but it can also cause diverse infections.

When colonizing *S. aureus* presents its main reservoir in the nasal mucosa, being this location one of the best to evaluate *S. aureus* carriage. There has also been described a correlation between nasal carriage and the possibility of suffering an infection [1]. The prevalence of colonization in healthy population is very high. Longitudinal studies suggest that 20% of the population are persistent carriers, 30% of the population are intermittent carriers and 50% are not colonized [2].

In a study performed at the Complutense University of Madrid in pre-clinical Podiatry students over two academic years, between 2018-19 and 2019-20, a prevalence of 22.7% of *S. aureus* nasal carriers was observed before the pandemic and the widespread use of face masks [3].

Several studies have shown the efficacy of face masks in preventing the transmission of viral diseases [4], as well as in preventing bacterial diseases such as meningitis [5]. However, as far as we know no studies have been found in the literature that analyse the impact of continuous use of face masks on the pandemic in the *S. aureus* carriage.

The objective of this study was to compare the evolution of *S. aureus* nasal carriage in a population of pre-clinical students of Podiatry and Medicine in the COVID-19 pandemic, in the 2021-22 academic year with a face mask, and in the academic year 2022-23 without a face mask.

A descriptive and transversal study was conducted in the Microbiology Area of the School of Medicine with 162 voluntary students of the Complutense University of Madrid. Out of these, 37 and 58 students coursed Podiatry in the academic year 2021-22 and 2022-23, respectively; whilst 31 and 36 coursed Medicine in the academic year 2021-22 and 2022-23, respectively.

Since the return of face-to-face classes in the academic year 2021-22, the use of face masks was mandatory in Spain due to the COVID-19 pandemic and, the use of face masks indoors ceased to be mandatory on 22nd April 2022. Therefore, in the academic year 2022-23 the use of face masks was no longer mandatory. In the Figure 1, we can observe the chronological sequence of when the samples were taken compared to each modification of COVID-19 pandemic regulation.

The samples were collected during the practical classes of Microbiology. Each swab was rubbed against the anterior of the nasal vestibular wall of both nares and immediately placed in 10 mL of Mueller-Hilton broth (BD™ Difco™) at 7,5% NaCl concentration and was then incubated at 35ºC for 24 hours. Afterwards, swabs were vortexed for 20 s before plating onto Mannitol salt agar (BD™ Difco™), incubated at 35°C for 24 hours. The isolates were characterized as *S. aureus* based on morphology, Gram stain, catalase test, coagulase test, and mannitol salt agar fermentation. Once *S. aureus* was identified, methicillin susceptibility was determined by disk diffusion.

A Fisher's test was performed to compare the different proportions of *S. aureus* carriers during the academic years of the podiatry degree and the medical degree separately. For the joint analysis, a Chi-square test was performed to compare the different proportions of *S. aureus* carriers during the academic years of the Podiatry degree and the Medicine degree.

In Figure 2 we can observe the evolution of prevalence in *S. aureus* nasal carriage in students of Podiatry and Medicine in both academic years. In Podiatry degree, 11 students (29.7%) and 11 students (19.0%) were *S. aureus* nasal carriers in the academic years 2021-22 y 2022-23, respectively. Regarding Medicine degree, 10 students (32.3%) y 8 students

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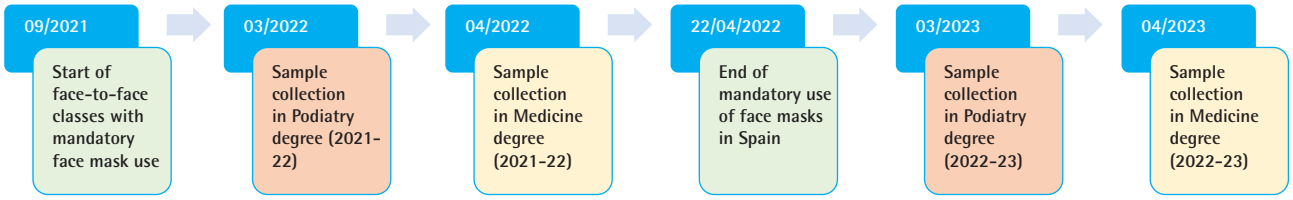

Figure 1 | **Flow chart study**

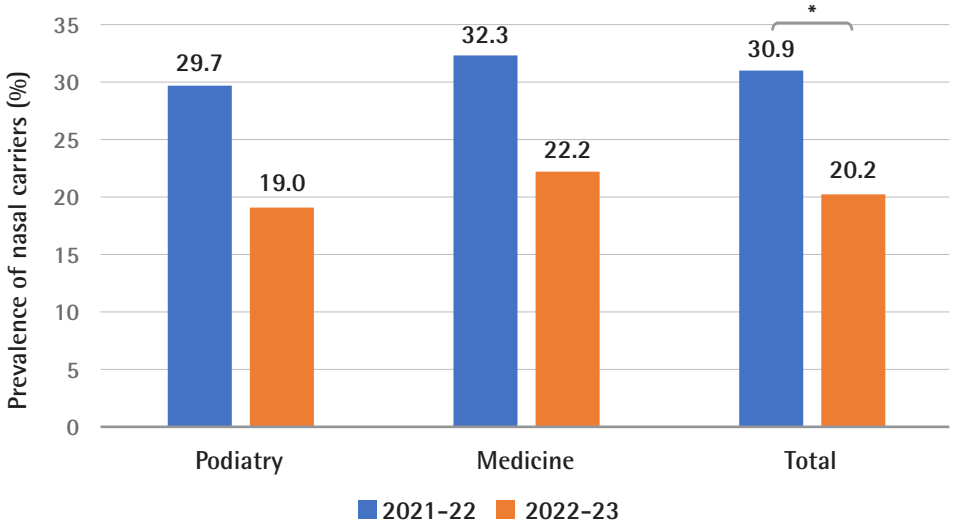

Figure 2 | **Prevalence of nasal carriers in the pre-clinical students of Podiatry and Medicine in the studied academic years.**

*p=0.0004

(22.2%) were *S. aureus* nasal carriers in the academic years 2021-22 y 2022-23, respectively. In both cases the percentage of *S. aureus* nasal carriers were higher in the year 2021-22 compared to the year 2022-23, however the differences were not statistically significant (p=0.22 and p=0.35). Nevertheless, when all students were analyzed jointly, the percentage of *S. aureus* nasal carrier was statistically higher in the year 2021-22 (30.9%) compared to the year 2022-23 (20.2%) (p=0.0004). In none of the academic years, a methicillin-resistant *S. aureus* was isolated.

The results of the study show a higher prevalence of *S. aureus* nasal carriers in both Podiatry and Medicine students during the mandatory use of face masks in the 2021-22 academic year compared to the 2022-23 academic year. These differences were not statistically significant, probably due to the sample size. However, when analysing the students as a whole, the percentage of *S. aureus* carriers was significantly higher in the 2021-22 academic year compared to the 2022-23 academic year.

If we compare our data with the prevalence percentages of *S. aureus* from previous years, we can see that the data for the 2022-23 academic year are similar to those obtained with students of the Podiatry degree in the 2018-19 and 2019-20 academic years, where a percentage of carriers of 21.4% and 23.6%, respectively, was observed [3].

The use of face masks is known to produce a number of effects, mainly nasal discomfort, breathing difficulties, excessive sweating, and pain around the ears [6,7]. Nasal discomfort may be attributable to the warm air and humidity present under the mask. Wearing a face mask may increase the oral temperature in healthy subjects [8]. Thus, one possible explanation for the increased prevalence of *S. aureus* carriers is that it may be related to the increased temperature and humidity in the nostrils caused by the face masks. Although this bacterium is able to grow between 6°C and 40°C, its optimal growth temperature is between 30°C and 37°C [9].

It has also been observed that factors such as viral mi-

crobiota are able to directly influence the bacterial microbiota [10] Thus, mild viral nasopharyngeal infections lead to an enrichment of aero-tolerant bacteria, including *S. aureus* [10]. The presence of SARS-CoV-2 during the pandemic may also have produced a variation in the nasal microbiota.

It is important to note that this study was conducted in pre-clinical students, as contact with the hospital environment has been observed to be a risk factor for nasal colonisation by *S. aureus*. Thus, a cohort study analysing a class of medical students at the Complutense University of Madrid during their in-hospital training between the third and sixth year at the Hospital Clínico San Carlos showed a statistically significant increase in the prevalence of nasal *S. aureus* carriage, which was 26.9% in students who had not had hospital training and 46.2% in students in the sixth year [11].

The main limitation of the study is that it is not a longitudinal study as the students were not followed up. We can conclude that in a preclinical student population of Podiatry and Medicine students, the use of face masks was correlated with an increased prevalence of *S. aureus* nasal carriers. Our results confirm that active carrier detection of *S. aureus* among future healthcare professionals is necessary to break the possible chain of transmission in different healthcare settings.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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