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LETTER
A preliminary analysis of luspatercept use and expenditure in Italy in the first semester of 2022

Key words
- anemia
- luspatercept
- drug use
- drug expenditure

To the Editor,

We read with interest the article by Pilunni and Navarra [1], in which the authors analysed compassionate use programs (CUPs) in Italy reporting data on the use of twelve different drugs including luspatercept (Reblozyl®). It is a recombinant fusion protein that stimulates the production of erythrocytes allowing late-stage erythroblast differentiation and erythroid maturation [2] and represents a potential treatment for adult patients with transfusion-dependent myelodysplastic syndromes [3] or β-thalassaemia [4]. On November 2021, a marketing authorization was issued for luspatercept by the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) and reimbursed by the National Health System [5] for the treatment of adult patients with transfusion-dependent anaemia caused by very low, low, and intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy, or those with transfusion-dependent beta thalassemia (BT). Luspatercept is available as powder for solution for injection containing 25 mg/vial or 75 mg/vial. The recommended starting dose is 1.0 mg/kg administered once every 3 weeks and it could be increased up to 1.75 mg/kg in non-respondent patients.

In order to evaluate the national consumption of luspatercept in the first semester of 2022, we conducted a preliminary analysis using National Observatory on the Use of Medicinals (OsMed) database of the AIFA, which collects data of the purchase by public health facilities. Moreover, public expenditure, compounded monthly growth rate (CMGR), number of treated patient and cost per patients were estimated.

From January to June 2022, 5,248 packages of luspatercept have been provided in Italy for treatment of targeted patients (2,403 units of 25 mg/vial and 2,845 of 75 mg/vial). The total expenditure was about 8.9 million euros (about 1.9 million euros for 25 mg/vial and about 7 million euros for 75 mg/vial). The CMGR was +37% (from 353,469 euros on January to 2,291,899 euros on June 2022); the steady increase of costs reflects the fact that the various Italian Regions/Autonomous Provinces progressively included luspatercept in the list of drugs that can be purchased by public health facilities. Based on the schedule of administration of luspatercept and the period of utilisation in each Region/Autonomous Province, we estimated that 424 patients were treated with an average increase of 62 patients per month. Moreover, using expenditure data from the OsMed database and the estimated patient number, a cost of 20,800 euros per patient was also estimated. Our estimations are consistent with recent published data on the luspatercept [1] that seems to fills a long-standing gap by providing a much-needed additional treatment option for a subset of adult patients with transfusion-dependent anaemia reducing transfusion burden, transfusion complications and use of iron-chelating agents. At the moment, the medical conditions in which luspatercept can be used for are limited but some studies are investigating its possible use in other haematological and non-haematological diseases with a potential enlargement of the patients who could benefit of this pharmacological treatment. Therefore, it is crucial to continue to collect data about its efficacy and safety in a real-world practice and our analysis, aimed to evaluate the luspatercept use in the first post-authorization semester, represents a starting point in order to perform permanent monitoring of its clinical and economic burden.

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A glimpse into Long COVID characteristics and the mental health impact within a highly vaccinated population: a Malta observational study

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Abstract

Background. Post-acute COVID-19 consequences are gaining global recognition. This study explores Long COVID characteristics and associated mental health impact/s among the highly vaccinated adult population of Malta.

Methods. A social media survey gathered demographics, vaccination, and COVID-19 data. Generalised Anxiety Disorder and Patient Health Questionnaire-9 assessment tools were used for anxiety and depression. Quantitative analyses were performed.

Results. 41% reported Long COVID, mostly female, 30-39 years, absence of chronic disease/s and vaccinated. Shortness of breath commonest persistent symptom among males, and fatigue for females. Significantly higher depression scores were present in Long COVID cohort compared to no persistent symptoms (p=0.001) and never acquiring COVID-19 (p=<0.01). A significant higher anxiety scores was present for Long COVID cohort than never acquiring COVID-19 (p=<0.01).

Conclusions. Long COVID occurs even in healthy individuals and vaccinated, while exacerbating mental health burdens. Urgent action is required to manage Long COVID and preventing the sequela.

Key words

- coronavirus
- vaccines
- population health
- mental health
- post-acute COVID-19 syndrome
- Malta

BACKGROUND

The coronavirus disease 2019 (COVID-19) has spread across the globe resulting in a spectrum of clinical outcomes from asymptomatic to fatal disease [1]. It became evident quite early on that some infected individuals were experiencing persistent symptoms beyond the acute phase due to prolonged viral involvement affecting multiple organs [2]. These individuals were labelled as experiencing Long COVID. Indeed, a plethora of different persistent symptoms were reported among Long COVID individuals [3]. Another pandemic induced problem is the increased mental health burden, especially in terms of stress, anxiety and depression that arose from implemented restrictions, isolation, job loss and fear of acquiring the viral infection [4, 5]. Furthermore, the occurrence of Long COVID also impacts on the mental health of the sufferer [6]. As COVID-19 vaccines became available, it was anticipated that the protection provided by the vaccine lowered the viral infectivity rate as well as the development of Long COVID when compared to unvaccinated [7]. A recent study reported that COVID-19 vaccine inoculation with at least one dose reduces the mental distress among the population [8]. As most countries are moving into the post-acute pandemic phase and vaccination rates have stabilised, it is essential that Long COVID and its associated burden including mental burden, are prioritised in the recovery agenda which brings forward the need for extensive research in this area.

The European Islands of Malta, like the rest of the world, experienced surges in COVID-19 infectivity rates with an estimated loss of 5,478 years of full health over the first year of the pandemic [9]. Indeed, similarities in COVID-19 epidemiological trends and mitigation measures were identified between Malta and other European countries and microstates [10, 11]. Additionally, it was noted that Long COVID led to the highest morbidity over one year in Malta [9]. Malta's COVID-19 vaccination rollout along with the low vaccine hesitancy among the population led to a successful

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rapid vaccination coverage of almost the whole eligible population by summer of 2021 [12]. The end of summer 2021 saw a surge in Delta variant cases and prompted the initiation of a booster dose [13]. The local high vaccination uptake and the fact that Long COVID was a predominant contributor to morbidity prior to vaccination makes Malta an ideal geographical location to evaluate the characteristics of Long COVID. Furthermore, Malta has been recognized by the director of the World Health Organization for the Region of Europe as being an exemplary country for the COVID-19 commitment over the two years of the pandemic [14]. Considering recent findings [7, 8], that a high vaccination rate could decrease the occurrence of Long COVID among populations with a reduction in mental health burden, Malta is the ideal research setting to validate this finding and understand the impact of Long COVID and the mental health burden. This study evaluates the presence and characteristics of Long COVID among the adult population of Malta and their perspectives on the COVID-19 vaccine while assessing anxiety and depression levels among these individuals.

MATERIALS AND METHODS

This study was a cross-sectional study conducted using an anonymous online survey. Google Forms® platform was used to host the survey that was designed by the authors to target adults residing in Malta. The survey was disseminated through social media via a snowball technique between the 25th of January and the 6th of February 2022. Social media is mostly used to share public opinion and its users represent a substantial proportion of the global population, making social media an ideal platform for dissemination of this survey [15]. Indeed, in 2021 it was reported that 420,000 social media users were registered in Malta [16]. Dissemination through snowball technique, also known as responder-driven sampling, was considered adequate due to the sensitivity of some of the questionnaire questions [17]. Additionally this sampling technique was reported to enable asymptotically unbiased estimates [18].

The survey gathered information on the demographic profile of the participants, their medical history, COVID-19 vaccination status, their perspectives on the COVID-19 vaccine, whether they acquired COVID-19 and had persistent symptoms post-acute infection that lasted beyond two months [19]. Additionally, the survey incorporated the GAD-7 (Generalised Anxiety Disorder) assessment tool to evaluate the level of anxiety the participants experienced by providing 7 different concerns with the following question stem "Since the end of Summer (2021), how often have you been bothered by any of the following concerns?" [20]. The PHQ-9 (Patient Health Questionnaire-9) assessment tool was used to evaluate the level of depression by providing 9 different concerns with the following question stem "Since the end of Summer (2021), how often have you been bothered by any of the following concerns?" [21]. The end of summer 2021 saw the shift from a low case number to a surge in COVID-19 cases and mortality in Malta, as well as a high population vaccination coverage with the initiation of the booster dose. This makes this period the ideal starting point to evaluate the anxiety and depression levels among the population.

Ethical approval was granted by the University of Malta Research Ethical Committee (MED-2022-00017).

Data analyses

The GAD-7 score was calculated as per published guidelines [22]. The sum of the GAD-7 questionnaire score for each participant was categorised into ≤4 as having no symptoms; 5-9 as mild symptoms; 10-14 as moderate symptoms and >15 severe symptoms. The PHQ-9 score followed published guidelines where the total score and depression severity were divided and defined as follows: 0- 4 score as "minimal depression"; 5-9 score as "mild depression"; 10-14 score as "moderate depression"; 15-19 score as "moderate severe depression" and 20-27 score as "severe depression" [23]. The GAD-7 and PHQ-9 scores were compared between those that reported to have persistent symptoms (Long COVID-19) and those that had COVID-19 with no persistent symptoms as well as with those that never acquired COVID-19, through Chi Square analysis. Descriptive analyses and chi squared testing for categorical comparisons were performed using Microsoft Excel®.

RESULTS

A total of 611 adults participated in the survey, with 20.20% (n=122) reporting having acquired COVID-19, with a female predominance (71.3%). Out of those having COVID-19, 41% (CI 95%: 32.7-49.9; n=50) reported having symptoms beyond 2 months following their initial diagnosis, with a female majority (82%; CI 95%: 69.0-90.5; n=41). None of the participants suffering from Long COVID-19 were admitted to hospital for their acute infection. Persistent symptoms were mostly reported among the younger age groups, especially those between 30-39 years of age, those that did not suffer from any chronic diseases and were vaccinated. A summary of the Long COVID-19's cohort characteristics is shown in *Table 1*. The commonest persistent symptom reported by males was shortness of breath (33.33% CI 95%: 12.0-54.9; n=3) while fatigue was predominately reported by females (17.1% CI 95%: 8.2-31.6; n=7). Different long-standing symptoms were reported, as can be seen in *Table 2*.

On exploring for anxiety and depression levels using the GAD-7 and PHQ-9 scores *(Figure 1)*, it was noted that those reporting having Long COVID-19 had a significantly higher anxiety score than those never acquiring COVID-19 (p=<0.01). Additionally, the Long COVID-19 cohort had significantly higher moderate and severe depression scores when compared to both those acquiring COVID-19 with no persistent symptoms (p=0.001) and those never acquiring COVID-19 (p=<0.01).

Although the majority opted to be fully vaccinated including taking the booster dose, their perception on the COVID-19 vaccination varied, as shown in *Table 3*. Indeed, a proportion perceived the vaccine to be restricting their freedom (48%) and that the vaccine is responsible for more side-effects than those reported (36%).

Table 1
Long COVID-19 cohort characteristics

		Acquired COVID-19 infection		
		Long COVID (*n*=50)	**No persistent symptoms (*n*=72)**	**Chi *p*-value**
Gender	male	18.0%	36.1%	0.03
	female	82.0%	63.9%	
Age group	18 - 19	0.0%	1.4%	0.04
	20 - 29	10.0%	25.0%	
	30 - 39	62.0%	33.3%	
	40 - 49	16.0%	23.6%	
	50 -59	10.0%	6.9%	
	60 - 69	2.0%	8.3%	
	70 - 79	0.0%	1.4%	
Chronic diseases	yes	16.0%	25.0%	0.23
	no/do not know	84.0%	75.0%	
Vaccination status	vaccinated/boostered	96.0%	80.6%	0.01
	no booster and anti-vax	4.0%	19.4%	
COVID-19 positive following vaccination	yes	47.9%	56.9%	0.36
	no	52.1%	43.1%	

Table 2
Persistent most common symptoms reported by the Long COVID-19 cohort

	Male (*n*=9)	**Female (*n*=41)**
Shortness of breath and back pain	33.3%	4.9%
Aches and pains in joints	11.1%	2.4%
Aches and pains in your joints, fatigue/tired, dizziness	11.1%	2.4%
Aches and pains in your joints, shortness of breath, fatigue/tired, aches in heels	0.0%	4.9%
Headaches	11.1%	0.0%
Headaches, cough, dizziness	11.1%	17.1%
Headaches, aches and pains in the joints, shortness of breath, Dizziness and back pain	0.0%	4.9%
Loss of smell and taste	0.0%	4.9%
Loss of taste and headaches	11.1%	0.0%
Shortness of breath and fatigue	11.1%	7.3%
Shortness of breath and cough	0.0%	4.9%
Back pain	0.0%	4.9%
Fatigue	0.0%	7.3%

DISCUSSION

A proper comprehension of the underlying pathophysiology leading to Long COVID among selected infected COVID-19 positive individuals is still in the early stages although various theories have been put forward including autoimmunity, aberrant immune response/s and virus persistence in immune-privileged sites [24]. Several continuing symptoms have been reported with fatigue and dyspnea being common ones [3, 25, 26], as noted in this study. Despite this, the current study observed a gender specific trend. The higher female susceptibility for Long COVID is consistent with other reports [27]. However in this study, unlike previously reported [28], the Long COVID cohort were mostly previously healthy and did not require hospitalization for their acute infection. It is currently debatable whether vaccination protects against the occurrence of Long COVID [29]. It has been reported that vaccination halves the chance of getting Long COVID, with the over-60s being at greater risk of experiencing this if a breakthrough infection occurs [30, 31]. While this is a relatively small study, the observations cannot be dismissed, where despite high vaccination rates, including uptake of the booster dose across all age groups, a high proportion of Long COVID was reported even among the younger adults (<60 years). Further research is recommended as these observations may have non-trivial public health consequences necessitating urgent action. This is particularly the case since long-term trajectory of this disability is unknown, [32] affecting the young generation with related economic, social and health sequela [33, 34]. It is therefore not surprising that experiencing Long COVID led to different perspectives on the COVID-19 vaccine, although inoculation was perceived as providing protection against the virus, coinciding with another study [35]. Additionally, Long COVID individuals expressed a positive perspective on the importance of mass vaccination especially among the vulnerable population even though vaccines were perceived to be responsible for more side effects than those reported. This demonstrates the individuals' acceptance of vaccines for the common good despite potential misgivings and fear of side effects.

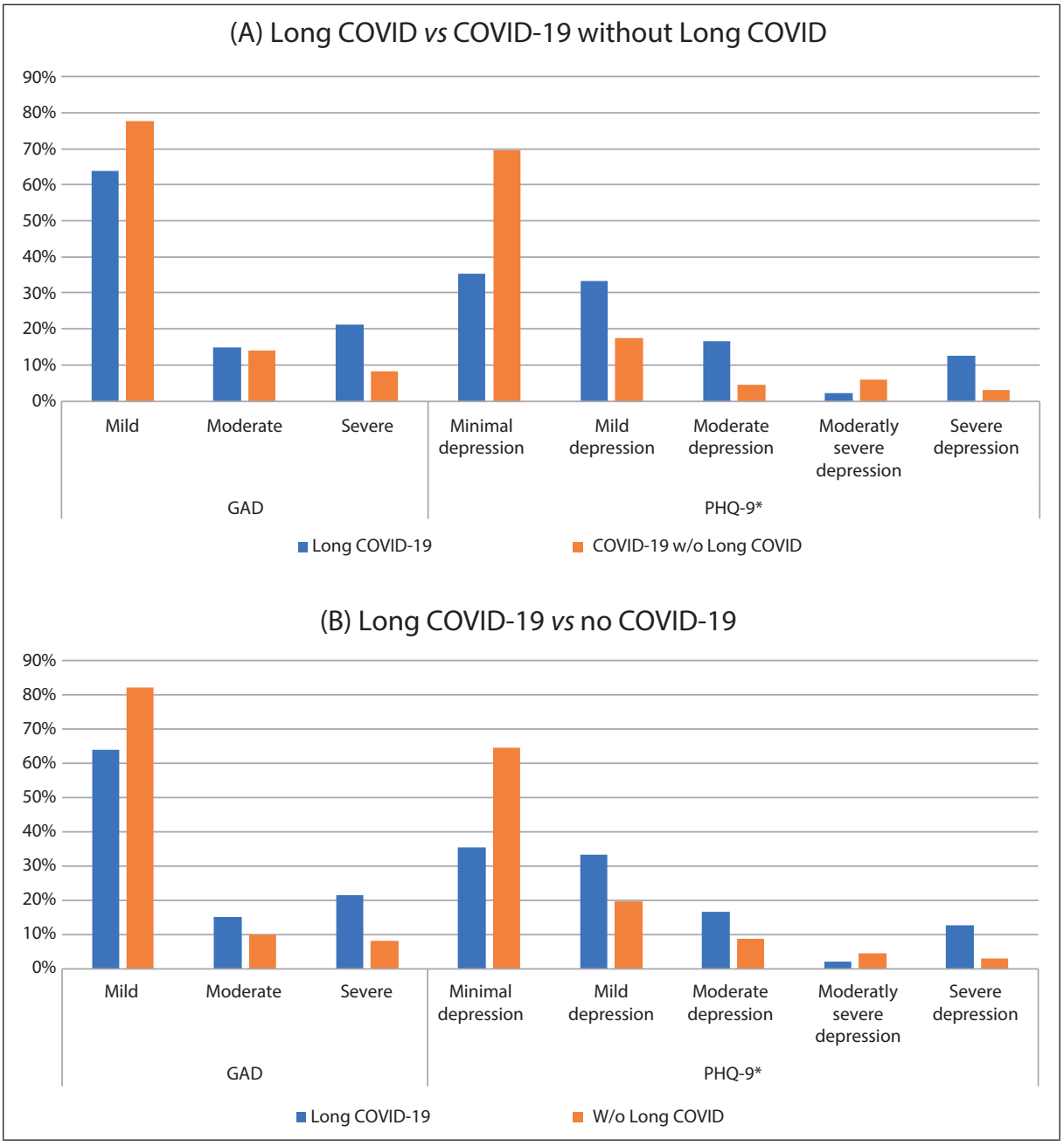

Figure 1
(A) Comparison analyses of the anxiety score (GAD) and depression score (PHQ-9) between the cohorts suffering from Long COVID, acquiring COVID-19 but have no persistent symptoms and (B) Comparative analyses between those suffering from Long COVID and those never acquiring COVID-19.
w/o: without.
*Chi square test between Long COVID cohort and COVID-19 w/o persistent symptoms.
**Chi square test between Long COVID cohort and those never acquiring COVID-19.

Negative perceptions were also evident including a significant impact on the mental health of the affected cohort. The population's mental health burden has been a public health concern since before the onset of the pandemic. The COVID-19 pandemic has driven this burden further exacerbated with the implemented restrictions in addition to COVID-19 morbidity and mortality [36, 37]. The continuous media coverage along with the unpredictable outcome of the disease also contributed to the negative impact on the population's mental health burden [38, 39]. Therefore, acquiring the infection while continuing to suffer from persistent symptoms is expected to take a toll on mental health. This was reflected in this current study. However, as the vaccination rate increased, it was expected to lead to a reduction in the occurrences of Long COVID and the associated mental health impact [6, 8]. Yet, as observed in this study, where most of the population was fully

Table 3
Perspectives of the Long COVID-19 cohort on vaccination

Perspectives on COVID-19 vaccination		Long COVID-19 cohort
The COVID-19 vaccine provides protection from getting the infection	Agree	38%
	Disagree	30%
	Undecided	32%
The COVID-19 vaccine causes more side effects than those reported	Agree	36%
	Disagree	34%
	Undecided	28%
Mass vaccination is essential for the population to be protection against COVID-19	Agree	68%
	Disagree	6%
	Undecided	26%
It is essential to continue wearing masks, maintaining physical distance and hand washing following vaccination	Agree	76%
	Disagree	8%
	Undecided	12%
The COVID-19 vaccine provides long term protection against COVID-19 infection	Agree	12%
	Disagree	48%
	Undecided	40%
Those suffering from health issues should take the vaccine	Agree	60%
	Disagree	10%
	Undecided	28%
The COVID-19 vaccine reduced deaths and hospitalisation	Agree	54%
	Disagree	16%
	Undecided	28%
Taking the COVID-19 vaccine is useless	Agree	6%
	Disagree	58%
	Undecided	34%
The COVID-19 vaccine is the solution to returning to normality	Agree	44%
	Disagree	16%
	Undecided	38%
The COVID-19 vaccine is controlling our lives and freedom	Agree	48%
	Disagree	32%
	Undecided	16%

vaccinated and some even had the booster, the occurrence of Long COVID along with the anxiety and depression aftermath were still evident. A potential reason to the Long COVID occurrence could be the reduced efficacy of the vaccination against the Delta and the Omicron variants [40]. This brings forward the need to investigate further these occurrences and their consequences with the possibility of labelling Long COVID a new chronic disease. The burden of mental health does not appear to be subsiding therefore it is imperative that psychological help is readily available to support affected individuals. Tackling mental health burden should be high up on agenda as its occurrence has multifactorial impacts on the quality of life, the work force as well as healthcare systems.

This study should be considered in the context of its strengths and limitations. This is the first study in Malta to explore Long COVID characteristics and its impact on mental health, providing timely information that public health officials and policy makers can utilize as part of the post-pandemic recovery plans. This observational study managed to capture a good proportion of adults across different socio-economic strata, even if its distribution was through social media. However, due to the study's mode of distribution it was deemed difficult to achieve a sample size based on the population, as was the calculation of a response rate. Every effort was made to recruit as many adult participants as possible. Yet, a small sample size was still achieved with potential low statistical power. The vast majority of the Maltese population are known to access social media platforms (420,000 users out of 443,000 population) and thus, with the usual provisos of selection bias inherent in any form of survey, participation was dependent on responder-driven dissemination with reasonable (albeit impossible to exactly define) coverage. [16]. It needs to be noted that both shortness of breath and fatigue symptoms, that for this study were considered as Long COVID symptoms, although these could have been the result of anxiety and depression, respectively. Therefore, we cannot exclude the possibility of over-estimation of Long COVID. This was a cross-sectional study, hence even though participants were instructed to provide an indication of their anxiety and depression levels since the end of summer, the scores provided are only indicative of their mental health status at the point in time of participation. Furthermore, more females participated than males in the survey, a phenomenon already reported where females tend to respond to surveys more than males [41], however this might have led to responders' bias. Considering that this study ran less than 2 months from the Omicron variant dominance in Malta, all participants reporting Long COVID had their acute infection during periods where the vaccines had substantial effectiveness against COVID. Therefore, it is safe to say that the Long COVID participants had breakthrough infections whilst being ostensibly vaccine protected. However, the sample size was small and does not necessarily reflect the complete experiences, attitudes, and perspectives of all the general adult population and COVID-19 positive individuals in Malta. This small size affected the ability to undergo regression analyses and fully test the current hypothesis, therefore a larger study is recommended. There is also the possibility of self-reporting and recall bias, as with any survey. Additionally, the occurrence of Long COVID among the participants might have changed following the completion of this survey.

CONCLUSIONS

Long-term sequela of COVID-19 are becoming a common occurrence among positive individuals, and it appears that being previously healthy, and young does not preclude suffering from Long COVID. Long COVID is exacerbating mental health burdens with potential long-term consequences at an individual and a national level. Therefore, Long COVID and mental health should be high up on the public health and policy mak-

ers agendas to ensure timely management and prevention of the associated debilitating consequences.

Authors' contributions

SC designed the concept of the study. All Authors were involved in the developing of the survey. SC was responsible for the data analysis and for writing the draft article. All Authors reviewed and approved the final version of the manuscript.

Availability of data and materials

Data is available upon request.

Ethics approval and consent to participate

Ethical approval was granted by the University of Malta Research Ethical Committee (MED-2022-00017). Participants provided their informed consent on accepting to participate in the survey.

Consent for publication

Participants provided consent for publication on accepting to participate in the survey.

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Conflict of interest statement

Authors declare they have no competing interests to declare.

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HCV prevalence and treatment outcomes among drug users in an outpatient center for drug addiction in Northern Italy

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Abstract

Introduction. We aimed at evaluating hepatitis C virus (HCV) prevalence and treatment referral outcomes in a large population of drug users in Northern Italy.

Material and methods. Each participant underwent a quick capillary blood test. Positive participants underwent HCV RNA quantification. HCV RNA positive subjects were referred to treatment and evaluated immediately at the end of treatment and at 3 and 6 months after treatment.

Results. Of the 636 participants tested, 244 were positive. Intravenous drug use was more frequent among subjects who tested positive for HCV antibodies (99%). Among subjects who tested positive, 68% were HCV-RNA positive while 32% were negative. Among people referred to treatment, nearly 30% did not show up while 70% completed the treatment with success. Over 99% of people who started direct-acting antiviral agent (DAA) have a sustained response.

Discussion. We observed a significant higher prevalence of HCV positive subjects among people who inject drugs (99%) and we observed a high success rate for HCV treatment engagement.

Conclusions. Rapid testing for HCV represents a potential tool for HCV screening among high-risk groups.

Key words

- chronic hepatitis C
- drug abuse
- HCV prevalence
- treatment outcome

INTRODUCTION

HCV-related hepatitis is a chronic and slow-progressing disease that can ultimately lead to cirrhosis and hepatocellular carcinoma. With over 70 million individuals affected worldwide, HCV has become highly prevalent [1]. Among the most affected are people who inject drugs (PWIDs), with an estimated 67% of them infected with HCV [2, 3]. Non-injecting drug users, such as intranasal heroin or cocaine users and crack smokers, also have a higher HCV prevalence than the general population (5-12% *vs* 2%) [4, 5].

Direct-acting antiviral agents (DAAs) have been seen as a breakthrough treatment for HCV. These agents have the ability to eliminate the infection in almost all patients regardless of viral genotype and have a short treatment period, lasting as little as 8 weeks [6]. Many developed countries, as well as some developing countries, now provide access to DAA treatment for all HCV-infected individuals regardless of the severity of liver disease, with approximately 1.5 million patients undergoing DAA treatment worldwide since 2016 [7]. In Italy, almost 175,000 patients have been successfully treated with DAAs [6].

Early diagnosis is essential to avoid the risks associated with disease progression. Unfortunately, diagnosis is often made only when the disease begins to manifest clinically, which can occur years after infection, and asymptomatic individuals can act as carriers of the virus, thereby contributing to its spread [8]. Rapid blood tests, such as the OraQuick® HCV, have shown high reliability and sensitivity of 100%, with a specificity of 89%, and could be used as a safe and economic tool for detecting HCV in high-risk populations like PWIDs [9, 10].

In Italy, it has been estimated that nearly 280,000 HCV patients have yet to be diagnosed and nearly 50% of this patient group are drug users. The Italian Government has recently provided HCV rapid tests to those

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enrolled in the health registry (born between 1969 and 1989), patients followed by Drug Addiction Centers, and individuals detained in prison. In addition, the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA) has facilitated access to DAAs for individuals who are unable to perform liver biopsy and/or fibroscan for social welfare reasons, such as drug users.

In this context, our study aims to report preliminary data on HCV prevalence and treatment referral and outcome in a large population of drug users attending the Drug Addiction Center of Pavia (Servizio per le Dipendenze Patologiche, SerD) in Northern Italy. Our study also proposes a simplified linkage-to-care model to rapidly diagnose and treat HCV infection.

MATERIAL AND METHODS

Study enrollment started in August 2020 and is still ongoing. Our results derived from data collected until February 2022.

Patients participated on a voluntary basis, after signing an informed consent. On entry, each subject was interviewed by an infectious disease specialist (AL) about injection behavior, duration of abuse, presence of comorbid infection. Then, each participant underwent a quick capillary blood test.

The capillary blood test was performed with a fast HCV antibody test (OraQuick®) which is a single-use lateral-flow indirect immunoassay FDA-approved for use in symptomatic and high-risk asymptomatic patients [9, 10]. The OraQuick® HCV showed high reliability with a sensitivity of 100% and specificity of 89%. The OraQuick® HCV has an overall accuracy of 98% and provide results in 20 minutes.

All the participants with positive results according to OraQuick® HCV underwent a blood sample for HCV RNA quantification, except for patients who had already started DAAs. When actual infection with HCV was confirmed by positive HCV RNA, further virologic tests were performed: complete blood count, viral genotype, HIV, hepatitis B virus (HBV), syphilis antibodies, aspartate transaminase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (GGT), blood glucose, azotemia, creatinine, prothrombin time, activated partial thromboplastin time and serum electrophoresis. Patients with chronic HCV were offered therapy with DAAs and those who accepted were treated according to the EASL guidelines [2], after staging the liver disease using transient elastography (EchoSense FibroScan ® device; EchoSense, Paris, France). Additionally, the fibrosis-4 (FIB-4) score was calculated for all the patients who started DAAs according to the following formula:

FIB-4 = (age (years) x AST (IU/L))/((PLT [10^9/L]) x ALT (IU/L)) [11].

Patients with HCV infection were referred to three hospitals in Lombardy where DAAs were prescribed. Subjects who completed treatment were followed-up with an HCV-RNA test immediately at the end of treatment and at 3 and 6 months after the end of treatment.

Statistical analysis

Data are presented as median and interquartile ranges or percentages and absolute numbers as appropriate. Differences between groups (i.e., positive and negative at HCV screening test) were determined by using the Mann-Whitney U test or the Chi-square test to compare continuous or categorical variables, respectively. Logistic linear regressions (with HCV antibody status detected by rapid test as a dependent variable) were performed to define factors associated with positive test results.

A two-tailed p-value<0.05 was regarded as statistically significant. Statistical analysis was done using IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY, USA).

RESULTS

The recruited sample consisted in 636 drug users, of which 20.1% were female (n=128). Mean age was 40.62 years with a standard deviation (SD) of 12.42 (age range, 15-69). Intravenous (IV) drug use was prominent (n=300, 47.1%), and opioid substitution treatment was present in 63.5% of the sample (n=404). The data flow of the study is depicted in *Figure 1* while sample characteristics are reported in *Table 1*.

Of the 636 participants tested with OraQuick® HCV, 392 patients were HCV antibody negative, while 244 were positive. Intravenous drug use, HIV coinfection, and isolated hepatitis B core antibodies (HBcAb) were more frequent among subjects who tested positive for HCV antibodies compared to the other group (p<0.001). Among the subjects who tested positive with OraQuick® HCV, 70 subjects had already received treatment with DAAs. Of the remaining 174 OraQuick® HCV positive subject, 11 refused to undergo serological confirmation of HCV infection. Among 163 tested subjects, 111 subjects were HCV positive (68%) while the remaining 52 (32%) were negative. HCV genotyping showed the following frequencies: genotype 1 0.9% (n=1); genotype 1A 54.05% (n=60); genotype 1B 4.5% (n=5); genotype 2 0.9.% (n=1); genotype 3 28.8% (n=32); genotype 3A 5.4% (n=6); genotype 4 5.4% (n=6). Gender did not impact HCV positivity as detected with the rapid test (chi-square=0.08, p=0.83). Having HIV did not change the positivity rate to HCV (chi-square=3.09, p=0.08). A logistic linear model using HCV positivity as the dependent variable and age and sex as the independent predictors did not yield significant results (chi-square=3.04, p=0.22). Characteristics of HCV RNA-positive patients are described in *Table 2*.

At univariate analysis, factors associated with anti-HCV antibody positivity (assessed by OraQuick® rapid test) were age (OR 1.09, 95% CI 1.06-1.10, p<0.001), intravenous drug use (OR 58.4, 95% CI 33.5-101.6, p<0.001), HIV infection (OR 14.4, 95% CI 3.4-61.7, p<0.001), opioid substitution treatment (OR 15.1, 95% CI 8.9-25.4, p<0.001). At multivariable analysis, age, intravenous drug use and opioid substitution treatment remained independently associated with positive antibodies for HCV (p<0.001, p<0.00, and p=0.049, respectively).

Patients with chronic C hepatitis

Among the 111 HCV positive subjects, 73 started DAAs during study period: of these, 71 completed

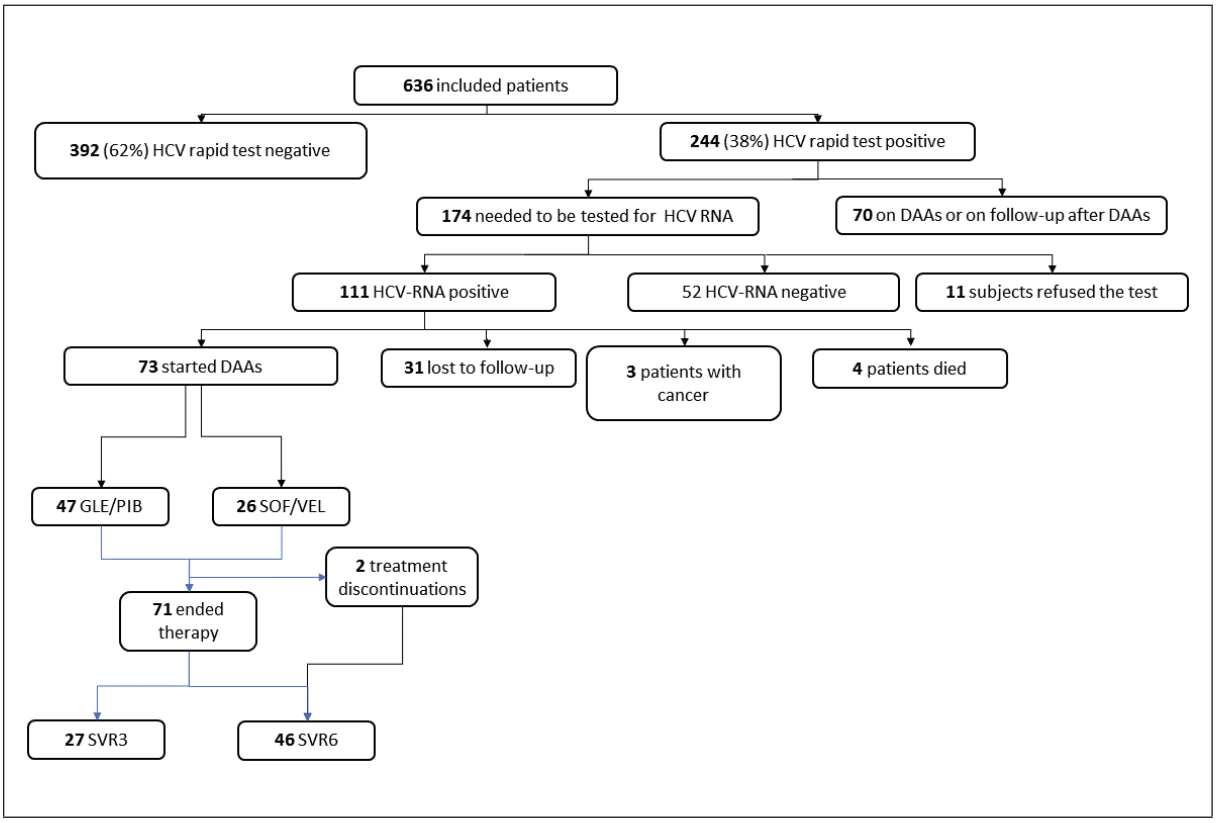

Figure 1
Flow-chart of the prospective study involving people who use drugs in the city of Pavia.
DAA: direct antiviral agents; GLE/PIB: glecaprevir/pibrentasvir; HCV: hepatitis C virus; SOF/VEL: sofosbuvir/velpatasvir; SVR3: sustained viral response at 3 months; SVR6: sustained viral response at 6 months.

Table 1
Characteristics of the total population screened for hepatitis C virus (HCV) in the city of Pavia

	Total screened population (n=636)	Ora-Quick positive (n=244)	Ora-Quick negative (n=392)	p-value
Ora-Quick positive, n (%)	244 (38.4%)	-	-	-
Male sex, n (%)	508 (79.9%)	193 (79%)	315	0.83
Age, median and range (years)	43 (15-69)	48 (25-61)	39 (16-69)	<0.001
Current IV users, n (%)	300 (47.2%)	227 (93%)	73 (18.6%)	<0.001
Current non-IV users, n (%)	33 (5.2%)	2 (0.8%)	31 (7.9%)	<0.001
OST, n (%)	404 (63.5%)	226 (92.6%)	178 (45.4%)	<0.001
HIV coinfected, n (%) (n=357)	28 (7.8%)	26 (14.3%)	2 (1.1%)	<0.001
HBV markers (n=264) **Negative, n (%)** **Isolated HBcAb positive, n (%)** **Isolated HBsAb positive, n (%)**	 91 (34.5%) 84 (31.8%) 89 (33.7%)	 50 (32.5%) 78 (50.6%) 26 (16.9%)	 41(37.3%) 6 (5.5%) 63 (57.3%)	 <0.001

IV: intravenous; OST: opioid substitution treatment; HBcAb: HBV-core antibody; HBsAb: HBV-surface antigen antibody; HBV: hepatitis B virus.

the treatment while 2 interrupted the treatment with DAAs but both showed sustained viral response at 6 months. Of note, three subjects could not be treated as they already had undetected cancer (two hepatocarcinoma and one hematological tumor), four subjects died after screening and before being sent to DAA prescriber, 31 subjects didn't show up at the prescription visit. Subjects who completed treatment were followed-up with an HCV-RNA test immediately after the end of treatment and at 3 and 6 months after the end of treatment. Only one patient with advanced liver disease presented a relapse of HCV at 6 months. As incidental findings, our study detected one case of syphilis, four HIV-positive patients (not yet under

Table 2
Characteristics and treatments of patients diagnosed with chronic C hepatitis in the city of Pavia

	HCV RNA positive (n=111)
Male sex, n (%)	89 (80.2%)
Age, median and range (years)	48 (42-52)
Current IV users	110 (99.1%)
OST, n (%)	106 (95.5%)
HIV coinfection, n (%)	14 (12.6%)
Isolated HBcAb positive, n (%)	52 (48.6%)
Isolated HBsAb positive, n (%)	17 (15.9%)
HCV genotype	
1	66 (59.5%)
2	1 (0.9%)
3	38 (34.2%)
4	6 (5.4%)
Metavir score	
F0-F2	56 (77%)
F3-F4	17 (23%)
FIB-4, median value	1.30
>3.25, n (%)	18 (18.4%)
DAAs initiation, n (%)	73 (65.8%)
Treatment type	
GLE/PIB, n (%)	47 (64.4%)
SOF/VEL, n (%)	26 (35.6%)

DAA: direct antiviral agents; F: fibrosis grade; FIB-4: Fibrosis-4; GLE/PIB: glecaprevir/pibrentasvir; IV: intravenous; HBcAb: HBV-core antibody; HBsAb: HBV-surface antigen antibody; HCV: hepatitis C virus; OST: opioid substitution treatment; SOF/VEL: Sofosbuvir/Velpatasvir.

treatment and who started antiretroviral therapy) and 67 cases of unvaccinated hepatitis B negative patients (who started the vaccination course directly at our outpatient service).

Of the 73 patients who started DAAs, 56 (77%) had absent or mild fibrosis and 17 (23%) had advanced fibrosis in the FibroScan (F3-F4 according to Metavir).

DISCUSSION

In 2016, the World Health Organization (WHO) established the goal of eliminating hepatitis C virus (HCV) by 2030, which requires a significant reduction in new cases of HCV infection and HCV-related deaths (by 80% and 60% respectively) [3].

One of the main barriers to HCV elimination is the large number of people who are unaware of their HCV infection status. Therefore, screening campaigns are critical to detect new infections, especially in high-risk groups such as drug users [2].

Screening campaigns typically involve detecting anti-HCV antibodies and using rapid diagnostic tests (RDTs) at point-of-care centers to improve linkage-to-care for individuals with positive results [2]. This approach has been adopted in Europe and in Italy, and examples of its implementation have been reported in the literature. For instance, Persico and colleagues described a screening program involving 593 drug users who were tested with oral salivary tests at Drug Addiction Centers. Among them, 41.8% were HCV positive, and 160 individuals were HCV RNA positive [7].

Unfortunately, screening campaigns and point-of-care-based approaches are still lacking. According to the last Italian report on active substance users, in 2020, only 22% of all individuals attending drug addiction services were screened for HCV as well as only 26% of the PWIDs [12].

Our study analyzed the prevalence of HCV antibody positivity among a large group of drug users and described a model of screening and linkage to care designed to increase patient engagement in HCV testing and treatment. The model was based on a robust network between Drug Addiction Centers and Infectious Diseases specialists working at the hospitals where patients with chronic HCV could undergo liver elastography and treatment. To our knowledge, we reported data on HCV rapid screening in the largest cohort of drug users in Italy. Similarly, Persico *et al*. tested 593 subjects attending several addiction centers, using the same rapid test but on saliva [7]. We included 636 individuals, with a 38% positivity rate; among subjects using intravenous drugs (n=300), prevalence of HCV antibody-positivity increased to 99%, in line with the data from an ECDC review on hepatitis prevalence in Europe, which reported a prevalence >50% among PWIDs [13]. More specifically, according to a systematic review [14], the median number of positive HCV antibodies among PWID tested for HCV in Europe was 82.9% (interquartile range, IQR 59-100%), and in eight out of the 14 countries in Europe, more than half of the PWID have been infected with HCV [14]. On the other hand, our prevalence of HCV positive subjects among PWID was significantly higher compared to recent estimates in Belgium (43%) [15]. This lower prevalence in Brussels could be attributed to the presence of intensive education programs and several needle exchange programs.

Prior to the beginning of the study, educational and informative material about chronic HCV was made available to all the patients who visited to the outpatient center. This approach might have played a key-role in increasing risk perception in our cohort and improving adherence to testing and treatment.

As expected, opioid substitution treatment and intravenous drug use were independently associated with HCV positivity ($p<0.001$). Likewise, age was independently associated with HCV rapid test positivity, with older age being a risk factor for HCV infection ($p<0.001$).

Despite the efforts to improve the linkage-to-care, only 65.8% of subjects with confirmed HCV (i.e., positive HCV RNA) started treatment with DAAs. This datum could be explained by various obstacles and barriers, including difficulties in reaching the hospitals where the visits were scheduled, long waiting lists due in part to the COVID-19 pandemic, and low compliance of the subjects. We could hypothesize that one possible major barrier to the treatment initiation was the need for individuals to move to a different center, rather than being treated at the drug addiction center by their physicians and nurses. Foschi *et al.* reported

high rates of linkage-to-care and anti-HCV treatment initiation (96.5%) when subjects received DAAs and completed their follow-up in their drug addiction center [16]. Similarly, Granozzi and colleagues described a higher rate of retention in care among drug users and homeless individuals treated with DAAs in an out-of-hospital setting rather than in hospital [17].

An additional incidental finding of our study was the high proportion of individuals who were diagnosed with infections other than HCV (HIV and HBV), of which they were not aware.

Our study has both strengths and limitations. One of the strengths was the large sample size, which is the largest in Italy so far, and the follow-up of treatment outcomes for up to 6 months. A limitation of this study was the lack of long-term follow-up data, which could provide information on reinfection rates and risks in our population. Additionally, administering questionnaires to those who continued to use the service could help identify and overcome treatment barriers and provide important information about the low rate of DAAs therapy initiation.

CONCLUSIONS

In conclusion, our findings highlight the role of RDTs as a tool for HCV screening among high-risk groups such as PWIDs to diagnose HCV infection among individuals unaware of being infected and engage patients with chronic HCV in DAAs therapy. Furthermore, our findings show the impact of a well-designed model to increase access to tests and therapy, based on an educational approach and networking. Further efforts will be necessary to make out-of-hospital treatment possible, in order to improve the linkage-to-care among these patients.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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ORIGINAL ARTICLES AND REVIEWS

Rural-urban variation in willingness to donate blood in Ibadan Region, Nigeria

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Abstract

Background. Although there are ongoing blood donation campaigns in Nigeria, the prevalence of voluntary blood donation is about 10% and there is limited information about the determinants of blood donation behavior, especially across rural-urban geographic areas. This study examines the rural-urban differences in willingness to donate blood.

Method. A cross-sectional study addressing adults from three rural and three urban communities was performed in 2021 to evaluate willingness, knowledge, attitude and practice of blood donation.

Results. A total of 287 individuals were surveyed. Most of the respondents across all communities have never donated blood (72%). Females aged 18-25, highly educated, and from urban communities were more incline to donate blood compared to their counterparts. The main reasons for not donating blood for rural dwellers were: never thought of it (39% *vs* 34.7%) and no one asked (34.4% *vs* 17%); fear of needles was declared mostly by urban dwellers (21.8% *vs* 12.5%) (p=0.02).

Conclusions. Willingness to donate blood varies across rural and urban communities and is influenced by socio-demographic characteristics. The gap between willingness to donate and actual blood donation has consequences for the establishment of blood transfusion services. Targeted public health interventions are required to enhance awareness and knowledge and modify attitudes towards blood donation.

Key words

- blood donation
- blood banks
- transfusion
- willingness
- rural-urban variation

INTRODUCTION

Blood donation, the process of collecting, testing, preparing, and storing blood and blood components from a donor and transfusing to another person (the recipient), is the main means of acquiring blood in emergencies, major surgeries, and blood-related obstetric complications [1]. It is an indispensable component of healthcare that saves millions of lives each year in both routine and emergency medical practices and permits complex medical and surgical interventions to improve life expectancy and reduce human afflictions [2]. Although the demand for blood transfusion far exceeds the supply, advanced medical technologies and the availability of more donors have improved healthy life expectancy [3]. The strategy recommended by the World Health Organization (WHO) to ensure the availability of safe blood supply worldwide is to promote blood donations from voluntary unpaid donors [4]. However, the goal of "100% voluntary non-remunerated donation of blood and blood components" set for 2020 has not been achieved yet [5].

In developing countries, chronic blood shortage is common and blood donations are largely dependent on blood provided by families or friends of patients who require transfusion [3]. Willingness to donate blood is mostly high in developed countries and generally low in developing countries. The average blood donation rate in high income countries is 31.5/1,000

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population and 5.0/1,000 population in low income countries [4].

In the African region, blood requirements were estimated at 8 million units in 2006, but only 3.2 million units were collected – about 41.5% of the demand [6]. According to the Nigeria's National Blood Transfusion Service (NTBS), the prevalence of voluntary blood donation in Nigeria is 10% [7], *i.e.*, only four in 1,000 people are voluntary donors although up to half of the total population are medically fit to donate [8]. According to the WHO, with over 200 million population, Nigeria needs an average of 1.8 million pints of blood annually [7], but the NBTS collects only 500,000 pints of blood every year, leaving a shortfall of about 73%. Moreover, only about 25,000 blood units sourced exclusively from voluntary donations of unpaid blood donors were collected, screened and distributed in 2019 and 2020 [9]. Nigeria has not been able to bridge the gap between the demand and supply of blood transfusion [7]. Therefore, it is essential to find the motivating factors among the current donors and the deterrents towards blood donation among nondonors. An empirical examination of whether socio-demographic and attitudinal factors influence the willingness to donate blood in the future, especially across rural-urban geographic areas, has not been adequately performed. The aim of this study is therefore to examine the rural-urban variation in the willingness to donate blood and to examine if the variation is associated with socio-demographic variables, attitudes, and personal motivators, incentives, or concerns in Ibadan region (southwest Nigeria).

MATERIALS AND METHODS

Data were collected among active blood donors, infrequent blood donors, and nondonors, using a pretested and structured interviewer-administered questionnaire *(available online as Supplementary Material 1)*. The questionnaire was composed of six sections. The first section was designed to collect information on the respondents' residential area. The second section collected information on socio-demographic characteristics, including gender, age, ethnicity, occupation, education, religion, income, and marital status. The third section collected data on respondents' history of blood donation, reasons for donating or not donating blood, and frequency of blood donation. The fourth section evaluated respondents' blood donation knowledge according to four items: i) knowledge of blood donation; ii) categories of people that can donate blood; iii) appropriate age for blood donation; and iv) blood donating centers. The fifth section collected information on respondents' attitudes and perceptions towards blood donation. Responses were graded on a 5-point Likert-type scale; namely, strongly agree, agree, undecided, disagree, and strongly disagree. The last section assessed respondents' willingness to donate blood, which was ranked based on categories: Yes, Maybe, and No. A question was designed to collect information regarding respondents' opinions on factors or motivational determinants that influence blood donation.

The first version of the questionnaire was administered to 10 randomly selected participants to test and refine the questions for clarity and comprehensiveness. The items were slightly edited after the pre-test. The final version of the questionnaire was administered from August to September 2021. Questionnaires were shared from house to house in each community, and all respondents were contacted personally. Oral consent was obtained from each participant prior to the survey. According to departmental rules, the approval of the lead researcher's advisor was the only required approval to conduct the study, and this was properly obtained.

Sample size and sampling

A multi-stage sampling method was used to select the study subjects for the quantitative survey. The total population of Ibadan region, based on the last official national population census in 2006, is 1,991,367 with an annual growth rate of 3.5% per year; the total population of Ibadan for the year 2021 is an estimated 3,552,000 [10]. Two Local Government Areas (LGAs), *i.e.*, Ibadan North and Akinyele representing urban and rural spatial areas respectively, were randomly selected from the list of 11 LGAs in the Ibadan region. Three communities were selected randomly from each of the LGAs. This was followed by the selection of random samples of neighborhoods at a regular interval of 2 buildings. Finally, an individual was selected randomly from the eligible adult population (18-60 years of age) in the selected households and was interviewed. Participants were considered eligible only on the basis of their age group, their medical conditions were not taken into account.

The selected communities differed significantly in population size; hence, a stratified proportional sampling technique was used to determine the sample size of the study. The population of the last census for each of the selected urban and rural communities, as well as the projected population, are reported in *Table 1S available online as Supplementary Material*. The projected population was used in calculating the sample size for each community. The six communities were divided into two population subgroups, which included group 1: population size of 20,001-40,000, and group 2: population size of 100-20,000. To obtain a realistic sample representation for each area, sampling ratios of 0.2% and 10.0% were used for urban and rural communities respectively.

Statistical analysis

Data were entered into the IBM statistical software SPSS v.26.0 for Windows (SPSS Inc. Chicago, Illinois, USA). Descriptive statistics (frequencies and percentages) was used to examine all variables in the study. The differences between urban and rural communities were calculated with the Chi-squared test. A binary logistic regression analysis, with backward elimination, was performed to assess the association between the dependent variable *willingness to donate blood* and the following covariates: *sex, age, ethnicity, marital status, educational qualification, occupation, religion,* and *urban-rural communities*. The crude (cOR) and adjusted (aORs) odds ratios of the covariates were calculated with 95% confidence interval (CI 95%). The analysis was carried out at the $p<0.05$ significance level. The model's goodness of

fit was evaluated using the Hosmer and Lemeshow Test [11]. Reliability, the measure of internal consistency of the constructs in the study, was assessed using Cronbach's alpha (α).

RESULTS

The highest value of Cronbach's alpha was obtained for the section on willingness to donate blood with 4 items (alpha=0.759), followed by willingness and knowledge sections with 7 items (alpha=0.640). Cronbach's alpha value above 0.6 is generally acceptable [12].

General characteristics of the sample

A total of 312 copies of the questionnaire were administered and 287 were retrieved, with a 92% response rate. Of the 287 respondents *(Table 1)*, the majority were from urban communities (69.7% *vs* 30.3%; p<0.001). Most respondents were male, especially in urban areas (75% *vs* 65.5%). Individuals aged 18-25 years (72.5%) were the majority in urban areas, while those aged 34-40 years (31%) were predominant in rural communities (p<0.001). A large proportion of the respondents were from the Yoruba ethnic group (79%)

Table 1
Socio-demographic characteristics of the respondents across rural and urban communities

Socio-demographic characteristics		Urban (N=200)	Rural (N=87)	p-value
		N (%)	N (%)	
Sex	Male	150 (75.0)	57 (65.5)	0.11
	Female	50 (25.0)	30 (34.5)	
Age	18-25	145 (72.5)	17 (19.5)	<0.001*
	26-33	22 (11.0)	13 (14.9)	
	34-40	17 (8.5)	27 (31.0)	
	41-48	12 (6.0)	22 (25.3)	
	>49	4 (2.0)	8 (9.2)	
Ethnicity	Yoruba	158 (79.0)	71 (81.6)	0.22
	Igbo	29 (14.5)	15 (17.2)	
	Hausa	8 (4.0)	0 (0.0)	
	Others	5 (2.5)	1 (1.1)	
Marital status	Single	153 (76.5)	23 (26.4)	<0.001*
	Married	45 (22.5)	61 (70.1)	
	Divorced	0 (0.0)	2(2.3)	
	Widowed	2 (1.0)	1(1.1)	
Educational qualification	No formal education	3 (1.5)	2 (2.3)	<0.001*
	Qur'anic	8 (4.0)	5 (5.7)	
	Primary	3 (1.5)	13 (14.9)	
	Secondary	65 (32.5)	40 (146.0)	
	Tertiary	120 (60.0)	27 (31.0)	
	Others	1 (0.5)	0 (0.0)	
Religion	Christianity	152 (76.0)	54 (62.1)	0.05
	Islam	45 (22.5)	31 (35.6)	
	Others	3 (1.5)	2 (2.3)	
Occupation	Farming	12 (6.0)	11 (12.6)	<0.001*
	Artisan	22 (11.0)	17 (19.5)	
	Civil/public servant	34 (17.0)	20 (23.0)	
	Trading/business	45 (22.5)	27 (31.0)	
	Student/unemployed	87 (43.5)	12 (13.8)	
Income (N=84)	<25,000	26 (40.0)	10 (52.6)	0.13
	26,000-50,000	26 (40.0)	5 (26.3)	
	51,000-75,000	5 (7.7)	0 (0.0)	
	76,000-100,000	6 (9.2)	1 (5.3)	
	>101,000	2 (3.1)	3 (15.8)	

*p<0.05.

and Christians (76%), particularly in urban areas. Regarding marital status, most respondents in urban areas were single (76.5%) while married participants (70%) were predominant in rural areas (p<0.001). Higher educational qualifications (tertiary education) were achieved by individuals residing in urban areas compared to their counterparts (60% *vs* 31%; p<0.001). The most encountered occupational category in urban communities was student/unemployed (43.5%), as opposed to rural communities where trading/business (31%) was the most common category (p<0.001). Information about income was provided by 84 (29.3%) of the sample, of which 65 (80%) urban dwellers declared an annual income ranging from less than 25,000 to 50,000 Nigerian Naira (NGN). Most rural dwellers (52.6%) declared an income under NGN 25,000/year.

Knowledge of blood donation

Regarding knowledge of blood donation, 167 (83.5%) in urban and 73 (83.9%) in rural communities declared that they had heard about blood donation *(Figure 1a)*. Most respondents (80.5% urban and 87.4% rural) stated that both females and males can donate blood. However, more urban respondents did not know who could donate blood compared to rural respondents (13% *vs* 2.3%; p=0.03) *(Figure 1b)*. Adult age resulted the most appropriate for blood donation across communities (85% urban and 83.9% rural). The second appropriate period for blood donation was during childhood according to 24 (12%) of urban participants, while 9 (10.3%) of rural participants indicated the elderly age (p=0.01) *(Figure 1c)*. Most respondents knew where to donate blood, especially those in rural communities (78.2% *vs* 57.5%; p=0.001) *(Figure 1d)*.

Practice of blood donation

Most of the respondents across all communities have never donated blood (72%). In urban areas, 53 (26.5%) of respondents had donated blood, likewise for 23 (26.4%) in rural communities. The most prominent reason for not donating blood *(Figure 2)*, especially for rural dwellers, was that they never thought of it (39.1% *vs* 34.7%). Another reason for most rural respondents was that no one asked them (34.4% *vs* 17.0%), while fear of needles was indicated mostly by urban respondents (21.8% *vs* 12.5%) (p=0.02). Of 76 (26.5%) blood donors in the sample, 36 (47.4%) donated for relatives or friends, 34 (44.7%) on voluntary basis and 6 (7.9%) in exchange for a remuneration. Among blood donors, 52 (68.4%) had donated only once.

Attitude and perception toward blood donation

The majority of the sample considered blood donation a safe practice (90% and 86.2%) and agreed that blood donation should be encouraged (91% and 81.6%) in both urban and rural settings respectively *(Table 2)*. Regarding the statement "donating blood can save other people's lives", most participants agreed but 14 (7%) of urban respondents were undecided and 4 (4.6%) of the rural participants disagreed (p=0.007). Most respondents from rural areas declared that blood donors should be paid (82.8% *vs* 48.5%; p<0.001).

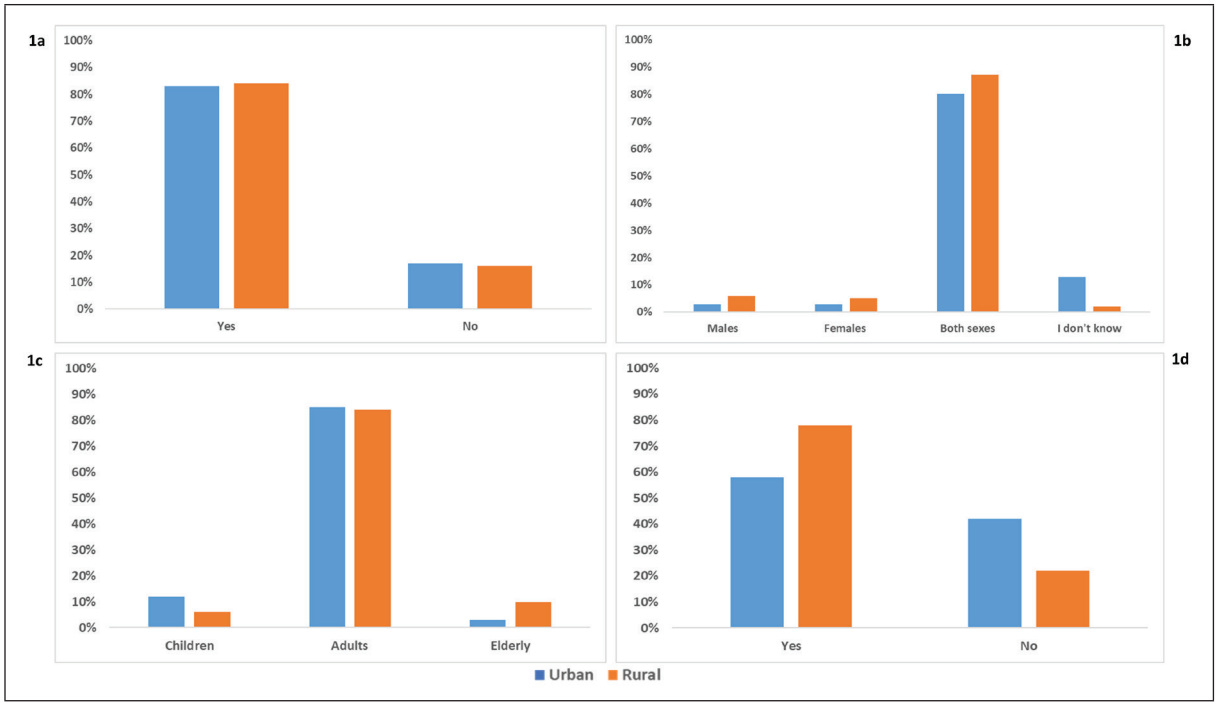

Figure 1
Knowledge of blood donation.
1a: awareness of blood donation; 1b: individuals that can donate blood; 1c: appropriate age for blood donation; 1d: knowledge of blood donation venues.

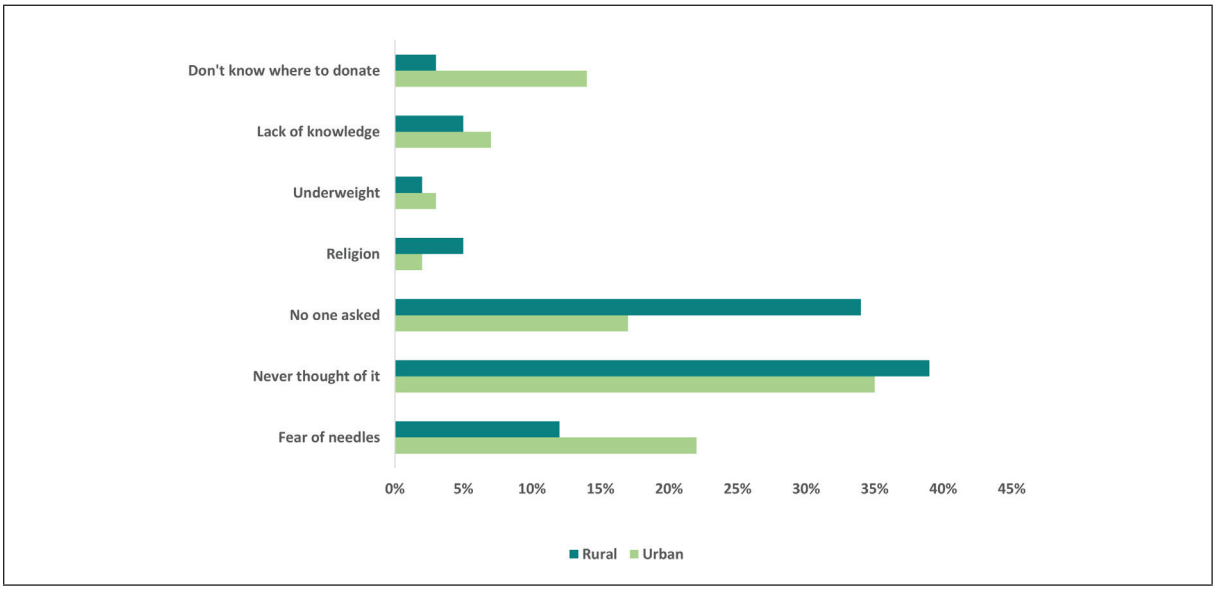

Figure 2
Urban-rural reasons for not donating blood.

Table 2
Attitude and perception towards blood donation in urban and rural communities

Attitudinal statement	Urban N (%)			Rural N (%)			
	Agree	Disagree	Undecided	Agree	Disagree	Undecided	p-value
Blood donation is safe	180 (90.0)	8 (4.0)	12 (6.0)	75 (86.2)	4 (4.6)	8 (9.2)	0.59
Donating blood can save other people's lives	184 (92.0)	2 (1.0)	14 (7.0)	83 (95.4)	4 (4.6)	0 (0.0)	0.007*
Blood donation causes health problems for the donor	39 (19.5)	100 (50.0)	61 (30.5)	15 (17.2)	54 (62.1)	18 (20.7)	0.14
People should be paid for donating their blood	97 (48.5)	41 (20.5)	62 (31.0)	72 (82.8)	10 (11.5)	5 (5.7)	<0.001*
Blood donation should be encouraged	182 (91.0)	5 (2.5)	13 (6.5)	71 (81.6)	6 (6.9)	10 (11.5)	0.06

*p<0.05.

Willingness to donate blood

Most urban dwellers were willing to donate blood (67% *vs* 58.6%; p=0.03) and declared that relatives or friends should not be the only recipients (62.5% *vs* 51.7%; p=0.03) *(Table 3)*. However, rural dwellers were more willing to donate blood to anonymous recipients (57.5% *vs* 46%; p=0.01) but were less incline to donate without any form of remuneration (41.4% *vs* 13.5%; p<0.001). The respondents were willing to encourage their relatives to donate blood, particularly the urban dwellers (66.5% *vs* 50.6%; p=0.001).

In the logistic regression analysis *(Table 4)*, three statistically significant factors associated with willingness to donate blood were retained in the final model: ethnicity, occupation, and rural-urban community. Respondents from the Yoruba ethnic group (cOR=0.16, aOR=0.20) and students/unemployed (cOR= 0.43, aOR=0.35) seem to be less prone to donate blood, while respondents from urban communities are more incline to donate blood (cOR=2.39, aOR=3.25) compared to their counterparts considered as reference. Although not statistically significant, the analysis showed that females (cOR=2.22; aOR=2.02), 18-25 years old (cOR=0.82, aOR=1.25), with high educational qualification (cOR=1.74; aOR=1.94) are more likely to donate blood. Singles (cOR=0.74; aOR=0.68) and Christians (cOR=1.06; aOR=0.70) seem to be less prone to blood donation. The Hosmer and Lemeshow Test gave a good value for the regression model, p=0.868.

For most participants, especially rural dwellers, offering incentives could encourage people to donate blood (85.1% *vs* 67.5%; p=0.002).

DISCUSSION

Addressing the concerns related to blood donation might help to bridge the gap between supply and demand. To this end, great importance has been placed on understanding the determinants of blood donation behavior [13]. The analysis of socio-demographic and motivation-related variables associated with the willingness to donate blood is considered one of the decisive

Table 3
Willingness to donate blood across urban and rural communities

Variables	Urban N (%)			Rural N (%)			p-value
	Yes	Maybe	No	Yes	Maybe	No	
Are you willing to donate blood if required?	134 (67%)	44 (22)	22 (11)	51 (58.6)	16 (18.4)	20 (23.0)	0.03*
Do you think blood should be donated ONLY for relatives/friends?	26 (13)	49 (24.5)	125 (62.5)	22 (25.3)	20 (23.0)	45 (51.7)	0.03*
Are you willing to donate blood for anonymous persons?	92 (46.0)	71 (35.5)	37 (18.5)	50 (57.5)	16 (18.4)	21 (24.1)	0.01*
Are you willing to donate blood without any form of remuneration?	109 (54.5)	64 (32.0)	27 (13.5)	38 (43.7)	13 (14.9)	36 (41.4)	<0.001*
Are you willing to encourage your family and friends to donate if necessary?	133 (66.5)	61 (30.5)	6 (3.0)	44 (50.6)	31 (35.6)	12 (13.8)	0.001*

*p<0.05.

Table 4
Results of the binary regression analysis with willingness to donate as the dependent variable

Covariates		Crude OR (95% CI)	Adjusted OR (95% CI)
Sex	Male (reference)	1	1
	Female	2.22 (0.93-5.31)	2.02 (0.79-5.15)
Age	>26 (reference)	1	1
	18-25	0.82 (0.42-1.60)	1.25 (0.38-4.08)
Ethnicity	Not Yoruba (reference)	1	1
	Yoruba	0.16 (0.04-0.67)	0.20 (0.04-0.87)
Marital status	Married (reference)	1	1
	Single	0.74 (0.37-1.47)	0.68 (0.24-1.91)
Educational qualification	*Low (reference)	1	1
	**High	1.74 (0.72-4.24)	1.94 (0.70-5.38)
Religion	Other religions	1	1
	Christianity	1.06 (0.51-2.19)	0.70 (0.30-1.62)
Occupation	Workers	1	1
	Students/unemployed	0.43 (0.22-0.86)	0.35 (0.16-0.77)
Community	Rural	1	1
	Urban	2.39 (1.20-4.74)	3.25 (1.49-7.09)

*Low, qur'anic and primary education; **High, secondary and tertiary education.

elements for the understanding of these determinants [14]. With the aim to close the knowledge gap, the present study examined the factors associated with the willingness to donate blood across urban and rural dwellers in Ibadan region. According to findings, geographical area (urban or rural), ethnicity and occupation are significantly associated with willingness to donate blood. In other words, students/unemployed are less prone to donate blood while urban dwellers and non-Yoruba ethnic groups are more incline to blood donation. Likewise, though non statistically significant, females aged 18-25 years, with high educational level are more likely to donate blood. Young age, high educational level [13, 15, 16] and female gender [16] have also been found in other studies as main factors associated with the intention to donate blood. Generally, individuals of younger age have higher educational qualification than the elderly, therefore the main influencing factor on the intention to donate blood could be education rather than young age. Similarly for the geographic area, individuals with higher academic achievements are mostly urban dwellers, hence urban communities are associated with higher willingness to donate blood. It was also observed that rural dwellers are not aware that donating blood can save other people's lives. Targeted public health interventions to improve knowledge about blood donation, especially in rural areas and among the disadvantaged population (*e.g.*, unemployed, elderly) are required.

According to the findings, non-Yoruba ethnic groups (*i.e.*, Igbo, Hausa) were more incline to blood donation. This is in contrast with the study by Salaudeen *et al.*, 2019 where Yoruba ethnic groups were more likely to donate blood [13]. This could be related to the different

composition of the samples. Although Yoruba ethnic group was predominant in the two studies, the present study had more students/unemployed participants that are less likely to donate blood. The study by Salaudeen *et al.*, 2019 [13] was composed mostly of traders/farmers and civil servants/professionals.

There is a gap between willingness to donate blood in the future and effective blood donation across the communities. Although the willingness is high, blood donors were about 26% of the sample and the majority have donated only once and mainly for relatives or friends. In accordance with the present findings, positive attitudes towards blood donation have been found in the literature [1, 17, 18]. Nonetheless, a substantial portion of the population was not willing to donate blood [1, 18, 19]. This is related to the fact that the intention to donate blood is complex and influenced by individual and social factors, such as the desire to be useful and help others, but also by the desire for recognition or incentives, and the cultural context [20]. Approaches to improve blood donation should be adapted to local or regional geographical areas and culture, while targeting motivating and deterring factors for blood donation.

Most rural dwellers declared that blood donors should be paid; consequently, they consider incentives as the most encouraging factor to enhance blood donation. This could be due to their low income. However, the main reasons for not donating blood were that they never thought of it, no one asked them, and fear of needles. Physical fear of harm and/or infection was also the most common reason for not donating blood [17, 19]. Other significant deterrents to donating blood where the health status of the individuals [17, 21], lack of knowledge about blood donation venues and operating hours [22], distance of blood collection sites and lack of time [17]. In accordance with the present study, non-donors in Pakistan and Trinidad and Tobago indicated that the main reason they had not donated blood was that no one had ever asked [23, 24]. The disparity between willingness to donate and the real practice of blood donation has implications for the establishment of blood transfusion services in Nigeria [9] and should be addressed through public health campaigns to increase awareness and modify attitudes and perceptions that undermine blood donation. Offering incentives, in terms of blood screening services, and a scrupulous use of monetary incentives could increase the rate of blood donation.

Limitations of this study are inherent to its cross-sectional design that could cause misinterpretation of the questionnaire items, underreporting, or recall bias. However, the survey was conducted face-to-face and trained interviewers administered the questionnaire and assisted the respondents when necessary. The presence of an interviewer could raise concerns of the respondents that their responses may not be correct, leading to socially favorable and biased responses [25]. Notwithstanding, the presence of an interviewer could motivate respondents to be more attentive to the survey questions, and limit respondents' tendency to respond quickly and with little effort to the questions [26]. To reduce interview bias, the interviewer's opinion should not be included into questions or explanations about the questionnaire items. Clear and concise definitions should be provided to the respondents, using plain language to avoid misinterpretation. Another limitation is the lack of inclusion in the questionnaire of other factors that could influence blood donation, such as distance from the collection sites and their opening hours. These are barriers to access to health care services and to active participation of the population in health campaigns. Future research studies should include these aspects by incorporating specific questions regarding access to and characteristics of blood donation centers in the survey instrument (*e.g.,* donation location, opening hours, waiting times, skills of the healthcare personnel, provision of invitations to donate blood, provision of monetary or non-monetary awards). In addition, questions about safety or willingness to donate blood could be influenced by the inclusion in the analysis of respondents who declared they had never heard of blood donation. However, an interviewer-administered approach was adopted in this study. During the face-to-face interview, which allows the respondents to ask for clarification about the items on the questionnaire, the definition of blood donation was given by trained interviewers to the participants, when requested. It appears that they could be familiar with the act of blood donation but not with the terminology, especially rural dwellers with low educational level. Consequently, this category of respondents was included in all analysis in order to assess how much needs to be done in terms of sensitization, hence, to educate and encourage the population about blood donation. Similar research approach was also applied in the study by Pule *et al.,* 2014 [15].

CONCLUSIONS

Blood donation was regarded as a positive and safe practice by both donors and non-donors, despite the fact that most respondents have never donated blood because no one had asked them, they had never considered it, or due to fear of physical harm. Willingness to donate blood is complex and influenced by socio-demographic factors, but also by the cultural context, and the need for incentives. As a result, high willingness to donate blood does not translate to active practice of blood donation. The lack of motivations and incentives, and misconceptions toward blood donation could be modified through adequate knowledge and information. To this end, local governments and civil society organizations should increase awareness about blood shortage, encourage and retain blood donors through public health interventions. The provision of incentives should be taking into consideration in areas where blood shortage is high. Approaches to improve the rate of blood donation should be targeted to the cultural context and geographical area.

Authors' contributions

FIG: conceptualization, methodology, investigation, writing – original draft, writing – review & editing. YP: conceptualization, methodology, writing – original

draft, writing – review & editing, project administration. FO: investigation, formal analysis, visualization, writing – review & editing. ROA: investigation, resources, validation, writing – review & editing. BU: validation, formal analysis, visualization, writing – review & editing, supervision.

Conflict of interest statement

The Authors declare that they have no conflict of interest.

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ORIGINAL ARTICLES AND REVIEWS

Gender and burden differences in family caregivers of patients affected by ten rare diseases

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Abstract

Objectives. Gender differences in caregiving may determine social and/or health inequalities among family caregivers (FCs). This study aimed to analyse gender specific differences of burden and quality of life (QoL) in FCs belonging to ten different rare diseases (RD).

Methods. Burden levels and QoL data, derived from a sample of 210 FCs of RD patients, were analysed by student t-test, Anova and Kruskal-Wallis followed by multiple comparisons and evaluation of factors, including sex, by correlation and multiple regression analyses.

Results. FCs caring for Prader Willi, X-fragile, mucopolysaccharidosis and epidermolysis bullosa patients showed significant higher levels of burden as compared to other RDs. Burden is related to FC's QoL and can be down modulated by the reduction of the number of hours/week devoted to care and by the improvement of patient's QoL. No gender-specific burden differences were observed among all FCs. However, female FCs devoted to care significant more numerous hours/week than men and perceived more emotional/physical burden and poorer psychological health than males. Women, who are more frequently early retired from work, not occupied or homemakers than men, suffered more burden as compared to men in the same conditions.

Conclusions. This study showed gender specific differences in RD caregiving, which are important for planning personalized health prevention policies.

Key words

- family caregivers
- burden, rare diseases
- gender differences

INTRODUCTION

Family caregivers (FCs) typically are the unpaid care providers for a not self-sufficient family member. In Italy, it is estimated that the number of FCs is about three million people (Italian National Institute of Statistics, Istituto Nazionale di Statistica, 2018). Most FCs are women, 45-55 aged, 60% of which have given up their job to devote themselves full time to the care.

The Italian Orphanet website has estimated two million of rare disease (RD) patients, 70% of which are pediatric. Based on the National Rare Disease Registry (NRDR) of the Italian National Health Institute (Istituto Superiore di Sanità, ISS), 20 cases per 10,000 inhabitants are estimated and about 19,000 new cases are reported each year by more than 200 health care centers (www.malattierare.gov.it).

The number of RDs fluctuates between 7,000 and 8,000, but this is a number that grows with the progress of genetic research (https://globalgenes.org/rare-list).

In the last two decades, many studies have shown a relation between FCs' mental and physical health and caregiving activity, being health negatively influenced by high levels of chronic stress [1-4]. Accordingly, it has been reported that FCs may develop depression, anxiety, worse sleep quality and poor physical health, more frequently than the general population [5-7]. However, few studies exist on FCs of RD patients, probably due to the low number of recruitable FCs as compared to other conditions.

RDs may contribute to enhance caregiver burden as compared to more common disorders, likely because of the additional challenges involved in the RD condition, such as complexity of clinical management, emotional impact on patients, long lasting wait to receive an accurate diagnosis, lack of information, uncertainty of the

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future and tension in the hope of a cure not yet available [8, 9].

Although no curative treatments are available for approximately 95% of the identified RDs, much can be done to improve patients' QoL, alleviation of physical suffering, preservation of individual autonomy, dignity, and support for caregivers [10].

Few studies to date have addressed gender focus among FCs, even if this should be a main research question for planning targeted interventions for a population, which is itself exposed to socio-cultural influences. Some studies have shown that gender differences in depression and physical health are indeed larger than those found in the general adult population, being in part explained by gender differences in facing caregiving stressors [11]. In particular, high levels of stressors and low levels of social resources accounted for elevated gender differences in burden [12]. Recently, the Health Related Quality of Life (HRQoL) score was reported useful for explaining health gender specific differences in population studies [13] and HRQoL resulted inversely correlated with burden in RDs caregivers [14]. Moreover, mothers of RDs' patients, as compared to fathers, were significantly more impaired in their QoL and mental health [15]. At the best of our knowledge, this study is the first looking for gender specific burden and HRQoL differences in FCs of patients with ten different RDs.

METHODS

This study analyses data from a cross-sectional study carried out in 2012 [16] coordinated by the Italian National Center for Rare Diseases in collaboration with Italian rare disease federations and patients' organizations in the framework of BURQoL-RD project, funded by the European Commission. The survey was fully anonymous. Data were collected via on-line questionnaires completed by FCs and included socio demographic characteristics (sex and age of the patients, sex and age of FCs, relationship with the care recipient, marital and occupational status), HRQoL of both patients and FCs, burden, number of hours/week devoted to care by the principal FC and by a secondary caregiver where present.

Rare diseases: we selected FCs of individuals with the following 10 RDs: 1. Prader Willi syndrome (PWS); 2. hemophilia (Hem); 3. Duchenne muscular dystrophy (DMD); 4. scleroderma (Scl); 5. cystic fibrosis (CF); 6. fragile X syndrome (FXS); 7. histiocytosis (His); 8. mucopolysaccharidosis (MPS); 9. juvenile idiopathic arthritis (JIA); 10. epidermolysis bullosa (EB). The RDs selected differ in terms of genetic origin, age at onset during adulthood or childhood, physical impairment and/or mental impairment, availability of effective therapies, and represent a wide range of effective examples of RDs for our analysis.

Study's instruments/tools: the HRQoL was measured with the EuroQoL 5-domain questionnaire (EQ-5D) for both patients and FCs. The EQ-5D includes six items and measures generic HRQoL with regards to 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression [17]. It also includes a Visual Analogue Scale (VAS) that patients and their caregivers use to rate their health status between 0 ("worst health") and 100 ("best health"). *Subjective burden* was measured with the 22-items version of the Zarit [18]. Each item is a statement which the caregiver is asked to respond to, using a five-point scale with options ranging from 0 (never) to 4 (nearly always) (burden scores: <21, little or no burden; 21-40, mild to moderate burden; 41-60, moderate to severe burden; >61, severe burden). *Barthel index* measures the patient's ability to perform ten basic activities of daily living, providing a quantitative estimate of the dependence degree [19]; it is recommended for measuring physical disability (scores: 90-99, mild dependence; 61-89, moderate dependence. 21-60, severe dependence; <20, complete dependence).

Statistical analysis: the analyses were performed on data from the FCs of the survey (n=210). Qualitative data are summarised by absolute and percent frequencies, while quantitative data by mean ± standard deviation (SD), median, range (minimum-maximum).

Patients and FCs were grouped according to patients' characteristics (rare diseases: 10 groups; age group: child *vs* adult) and FCs' characteristics (sex: male *vs* female; age class: up to 39, 40-54, 55 years and over; work condition: occupied *vs* retired *vs* homemaker *vs* other). Differences among subgroups with respect to categorical variables were analysed by chi-square test, or Fisher's exact probability test when appropriate. For the analysis of the quantitative variables, that is Zarit index, Barthel index, EQ-5D-VAS for both patients and FCs and the number of hours/week devoted to care, we used parametric analysis of variance (ANOVA) or non-parametric Kruskal-Wallis test. Multiple comparisons were performed by Tukey test. Since results were in accordance, only nonparametric analyses are reported.

Association between quantitative variables was assessed by Pearson linear correlation coefficient. Multiple linear regression analysis was performed to assess the effect of selected quantitative and/or categorical variables on the quantitative outcomes burden and FCs' HRQoL. Two regression models were applied, including different sets of potential explanatory variables. Model A included FCs' sex, patient's HRQoL, Barthel index, principal and support caregiver's number of hours/week devoted to care, and burden (the latter when assessing the effect of variables on FCs' HRQoL). Model B included Barthel index, patient's age, kind of pathology. For the latter, DMD was chosen as the reference level being the pathology with the more numerous FCs. The variance inflation factor (VIF) was calculated to test for multicollinearity among the independent variables, which was excluded for VIF values lower than 5. All VIF values were actually lower than 1.5.

The statistical analyses were then repeated on the subsample of FCs who were parents of the patients (n=182).

In particular, to assess the hypothesis that FCs are more frequently females than males we analyzed data on the subset of RDs patients living with both parents, using the Binomial test to assess if the proportion of female FCs in the parental couples was significantly different from the chance level of 50%.

All the analyses were performed using STATA release 16.0.

Limits of this study were: convenience samples, low number of caregivers and too few male FCs; no data on disease severity or phenotypic classification was collected by the questionnaire.

RESULTS

Family caregivers' characteristics and sex/gender differences

As reported in *Table 1a*, FCs showed significant sex/gender specific differences of the number of hours/week devoted to care with women dedicating a higher number of hours (53.7±34.1) as compared to men (41.8±32.7). Differently, no significant sex/gender-specific differences were detected for burden or HRQoL.

However, on regard to burden, we detected significant differences between males and females in the answers to Zarit single items. Specifically, to the question "do you feel fear for the future" 68.5% of women *vs* 43.4% of men answered "always" or "very often". Similarly, 54.7% of men *vs* 31.5% of women answered "never" to the question "do you believe that taking care of your family member has adversely affected your health" (*Tables 1aS* and *1bS* available online as *Supplementary Material*).

Since the significant sex/gender specific differences in the caregiver's age and employment status, we analysed burden in FCs grouped by sex (males *vs* females), age groups (up to 39 years, 40-54 years, over 55 years), and working condition (occupied *vs* retired *vs* homemaker *vs* others) (see *Table 2S* available online as *Supplementary Material*). Our results indicate that: a) in the 40-54 age

Table 1a
Socio-demographic characteristics of family caregivers by sex

Characteristics	Males	Females	Total	Significance level p
	n mean (SD) median (min-max)	n mean (SD) median (min-max)	n mean (SD) median (min-max)	Mann-Whitney U test
Age	56 51.2 (11.2) 50 (28-78)	152 44.0 (9.1) 43 (25-82)	208 45.7 (10.2) 45 (25-82)	**<0.001*** **
Zarit tot	53 25.6 (12.6) 22 (0-60)	146 28.1 (12.6) 27 (6-59)	199 27.4 (12.5) 25 (0-60)	0.185
EQ5D-VAS	49 78.9 (17.5) 80 (30-100)	144 78.7 (14.5) 80 (30-100)	193 78.7 (15.3) 80 (30-100)	0.563
FC n hours/week	57 41.8 (32.7) 36.8 (0-112)	153 53.7 (34.1) 47.7 (0-112)	210 50.5 (34.1) 46.7 (0-112)	**0.023***
	n (%)	***n (%)***	***n (%)***	***Fisher's exact probability test***
Marital status	56	150	206	0.600
Single + widow	4 (7.1%)	17 (11.3%)	21 (10.2%)	
Divorced + Separated	2 (3.6%)	9 (6.0%)	11 (5.3%)	
Married	50 (89.3%)	124 (83.7%)	174 (84.5%)	
Occupational status	57	153	210	**<0.001*** **
Employed	42 (73.7%)	76 (49.6%)	118 (56.2%)	
Retired	9 (15.8%)	16 (10.5%)	25 (11.9%)	
Homemakers	3 (5.3%)	45 (29.4%)	48 (22.9%)	
Other	3 (5.3%)	16 (10.5%)	19 (9.0%)	

FC: family caregiver; Other: never occupied or forced to leave job.
SD: standard deviation; min-max: minimum-maximum; p: significance levels of the Fisher's exact probability test or of the Mann-Whitney U test: * p≤0.05; *** p≤0.001.

Table 1b
Married/cohabiting family caregivers grouped by sex and age

Married/cohabiting FCs	<39 age n (%)	40-54 age n (%)	>55 age n (%)	Total n (%)
	p<0.001* **	**p<0.001*** **	p=0.315	
Males	5 (11.1%)	25 (27.5%)	7 (41.0%)	37 (24.1%)
Females	40 (88.9%)	66 (72.5%)	10 (59.0%)	116 (75.8%)
Total	45 (100.0%)	91 (100.0%)	17 (100.0%)	153 (100.0%)

FC: family caregiver.
p: significance level with binomial test: *** p≤0.001.

group, commonly representing the working age, 9% of women were already retired and reported moderate levels of burden, whereas no man was retired in the same age group. The occupied women were less numerous than men and female homemakers were more numerous than males with burden levels double than men; b) not considering age, women never occupied or forced to leave work (named as others), suffered higher levels of burden as compared to men; c) female FCs, under 39 years of age and occupied, reported more burden than males of the same age group, likely for the presence of additional stressors, such as reconciling time for family care with work outside home. Despite the not significant differences found between the different groups, due to the small sample size, the above data suggest that gender specific burden differences can be associated with FCs' age and working status conditions.

Among the 179 FCs respondents to the marital status item, we selected the 153 cohabiting/married FCs, assuming that they are one of the two members of a parental couple with a rare disease patient in a home care context. We stratified them by sex and age in order to investigate if an equal sex/gender distribution of the care activity might exist between the two members of a parental couple. Results, shown in *Table 1b*, indicate that there is a significant sex/gender difference of the care activity in the age groups under 39 and 40-54 years of age with women representing 88.9 and 72.5% respectively ($p<0.001$ in both groups when compared to the 50% expected in case of parity). Only in the over 55 years age group, the percentage of females dropped, being only slightly over the 50% expected parity frequency ($p=0.31$).

We also stratified FCs by patient's age, child *vs* adult. We did not observe significant differences in burden, HRQoL or number of hours/week between FCs who care for children or adults patients. We indeed observed a significant difference in the answers to the EQ-5D item, asking caregivers to refer their actual pain and discomfort. FCs caring for adults showed pain and discomfort more frequently (63% *vs* 37%; *Table 3S* available online as *Supplementary Material*) and with high intensity as compared to those caring for child patients. Specifically for those caring children the median was positioned in the answer "no pain and discomfort", while for those caring adults the median was positioned in the answer "mild pain and discomfort".

Family caregivers grouped by the 10 RDs

Table 2 reports the characteristics of FCs grouped according to the 10 RDs. Sex distribution of FCs among RDs was not so much different, being females more than 62% in all RDs, except for Scl with 58.8% males. This exception can be explained by the fact that Scl patients are mainly adult females and their FCs are primarily their partners. FCs age was significantly different among 10 RDs with a mean value of 45.9±10.2. Multiple paired comparisons showed that FCs of Scl patients were significantly older than FCs of PWS, DMD, CF and FXS patients, due to the fact that Scl arises in adulthood, while other pathologies mostly arise in pediatric age (although can also occur in adolescence/adulthood).

Burden levels, as measured by the total Zarit score, showed large significant differences among RDs with an overall mean value of 27.4±12.5. We classified RDs in two subgroups, based on the mean FCs' burden level, above or below the overall mean: FCs of PWS, FXS, EB and MPS patients reported moderate levels of burden, while FCs of Hem, JIA, CF, DMD and Scl patients reported light/mild levels of burden. Due to the presence of only 6 FCs of His patients, the statistical power of the comparisons involving His is too low to make results of such comparisons reliable. Multiple paired comparisons stated that PWS specific burden is significantly heavier than that of Hem, JIA, CF and DMD; FXS heavier than that of Hem and JIA, while EB and MPS higher than that of Hem.

No HRQoL significant differences were observed among the 10 selected RDs.

The overall mean number of hours/week devoted to care was 50.5±34.1, with significant differences among 10 RDs. We distinguished three different FCs groups: MPS, EB and PWS requiring the highest number of hours/week devoted by FCs, DMD, FXS and CF the intermediate number and Hem, Scl and JIA the lowest number. The quite large SDs, within any disease group, suggest that the kind of pathology is only one of the factors determining the number of hours/week that are necessary to patient's care. As consequence of this high variability, no paired comparison was statistically significant.

Patients' characteristics

Out of the 683 RD patients of the BURQoL survey, we selected the 210 of them that reported to be assisted by a FC. About the rest, the information was lacking or patients were cared by a formal caregiver [16].

A description of the 210 RD patients' characteristics is shown in *Table 3a*. Patients were 67.6% males *vs* 32.4% females, being sex distribution significant different among RDs: all males in Hem and DMD; mostly males in CF, FXS, MPS and JIA; mostly females in PWS and Scl and the same percentage of males and females in His and EB.

The mean value of patient's age was 17.3±16.5 and Scl patients were significantly older than all the other RD patients.

Patients showed a Barthel index mean value of 66.9±32.4, which is in the range of moderate dependence. DMD and MPS patients reported severe dependence while PWS, Scl, FXS and EB moderate dependence and Hem, CF and JIA mild dependence.

Patient's HRQoL mean value was 60.7±20.6. Better HRQoL was observed in JIA, CF and Hem patients, in agreement with their good levels of self-sufficiency. FXS patients reported a similar better HRQoL, even if they are more dependent than JIA, CF or Hem patients. PWS and DMD patients showed an intermediate HRQoL score. The worst scores were reported by EB, MPS and Scl patients.

Interestingly, we observed a very large HRQoL difference between child and adult patients, with adults showing a worse HRQoL than children, and a smaller Barthel difference between the two groups (*Table 3b*).

Table 2
Characteristics of family caregivers grouped by 10 rare diseases

Rare diseases	Family caregivers					
	Subjects n	Sex n (%)	Age n mean (SD) median (min-max)	Zarit n mean (SD) median (min-max)	EQ5D-VAS n mean (SD) median (min-max)	n hours/week n mean (SD) median (min-max)
		p=0.061	**p=0.005****	**p<0.001*****	p=0.826	**p=0.020***
1. PWS	24	M: 4 (16.7) F: 20 (83.3)	24 44.3 (9.7) 43 (28-66)	23 36.7 (12.9) 37 (16-60)	22 76.8 (16.0) 80 (50-95)	24 58.2 (36.4) 61.5 (0.0-112.0)
2. Hem	14	M: 2 (14.3) F: 12 (85.7)	14 45.3 (11.0) 42 (33-70)	14 16.4 (5.7) 16 (9-28)	14 82.1 (15.3) 85 (60-100)	14 36.0 (41.2) 16.3 (0.0-112.0)
3. DMD	51	M: 18 (35.3) F: 33 (64.7)	51 46.8 (8.8) 46 (28-66)	50 25.4 (10.3) 26 (0-50)	49 79.4 (14.2) 80 (50-100)	51 52.3 (29.6) 46.7 (6.4-112.0)
4. Scl	17	M: 10 (58.8) F: 7 (41.2)	16 56.5 (12.6) 57 (31-78)	16 26.1 (10.8) 23.5 (11-46)	14 71.4 (20.6) 75 (40-100)	17 34.9 (26.6) 26.5 (0.0-102.0)
5. CF	43	M: 11 (25.6) F: 32 (74.4)	43 42.7 (8.0) 43 (25-57)	40 24.6 (9.8) 24 (6-53)	39 82.4 (12.1) 85 (50-100)	43 46.7 (33.7) 38.5 (0.6-112.0)
6. FXS	12	M: 2 (16.7) F: 10 (83.3)	12 44.6 (13.5) 40 (31-76)	12 34.6 (12.7) 36 (15-59)	12 76.7 (11.3) 77.5 (60-95)	12 49.9 (27.1) 44.2 (22.0-102.1)
7. His	6	M: 0 (0.0) F: 6 (100.0)	6 38.7 (3.5) 37.5 (35-43)	6 33.0 (20.9) 33.5 (6-56)	6 77.5 (17.3) 80 (50-95)	6 54.1 (27.7) 64.3 (0.0-76.0)
8. MPS	19	M: 3 (15.8) F: 16 (84.2)	18 48.3 (11.0) 46 (36-82)	16 32.1 (12.3) 29.5 (17-56)	16 76.1 (19.5) 77.5 (30-100)	19 66.0 (41.8) 56.0 (0.0-112.0)
9. JIA	8	M: 3 (37.5) F: 5 (62.5)	8 44.8 (7.0) 42 (38-58)	8 16.9 (7.0) 14 (11-32)	8 79.4 (18.0) 87.5 (45-100)	8 27.8 (28.3) 21.9 (0.0-63.5)
10. EB	16	M: 4 (25.0) F: 12 (75.0)	16 46.3 (10.0) 45 (29-64)	14 32.4 (14.7) 30 (11-52)	13 78.1 (16.7) 80 (30-95)	16 64.2 (33.6) 61.6 (0.0-112.0)
Total	210	M: 57 (27.1) F: 153 (72.9)	208 45.9 (10.2) 45 (25-82)	199 27.4 (12.5) 25 (0-60)	193 78.7 (15.3) 80 (30-100)	210 50.5 (34.1) 46.7 (0.0-112.0)

1. PWS: Prader Willi syndrome; 2. Hem: hemophilia; 3. DMD: Duchenne muscular dystrophy; 4. Scl: scleroderma; 5. CF: cystic fibrosis; 6. FXS: fragile X syndrome; 7. His: histiocytosis; 8. MPS: mucopolysaccharidosis; 9. JIA: juvenile idiopathic arthritis; 10. EB: epidermolysis bullosa.
M: males; F: females.
SD: standard deviation; min-max: minimum-maximum; p: significance level of the Chi-squared test comparing ten rare diseases with respect to sex distribution and of the Kruskal-Wallis test comparing ten rare diseases with respect to age, Zarit, EQ5D-VAS and n of hours/week values:
* p≤0.05; ** p≤0.01; *** p≤0.001. n: number of respondent subjects, when n is lower it means that not all subjects answered to that item.

The worst HRQoL of the Scl patients is in agreement with their older age as compared to other RDs. However, older age is not the only variable playing a role in worsening patient's HRQoL because MPS and EB patients are younger and more dependent than Scl patients and yet they have similar bad HRQoL.

Factors influencing family caregivers' burden

Correlation analyses between the quantitative variables, patients' HRQoL and Barthel index, Zarit, FCs' HRQoL, principal or support FCs' number of hours/week, are shown in *Table 4*. Our results indicate that burden is inversely associated with FCs' HRQoL and, at lesser extent, with patient's HRQoL, while directly to the number of hours/week devoted to care by the principal FC. FCs' HRQoL is directly associated with patient's HRQoL. Finally, the number of hours/week devoted to care by the principal FC are inversely associated with the Barthel index and directly with the number of hours/week devoted to care by a support FC. As for the principal FC, also the number of hours/week devoted to care by a support FC is inversely associated with the Barthel index.

Multiple linear regression analyses are reported in *Table 5*. Considering Model A, burden resulted negatively affected by patient's HRQoL and positively by the number of hours/week devoted to care by the principal FC. Considering Model B, burden levels were affected by the kind of pathology, and not by patient' age or dependence level, with significantly higher levels in PWS,

Table 3a
Characteristics of patients grouped by 10 rare diseases

Rare diseases	Patients				
	Subjects n	Sex n (%)	Age n mean (SD) median (min-max)	Barthel index n mean (SD) median (min-max)	EQ5D -VAS n mean (SD) median (min-max)
		p<0.001***	p<0.001***	p<0.001***	p<0.001***
1. PWS	24	M:11 (45.8) F:13 (54.2)	24 11.4 (8.0) 10 (1-29)	19 70.5 (25.2) 75 (10-100)	19 60.0 (15.3) 55 (35-90)
2. Hem	14	M:14 (100.0) F:0 (0.0)	14 23.2 (22.4) 9 (2-64)	10 89.5 (14.0) 95 (65-100)	10 65.5 (26.5) 65 (30-100)
3. DMD	51	M:51 (100.0) F:0 (0.0)	51 14.0 (8.0) 12 (1-35)	46 43.2 (30.2) 40 (0-100)	46 60.7 (21.5) 60 (10-100)
4. Scl	17	M:3 (17.6) F:14 (82.4)	17 56.5 (14.0) 59 (20-75)	17 75.9 (19.0) 80 (20-95)	16 43.4 (18.5) 42.5 (5-80)
5. CF	43	M:26 (60.5) F:17 (39.5)	43 10.9 (9.0) 10 (0-41)	28 90.5 (25.8) 100 (0-100)	28 69.8 (17.9) 70 (20-100)
6. FXS	12	M:9 (75.0) F:3(25.0)	12 14.7 (11.3) 12 (5-46)	11 70.9 (29.7) 80 (5-95)	11 71.4 (16.6) 70 (30-95)
7. His	6	M:3 (50.0) F:3 (50.0)	6 4.2 (2.9) 3 (3-10)	1 90 90	1 50 50
8. MPS	19	M:12 (63.2) F:7 (36.8)	19 18.6 (14.9) 13 (1-55)	16 45.6 (37.9) 47.5 (0-100)	15 50.7 (20.5) 50 (10-90)
9. JIA	8	M:5 (62.5) F:3 (37.5)	8 8.3 (4.0) 8 (2-13)	6 97.5 (6.1) 100 (85-100)	6 75.0 (8.9) 72.5 (65-90)
10. EB	16	M:8 (50.0) F:8 (50.0)	16 16.3 (12.5) 14.5 (0-42)	12 72.9 (13.6) 70 (55-90)	12 55.4 (16.8) 52.5 (30-90)
Total	210	M:142 (67.6%) F:68 (32.4%)	210 17.3 (16.5) 12 (0-75)	166 66.9 (32.4) 75 (0-100)	164 60.7 (20.6) 60 (5-100)

1. PWS: Prader Willi syndrome; 2. Hem: hemophilia; 3. DMD: Duchenne muscular dystrophy; 4. Scl: scleroderma; 5. CF: cystic fibrosis; 6. FXS: fragile X syndrome; 7. His: histiocytosis; 8. MPS: mucopolysaccharidosis; 9. JIA: juvenile idiopathic arthritis; 10. EB: epidermolysis bullosa.
M: males; F: females.
SD: standard deviation; min-max: minimum-maximum; p: significance level of the Chi-squared test comparing ten rare diseases with respect to sex distribution and of the Kruskal-Wallis test comparing ten rare diseases with respect to age, Barthel index and EQ5D-VAS values: *** p≤0.001.
n: number of respondent subjects, when n is lower it means that not all subjects answered to that item.

FXS and MPS compared to DMD, and lower levels in Hem. On the contrary, the kind of pathology did not affect FC's HRQoL.

DISCUSSION

The study of sex/gender-specific health differences in FCs is of considerable importance in order to address precision medicine. FC population may present some health risk factors associated to home care activity, impacting males and females differently [1]. A recent study on RD patients reported that female FCs perceived the condition of their child to be highly symptomatic and requiring disease control, with negative consequences. By contrast, male FCs had stronger perceptions regarding the negative effects of the disease on the child's QoL. This sex/gender discrepancy of illness perception may contribute to female higher levels of stress and depressive symptoms than males [20]. In addition, mothers of RD patients were significantly more impaired in their QoL and mental health, as compared to fathers [15].

Indeed, not only the care activity itself but also the socio-cultural influencing factors may impact FCs' health in a gender specific way. At this regard, a recent study, about caregiving experiences of fathers and mothers of RD children in Italy, showed that gender differences emerged in the social support experienced, in the different challenges to be faced and in the narratives about the specific experience of the caregiving impact on job and, more in general, on worries [21]. Moreover, the enhanced cost of informal care, other than resulting in

Table 3b
Characteristics of patients with rare diseases grouped by age: children *vs* adults

Group	Patients			
	Subjects n	Sex n (%)	Barthel index n mean (SD) median (min-max)	EQ5D -VAS n mean (SD) median (min-max)
		p=0.038*	p=0.025*	p<0.00***
Child	145	M: 105 (72.4) F: 40 (27.6)	101 71.0 (30.3) 80 (0-100)	100 66.8 (19.2) 70 (10-100)
Adult	65	M: 37 (56.9) F: 28 (43.1)	65 60.5 (34.6) 70 (0-100)	64 51.0 (19.0) 50 (5-90)
Total	210	M: 142 (67.6) F: 68 (32.4)	166 66.9 (32.4) 75 (0-100)	164 60.7 (20.6) 60 (5-100)

EQ5D-VAS: EuroQoL-5 dimensions Visual Analogue Scale.
SD: standard deviation; min-max: minimum-maximum; p: significance level of the Chi-squared test comparing child versus adult patients with respect to sex distribution and of the Kruskal-Wallis test comparing child *vs* adult patients with respect to Barthel index and EQ5D-VAS: * p≤0.05; *** p≤0.001.
M: males; F: females. n: number of respondent subjects, when n is lower it means that not all subjects answered to that item.

Table 4
Pearson's pairwise correlation coefficients

	Patients EQ5D-VAS	Barthel	Zarit	FCs' EQ5D-VAS	Principal FCs' n hours/week	Support care n hours/week
Patients' EQ5D-VAS		0.290***	-0.236**	0.347***	-0.188*	-0.138
Barthel	0.290***		-0.074	0.010	-0.318***	-0.391***
Zarit	-0.236**	-0.074		-0.282***	0.229***	0.115
FCs' EQ5D-VAS	0.347***	0.010	-0.282***		-0.105	-0.090
Principal FCs' n hours/week	-0.188*	-0.318***	0.229***	-0.105		0.468***
Support care n hours/week	-0.138	-0.391***	0.115	-0.090	0.468***	

FC: family caregiver.
The significance levels of the Pearson correlation coefficients r reported in the table are denoted as:: * p≤0.05; ** p≤0.01; *** p≤0.001. The number of subjects was ranging from 144 to 203.

a better patient's QoL, involves a loss of the productivity, as reported in FCs who care for child patients with haemophilia, because of early retirement or loss of working days [22]. Nazco and coauthors recently published an article on burden and HRQoL from FCs of RD patients from six European countries based on the 2012 BURQoL survey. They showed that higher levels of burden are associated with lower caregiver's HRQoL. However, their study did not look at gender-specific differences [13].

Our study showed a significant difference in the number of hours/week devoted to care by women as compared to men FCs. This data is important for the prevention of women's health, considering that a high number of weekly hours of informal caregiving, as opposed to few weekly hours, is associated with a higher risk of cardiovascular disease [23]. Indeed, as the number of hours/week devoted to care resulted directly associated with burden, we suggest that women are at higher risk for burden than men. At this regard, we showed significant gender differences in two Zarit single item answers, reported more frequently by women and consisting in "a strong feeling of fear for the future" and "the belief that the care activity has harmed their own health". It is possible that larger sex/gender associated differences may exist but could be hidden due to the numerical limit of our sample with few male FCs. The higher numerosity of men, mostly husbands, taking care of Scl patients, due to the prevalence of female adult patients (Scl F/M ratio 3:1) [24], makes Scl a useful model for future studies with the aim to verify the true nature of burden and/or HRQoL differences between men and women.

Interestingly, we also detected some sex/gender-specific burden differences according to FCs' socio demographic characteristics, albeit not statistically significant due to the small number of caregivers stratified by sex/gender and occupation: women that have difficulty in keeping their occupation outside home or in reconciling the time necessary for family care with work outside home, showed higher burden levels than men, suggesting that burden levels of female FCs can be influenced by their occupation status. In addition, we observed that care activities are not equally distributed

Table 5
Regression analysis

Model A - Zarit

Independent variables	coeff	95% CI lower; upper	p
FCs' sex	1.352	-3.083; 5.786	0.548
patient' QoL	**-0.121**	**-0.221; -0.021**	**0.018***
Barthel index	0.032	-0.035; 0.098	0.349
FCs' n hours/week	**0.082**	**0.009; 0.154**	**0.028***
Support care n hours/ week	0.031	-0.045; 0.107	0.426

Model A - FC's EQ5D-VAS

Independent variables	coeff	95% CI lower; upper	p
FCs' sex	-1.643	-7.080; 3.794	0.551
Zarit	**-0.296**	**-0.494; -0.098**	**0.004****
patient' EQ5DVAS	**0.214**	**0.091; 0.336**	**<0.001*****
Barthel index	-0.072	-0.154; 0.009	0.081
FCs' n hours/week	-0.063	-0.153; 0.027	0.170
Support care n hours/ week	-0.030	-0.123; 0.063	0.522

FC: family caregiver; coeff: regression coefficient; 95% CI: 95% Confidence Interval;
p: significance levels: * p≤0.05; ** p≤0.01; *** p≤0.001.

Model B - Zarit

Independent variables	coeff	95% CI lower; upper	p
Barthel index	-0.004	-0.076; 0.068	0.906
Patient's age	-0.042	-0.220; 0.136	0.643
Rare disease *(vs DMD)*			
PWS	**11.624**	**5.029; 18.219**	**<0.001*****
Hem	-8.425	-17.706; 0.857	0.075
Scl	2.435	-8.082; 12.953	0.648
CF	0.259	-6.236; 6.754	0.937
FXS	**10.559**	**2.680; 18.438**	**0.009****
His	-11.500	-34.644; 11.644	0.328
MPS	**7.755**	**0.544; 14.966**	**0.035***
JIA	-7.134	-17.685; 3.416	0.183
EB	2.974	-5.333; 11.280	0.480

PWS: Prader Willi syndrome; Hem: hemophilia; DMD: Duchenne muscular dystrophy;
Scl: scleroderma; CF: cystic fibrosis; FXS: fragile X syndrome; His: histiocytosis; MPS: mucopolysaccharidosis; JIA: juvenile idiopathic arthritis; EB: epidermolysis bullosa;
Reference group: Duchenne muscular dystrophy. coeff: regression coefficient; 95% CI: 95% Confidence Interval; p: significance levels: * p≤0.05; ** p≤0.01; *** p≤0.001.

between mothers and fathers of the parental couples, with mothers being prevalent. As consequence, women may undergo to social and health inequality because of sex and gender differences [25, 26].

Moreover, our results showed that there are significant burden differences among FCs, depending on the kind of rare disease: FCs of patients with PWS, FXS, MPS and EB are those reporting the highest levels of burden. We suggest that PWS, FXS, MPS and EB patients may have specific challenges, independently from dependence, that can be more stressful for their FCs, as for example: hyperphagia and obesity in PWS; developmental delay and autism in FXS; progressive damage which affects patient's appearance, physical abilities, organ function and mental development in MPS patients; only palliative treatment available and reduced life expectancy in EB patients [27-30]. On the contrary, the good levels of self-sufficiency and better HRQoL, reported in Hem, JIA and CF patients, may be responsible for the lowest burden levels. The highest number of hours/week devoted to care by PWS, MPS and EB caregivers, suggests that this can be one of the factors enhancing their burden. In MPS and EB patients, it is possible that their reported worst HRQoL can contribute to increase burden too, while it is not in PWS and FXS patients that reported a better HRQoL. In addition, those FCs showing more burden than others could be at higher risk for their health. However, we need further research to identify the specific RD challenges involved in health risks, for example comparing burden with both patient's clinical diagnosis and mental and physical health data derived from their FCs. Surprisingly, the enhanced burden in PWS, FXS, MPS and EB was not accompanied by a poorer FC's HRQoL, as expected. We suggest that it may depend both on the peculiarities of our Italian sample compared to other European countries [14] and/or on the limit of the EQ-5D tool. In fact, the EQ-5D is a generic tool more suitable for patients with physical disability and dependency [17] than for the generally not dependent FCs. However, we observed a significant HRQoL difference in the answers to one of the five EQ-5D items, asking caregivers to refer their actual pain and discomfort: FCs caring for adults showed more frequently pain and discomfort and with higher intensity, as compared to those caring for child patients, suggesting that physical health is more frequently impaired in FCs of adult rather than child patients.

The UN Resolution "Addressing the challenges of persons living with a rare disease and their families" recently approved by the United Nations General Assembly [31] affirms the need to achieve gender equality, also taking into account "that women and girls undertake a disproportionate share of unpaid care and domestic work when a member of their household or family lives with a rare disease, and that women face more barriers in accessing decent work". Hence, the UN Resolution "Encourages Member States to adopt gender-sensitive national strategies, action plans and legislation, to contribute to the well-being of persons living with a RD and their families, including on the protection and enjoyment of their human rights, consistent with their obligations under international law" [32]. Notably this Resolution contributes to the UN Agenda 2030 Sustainable Development Goals (SDG) and it fits for persons living with a RD patient. Women are disproportionately discriminated in society, either as patients or as mothers of RD patients (SDG5 "Gender inequality"). Families

with a member living with a RD are at greater risk of impoverishment, as they have more expenses and less income (SDG1 "No poverty") [33]. The informal care is a major challenge and it is likely to become even more important in the field of RDs. Informal care is often seen as a cost-effective way of preventing institutionalization and enabling patients to remain at home. In Italy, the family had traditionally a strong role, probably due to largely underdeveloped formal care systems at national level. The findings suggest that formalising informal care through cash payments, legal rights, social security, and training opportunities can have important beneficial effects on informal careers and the patients that they care for.

In conclusion, the significant gender disparity of the number of hours/week devoted to care by female FCs, who have also a social disadvantage in the occupation status because of their traditional family role, suggests that women may be exposed to health risks more than men. These data, together with the identification of those RDs associated to higher burden and likely to worse caregiver's health, provide useful information for socio-health policies in order to improve accuracy and equity in health prevention interventions.

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ORIGINAL ARTICLES AND REVIEWS

Epidemiology and drug susceptibility of nontuberculous mycobacteria (NTM) in Italy in 2016-2020

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Abstract

Introduction. Nontuberculous mycobacteria (NTM) are environmental mycobacteria which may cause pulmonary and extrapulmonary diseases. These organisms are difficult to treat due to their intrinsic drug-resistance. In Italy, no major nationwide study on NTM epidemiology and drug susceptibility was performed.

Methods. Data on the epidemiology of 7,469 NTM clinical isolates identified in Italy in 2016-2020 and on the minimum inhibitory concentrations (MICs) of 1,506 of these strains were analysed.

Results. Overall, 63 species were identified in 42 hospital laboratories located in 16 out of 20 regions, with *Mycobacterium avium* complex (MAC) being the most frequently isolated, followed by *M. gordonae*, *M. xenopi*, *M. abscessus*. The MICs of 12 drugs for MAC, *M. xenopi*, *M. kansasii*, *M. abscessus*, *M. fortuitum* and *M. chelonae* were interpreted for clinical significance (susceptible, intermediate, resistant) based on the guidelines published by the Clinical and Laboratory Standards Institute in November 2018.

Conclusions. Our data are in line with other nationwide studies and may be of value for further update of microbiological and clinical guidelines.

Key words

- *Mycobacterium avium* complex
- *Mycobacterium abscessus*
- drug resistance, clarithromycin
- amikacin

INTRODUCTION

The nontuberculous mycobacteria (NTM) include approximately 200 species, some of which may cause diseases in humans by infecting pulmonary and extrapulmonary tissues [1-4]. Lungs are the most affected, however NTM species are phenotypically different, and generate a wide spectrum of clinical manifestations also in other organs. *Mycobacterium avium* complex (MAC), *M. xenopi*, *M. kansasii* and *M. abscessus* are the most frequent responsible of pulmonary diseases. *M. avium* complex may also cause disseminated infections, while *M. fortuitum*, *M. chelonae* and *M. marinum* are primarily responsible for skin and soft tissue infections initiated via surgery or accidental lesions.

For many years, the classification of Runyon differentiated NTM in two wide categories according to their growth rate, namely the rapidly growing mycobacteria (RGM) (e.g., *M. abscessus, M. fortuitum* and *M. chelonae*) and the slowly growing mycobacteria (SGM) (e.g., MAC, *M. xenopi, M. kansasii, M. simiae*), requiring ≤7 days and >7 days, respectively, to produce colonies on solid media [1-4]. With the increasing use of molecular methods of identification, this phenotypic classification was less used, however recent phylogenetic studies confirmed the separation of RGM and SGM species [5]. Among the RGM, the species of the *M. chelonae-abscessus* complex belonged to the most ancestral cluster, while members of the *M. terrae* complex appeared to be as the most ancestral SGM.

The NTM are highly abundant in the environment (soil, dust, water sources, shower-based aerosols), leading to high rates of human-mycobacterium contacts [2, 3]. Furthermore, host factors such as increasing age of the global population, pulmonary diseases (e.g., bronchiectasis and cystic fibrosis) and immunosuppression, contribute to the rise of NTM lung diseases, increasing worldwide health concern. In addition, mutations in the interferon-gamma-pathway and the use of tumor necrosis factor inhibitors for treatment of inflammatory diseases, increase the risk of MAC and *M. ascessus* infections. The growing availability of molecular tools also increases the detection of NTM infections, which are difficult to treat due to their intrinsic resistance to several antibiotics.

As to the geographical distribution of NTM, a study found that after examination of NTM data received

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from 30 countries across six continents, the species distribution among NTM isolates from pulmonary specimens differed by continent and by country within these continents [6]. Thus, differences in species distribution may partly determine the frequency and manifestations of pulmonary NTM disease in each geographical location. Other investigators found also fluctuations in NTM isolation and distribution. For instance, a systematic review and meta-analysis in mainland China, showed that *M. abscessus* was the prevalent species isolated in 2000-2014, while *M. intracellulare* was more prevalent in 2015-2019 [7, 8]. The geographic diversity of different species showed the effects of environmental and economic factors on NTM distribution. Overall, this epidemiological information can provide important clues on the discrepancies in clinical relevance and treatment outcome of NTM diseases [6].

Surveillance of NTM for monitoring dominant species and their drug resistance profiles would be important to improve the management and treatment of these infections. Reporting of NTM disease to health authorities is not mandated in several countries. However, retrospective cohort studies or laboratory-based studies were recently reported in Germany [9], China [7, 8], United States of America (USA) [10], and other countries.

In Italy, no major information on the epidemiology and drug susceptibility of NTM infections is known [6, 11-13]. Here, we report nationwide data regarding NTM clinical strains isolated in our country in 2016-2020.

EPIDEMIOLOGY

In Italy, the monitoring of demographic and microbiological data on NTM species identification and minimum inhibitory concentrations (MICs) is coordinated by the Istituto Superiore di Sanità (Italian National Institute of Health, Rome, Italy), which operates in collaboration with a network of 42 hospital laboratories located in 16 out of 20 regions (Studio Multicentrico Italiano Micobatteri Non Tubercolari, IMS-NTM, Italian Multicentre Study on Nontuberculous Mycobacteria). The organisms are routinely identified by commercial methods [1] including line probe assay (LPA) (GenoType Mycobacterium CM, AS and NTM-DR; Hain Lifesciences, Nehren, Germany), matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS), and DNA sequencing. The MICs are determined by the broth microdilution method using the SLOMYCOI and RAPMYCOI Sensititre plates (ThermoFisher Scientific, Waltham, MA, USA) [1].

In 2016-2020, the IMS-NTM laboratories reported data on 7,469 nonduplicate NTM clinical isolates belonging to 63 species, including 6,319 SGM (37 species), and 1,150 RGM (26 species). *Figure 1* shows the 15 species representing 97.6% of all NTM isolates. Among the SGM, the MAC (*M. avium, M. intracellulare, M. chimaera*) accounted for 56.5% of all NTM isolated (28.6%, 19.8%, 8.1%, respectively), followed by *M. gordonae* (10.8%), *M. xenopi* (9.7%), *M. kansasii* (2.3%), and other 5 species. The most frequent RGM were *M. abscessus* spp. (6.6%, including the subspecies *M. abscessus ascessus, M. abscessus bolletii, M. abscessus massiliense*: 6.0%, 0.3%, 0.3%, respectively), *M. fortuitum* (4.4%), *M. chelonae* (2.9%), *M. mucogenicum* (0.7%). The methods used for identification were LPA (86%), DNA sequencing (11.2%) and MALDI-TOF MS (2.8%).

Overall, these observations showed that the species distribution in Italy in 2016-2020 was similar to that reported for NTM pulmonary samples in other European countries [6], with MAC organisms being the most frequently isolated, followed by *M. gordonae* and *M. xenopi*.

In 14 out of the 15 species shown in *Figure 1*, ≥64.5% of strains were isolated from pulmonary specimens, while 90.6% of *M. marinum* strains were isolated from extrapulmonary samples. This is in line with the knowledge that *M. marinum* is the causative agent of swimming pool or fish tank granulomas, as the result of finger, hand, arm or elbow soft tissue injuries [1].

Analysis of health-related and demographic characteristics showed that about half (50.3%) of NTM strains were isolated from male patients. In addition, 92.1% were isolated from Italian-born persons (IBP) and 7.9% from foreign-born persons (FBP), with mean ages of 65.1±19.9 and 45.5±19.3 years, respectively. In Italy, in 2019 the IBP and the FBP were 91.1% and 8.9% of resident population, respectively [14]. Thus, the risk of developing NTM infections was similar in IBP and FBP (mostly migrants), likely due to the knowledge that NTM are mostly of environmental origin worldwide. This conclusion is in keeping with a study carried out in Canada, in which NTM colonization risk was not so different between Canadian-born people and foreign-born people residing in Canada for at least 10 years [15].

Noticeably, the pattern of NTM infections is different from that seen in tuberculosis (TB) patients, in which FBP often move from countries with endemic disease to countries with low TB levels, in the search for better living conditions and quality of life. Indeed, in a

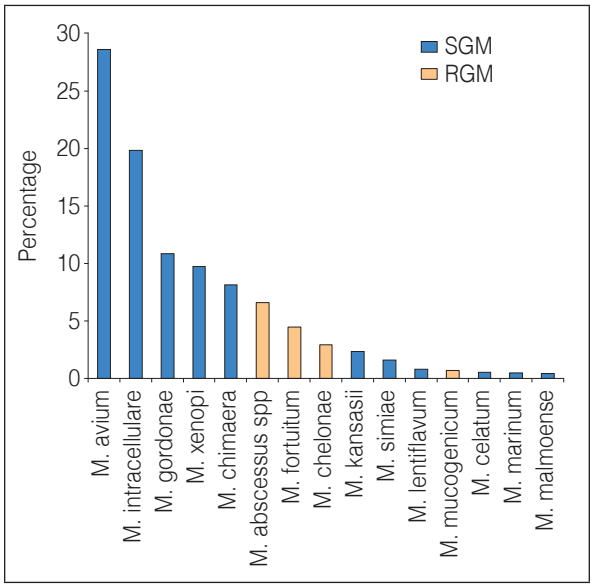

Figure 1
Species distribution among slowly growing mycobacteria (SGM) and rapidly growing mycobacteria (RGM).

recent paper of our group on the extent of TB in Italy in 2011-2020, we showed that 65% of cases were related to young FBP, mostly arrived from Romania, Morocco, Pakistan, Senegal, India [16]. For comparison, the FBP with NTM infections arrived in Italy from 83 countries, with the top six being Morocco (10.9%), Romania (7.8%), Albania (6.2%), Pakistan (5.6%), Nigeria and Senegal (4.9% each), corresponding to most of the countries of FBP with TB. In 2016-2020, the FBP arrived from these six countries represented 43.9% of migrants in Italy [17].

DRUG SUSCEPTIBILITY

The NTM are intrinsically resistant to several drugs, including anti-TB agents, and need to be treated with combinations of antibiotics, based on susceptibility testing. This poses major challenges for new drugs discovery and for therapy of pulmonary and extrapulmonary infections caused by these organisms [18, 19].

Drug resistance of NTM can be intrinsic (natural) or acquired [19]. During the evolution, several mechanisms of intrinsic resistance developed, including decreased permeability of the cell envelope, increased efflux systems and other mechanisms (e.g., drug degradation and target changes), or NTM presence in biofilms and granulomas, which effectively decreased drug uptake. Instead, acquired resistance refers to cases in which, often due to prolonged antibiotic treatments, a resistant strain emerges from a previously drug-susceptible population. Acquired resistance is particularly severe if the target protein is encoded by a single gene copy, increasing the possibility of acquiring mutations after single-drug treatments [19].

The guideline for antimycobacterial susceptibility testing (AST) set in 2011 by the Clinical and Laboratory Standards Institute (CLSI) was updated and expanded in November 2018 [20]. Both guidelines contained recommendations for NTM AST based on clinical data, comparative breakpoints, population distribution and the experience of panel of experts in the field of mycobacteriology [21].

The NTM may colonize the respiratory tract and other sites, thus it is not easy to correlate their isolation with clinical diseases. To this end, specific guidelines for establishing the clinical significance of NTM in patient specimens were published by the American Thoracic Society (ATS) and other scientific organizations in 1990, 1997, 2007 [22], and then updated in July 2020 [23].

Overall, the IMS-NTM laboratories tested 1,506 strains (291 RGM and 1,215 SGM) including 1,275 isolates originated from respiratory samples (84.7%), 201 from non-respiratory specimens (13.3%) and 30 from unknown sources (2%). MICs were interpreted as susceptible (S), intermediate (I), resistant (R), according to the CLSI breakpoints [20]. *Table 1* shows the antimicrobial susceptibility profiles of 12 drugs for 8 species (≥20 MIC values for each drug), including modal MIC, MIC_{50} and MIC_{90}.

The MICs of clarithromycin (CLA), amikacin (AMI), moxifloxacin (MXF) and linezolid (LZD) were interpreted in terms of S, I or R rates. The MICs of *M. xenopi* and *M. kansasii* were interpreted also for RIF, rifabutin (RFB), ciprofloxacin (CIP), doxycycline (DOX), trimethoprim-sulfamethoxazole (SXT). Finally, the MICs of the RGM *M. abscessus* spp., *M. fortuitum* and *M. chelonae* were interpreted also for CIP, DOX, SXT, cefoxitin (FOX), imipenem (IMI) and tobramycin (TOB).

Assuming that a susceptibility rate ≥90% (highlighted in bold) represents high activity of a drug, CLA was highly active against 6 species/complex (MAC, *M. xenopi, M. kansasii, M. chelonae*), AMI against 3 species (*M. xenopi, M. kansasii, M. fortuitum*), MXF against 2 species (*M. xenopi, M. fortuitum*), LZD and RFB against 2 species (*M. xenopi, M. kansasii*), CIP against 1 species (*M. fortuitum*). Rifampicin, DOX, SXT, FOX, IMI and TOB showed susceptibilities <90%.

A comprehensive examination of the MICs of *Table 1*, and of their interpretation in light of the treatments recommended in the 2020 clinical practice guideline [23], is shown below.

MAC

Clarithromycin was the most effective drug against *M. avium, M. intracellulare* and *M. chimaera,* as shown by susceptibility rates of 95.3%, 95.1% and 98.3%, respectively, and modal MICs of 2 µg/mL for each species. *M. avium, M. intracellulare* and *M. chimaera*-resistant isolates were few (2.5%, 3.8% and 0%, respectively), as well as isolates with intermediate macrolide MICs (1.1-2.2%), which may indicate emerging resistance [20]. Higher susceptibility of *M. chimaera* to CLA was reflected also in its MIC_{90} (4 µg/mL), which was 1 dilution lower than those of *M. avium* and *M. intracellulare* (8 µg/mL). In keeping with the modal MICs shown here, CLA is considered a first-line agent for MAC [20]. CLA and AMI are drugs for which a clear correlation between *in vitro* and clinical activity was reported [21].

Amikacin (intravenous, or by inhaled liposomal formulation) is also considered a first-line agent for MAC [20, 21]. Here, the modal MICs were high (*M. avium* and *M. intracellulare,* 16 µg/mL; *M. chimaera*, 8 µg/mL). However, based on the CLSI interpretation [20], most MAC strains were susceptible to AMI (*M. avium,* 72.6%; *M. intracellulare,* 70.8%; *M. chimaera*, 88.4%), and resistance was not very high: *M. avium,* 6.6%; *M. intracellulare,* 4.7% *M. chimaera*, 1.9%. However, unlike what it was observed for CLA, several strains showed high levels of intermediate MICs: *M. avium,* 20.8%; *M. intracellulare,* 24.5%; *M. chimaera*, 9.7%, indicating probable emerging of resistance. Intrinsic resistance to aminoglycosides is due to modification of their hydroxyl and amino groups by specific enzymes, while acquired resistance may be related to their prolonged use in monotherapy, generating mutations in *rrs*, the 16S rRNA gene [2, 21, 24].

Overall, CLA and AMI were more active against *M. chimaera* than *M. avium* and *M. intracellulare*. MICs of CLA and AMI for these three organisms were very similar to those reported in a large European study which analysed a comparable number of MAC isolates [25].

Moxifloxacin and LZD were low active against *M. avium*, *M. intracellulare* and *M. chimaera* (susceptibility

≤33.6%). However, MXF showed modal MICs (2-4 µg/mL) and MIC_{90} (4 µg/mL) lower than those of LZD (16-32 µg/mL and ≥64 µg/mL, respectively). Overall, our data are in keeping with the CLSI indication that MXF and LZD are second-line agents against MAC [20].

According to the 2020 clinical guidelines [23], standard treatment of MAC infections includes ≥3-drug combinations containing the macrolides azithromycin (AZI) or CLA, the rifamycins RIF or RFB and ethambutol (EMB). If a more aggressive therapy is required (e.g., in cases of cavitary disease, extensive bronchiectatic disease, macrolide-resistant MAC), an injectable aminoglycoside (AMI or streptomycin), or liposomal AMI inhalation, may be added. Alternative drugs for patients who are intolerant of, or whose isolate is resistant to CLA and AMI, include MXF, LZD and clofazimine (CLO) [23].

M. xenopi

Clarithromycin, AMI, MXF, LZD and RFB were the most active against this species, as shown by

Table 1
Drug resistance profiles of 8 nontuberculous mycobacteria (NTM) species for 12 drugs

		Drugs											
Organisms	**Parameters**	**CLA**	**AMI**	**MXF**	**LZD**	**RIF**	**RFB**	**CIP**	**DOX**	**SXT**	**FOX**	**IMI**	**TOB**
M. avium	Strains (number)	588	481	562	563								
	Modal MIC (ug/ml)	2	16	2	32								
	MIC50 (ug/ml)	2	16	2	32								
	MIC90 (ug/ml)	8	32	4	≥64								
	Susceptible (%)	**95.3**	72.6	22.8	8.3								
	Intermediate (%)	2.2	20.8	39.1	12.3								
	Resistant (%)	2.5	6.6	38.1	79.4								
M. intracellulare	Strains (number)	367	318	354	352								
	Modal MIC (ug/ml)	2	16	2	32								
	MIC50 (ug/ml)	2	16	2	32								
	MIC90 (ug/ml)	8	32	4	≥64								
	Susceptible (%)	**95.1**	70.8	11.1	8.5								
	Intermediate (%)	1.1	24.5	43.2	10.5								
	Resistant (%)	3.8	4.7	45.7	81								
M. chimaera	Strains (number)	115	103	113	113								
	Modal MIC (ug/ml)	2	8	4	16								
	MIC50 (ug/ml)	2	8	4	32								
	MIC90 (ug/ml)	4	32	4	≥64								
	Susceptible (%)	**98.3**	88.4	18.5	33.6								
	Intermediate (%)	1.7	9.7	31	53.1								
	Resistant (%)	0	1.9	50.5	13.3								
M. xenopi	Strains (number)	88	82	87	87	87	85	87	65	71			
	Modal MIC (ug/ml)	≤0.06	4	0.25	4	1	≤0.25	1	≥16	0.5/9.5			
	MIC50 (ug/ml)	0.25	4	0.5	4	1	≤0.25	1	8	0.5/9.5			
	MIC90 (ug/ml)	1	16	1	8	4	1	2	16	8/152			
	Susceptible (%)	**97.8**	**96.3**	**90.8**	93	81.6	**97.7**	68.9	7.6	85.9			
	Intermediate (%)	1.1	0	6.9	1.2	-	-	23	33.9	-			
	Resistant (%)	1.1	3.7	2.3	5.8	18.4	2.3	8.1	58.5	14.1			
M. kansasii	Strains (number)	48	43	45	44	48	46	47	33	40			
	Modal MIC (ug/ml)	0.5	4	0.5	2	0.5	≤0.25	2	≥16	8/152			
	MIC50 (ug/ml)	0.5	4	0.5	4	0.5	0.5	4	16	8/152			
	MIC90 (ug/ml)	2	16	2	8	2	≤0.25	16	≥16	≥8/152			
	Susceptible (%)	**100**	**90.7**	77.8	**90.9**	87.5	**97.8**	23.4	12.1	37.5			
	Intermediate (%)	0	2.3	17.8	6.8	-	-	23.4	15.2	-			
	Resistant (%)	0	7	4.4	2.3	12.5	2.2	53.2	72.7	62.5			

Continues

Table 1
Continued

Organisms	Parameters	Drugs											
		CLA	AMI	MXF	LZD	RIF	RFB	CIP	DOX	SXT	FOX	IMI	TOB
M. abscessus spp	Strains (number)	186	195	175	194			189	174	177	189	171	106
	Modal MIC (ug/ml)	≥16	16	≥8	≥32			≥4	≥16	≥8/152	64	≥64	≥16
	MIC50 (ug/ml)	2	16	8	16			4	≥16	≥8/152	64	16	16
	MIC90 (ug/ml)	≥16	32	≥8	≥32			≥4	≥16	≥8/152	≥128	≥64	≥16
	Susceptible (%)	52.7	76.4	9.3	47.4			11.6	3.5	11.9	22.2	14	13.7
	Intermediate (%)	7	13.3	14.9	22.2			11.1	3.4	-	52.9	42.7	12.7
	Resistant (%)	40.3	10.3	75.8	30.4			77.3	93.1	88.1	24.9	43.3	73.6
M. fortuitum	Strains (number)	44	44	43	43			44	42	42	43	42	22
	Modal MIC (ug/ml)	≥16	≤1	≤0.25	2			≤0.12	≥16	≥8/152	16	4	≥16
	MIC50 (ug/ml)	2	≥1	≤0.25	2			≤0,12	8	≥8/152	32	4	8
	MIC90 (ug/ml)	8	4	0.5	16			0.25	≥16	≥8/152	≥128	32	≥16
	Susceptible (%)	50.6	**100**	**100**	88.4			**100**	23.8	83.3	44.2	59.5	9.1
	Intermediate (%)	9.1	0	0	2.3			0	11.9	-	39.5	19.1	31.8
	Resistant (%)	40.3	0	0	9.3			0	64.3	16.7	16.3	21.4	59.1
M. chelonae	Strains (number)	37	36	23	22			35	36	20	36	35	34
	Modal MIC (ug/ml)	0.25	32	≥8	16			≥4	≥8	≥8/152	≥128	≥64	2
	MIC50 (ug/ml)	0.5	16	4	16			2	≥8	≥8/152	≥128	32	2
	MIC90 (ug/ml)	2	32	≥8	≥32			≥4	≥8	≥8/152	≥128	≥64	4
	Susceptible (%)	**94.6**	72.2	26.1	40.9			31.4	19.4	15	6.6	14.2	61.7
	Intermediate (%)	0	27.8	17.4	40.9			20	16.7	-	21.2	28.6	32.4
	Resistant (%)	5.4	0	56.5	18.2			48.6	63.9	85	72.2	57.2	5.9

CLA: clarithromycin; AMI: amikacin; MFX: moxifloxacin; LZD: linezolid; RIF: rifampicin; RFB: rifabutin; CIP: ciprofloxacin; DOX: doxycycline; SXT: trimethoprim-sulfamethoxazole; FOX: cefoxitin; IMI: imipenem; TOB: tobramycin; (-): MIC value not indicated in the Clinical and Laboratory Standards Institute (CLSI) M62 document [20]; empty spaces: MIC interpretation not reported in the M62 document; percentages of drug susceptibility ≥90% are highlighted in bold. MIC: minimum inhibitory concentration.

susceptibility of 90.8-97.8%, modal MICs of ≤0.06-4 µg/mL, and MIC_{90} of 1-16 µg/mL to these drugs. Based on susceptibility, RIF was less active than RFB, and CIP was less active than MXF. Trimethoprim-sulfamethoxazole was very active, while DOX was not active (susceptibility of 85.9% and 7.6%, respectively).

The 2020 guideline on the therapy of NTM pulmonary diseases [23], recommended regimens of ≥3 drugs including the macrolides AZI (or CLA) and/or MXF, RIF or RFB, EMB. As suggested for MAC infections, treatment of *M. xenopi*-infected patients with cavitary or advanced/severe bronchiectatic diseases, should include addition of parenteral AMI to above drugs, and obtaining expert consultation for the management of these complicated infections [23], Our data that *M. xenopi* isolates showed high susceptibility not only to CLA, AMI, MXF and RFB, but also to LZD, adds another drug to the therapeutic armamentarium for these patients, which should be treated aggressively given the high mortality of the disease. The high activity of LNZ against *M. xenopi* was previously reported by other investigators [26].

M. kansasii

Similar to that seen with *M. xenopi,* CLA, AMI, LZD and RFB were the most active also against *M. kansasii* (susceptibility of 90.7-100%, modal MICs of ≤0.25-4 µg/mL, MIC_{90} of ≤0.25-16 µg/mL). Moxifloxacin was less active against *M. kansasii* than against *M. xenopi* (susceptibility of 77.8% and 90.8%, respectively). Susceptibilities to SXT, CIP and DOX were ≤37.5%. Clarithromycin and RIF are considered to be the first-line agents for *M. kansasii* infections [20]. Here, RIF was a bit less active than RFB (susceptibilities of 87.5% and 97.8%, respectively). The therapeutic regimen against *M. kansasii* recommended in the 2007 guideline contained isoniazid (INH), EMB and RIF [1, 22]. However, two subsequent studies demonstrated good treatment outcome when CLA was substituted for INH [23]. Thus, the guidelines updated and expanded in 2020 [23] recommended 3-drug oral regimens containing either INH or a macrolide (AZI or CLA) in combination with RIF (or RFB) and EMB. The parenteral use of AMI is not warranted unless it is impossible to use oral regimens, or severe disease is present [23]. As for *M. xenopi,* also *M. kansasii* showed high susceptibility to LZD [26].

M. abscessus spp.

None of the 12 drugs tested showed ≥90% susceptibility against this species. All modal MICs and MIC_{90}

were ≥4 µg/mL. Clarithromycin and AMI were the most active against these difficult-to-treat pathogens (susceptibility of 52.7% and 76.4%, respectively); all other drugs had susceptibilities ranging from 3.5% (DOX) to 47.4% (LZD). A large study on RGM showed a similar MIC pattern [27].

Acquired resistance to CLA may be due to mutations in the *rrl,* the 23S rRNA gene. Furthermore, adaptive resistance is related to over-expression of erm(41), a CLA-inducible enzyme methylating a nucleotide in the 23S rRNA [2, 21, 24]. Clarithromycin-resistant strains (40.3%) had MICs ≥8 µg/mL.

M. abscessus was quite susceptible to AMI (76.4%). However, the modal MIC was high (16 µg/mL) and 10.3% of isolates had MICs ≥64 mg/ml, likely due to mutations in the *rrs*, the 16S rRNA gene [2, 21, 24].

Thus, treatments of *M. abscessus* infections are related to the macrolide susceptibility pattern, including mutational resistance (*rrl* mutations) or inducible resistance (functional erm(41) gene: resistant; non-functional erm(41) gene: susceptible) [23]. They comprise surgical resection of lung tissue, and/or multidrug therapy with AZI (or CLA), AMI, FOX, IMI, LZD, tigecycline and CLO, a drug that may act synergistically with AMI and macrolides [23]. Overall, our MICs values are fully in line with the great difficulty to treat these infections.

M. fortuitum

Amikacin, MXF and CIP were the most active against this species (susceptibility of 100%). High susceptibility to MXF and AMI was also reported by other investigators [27, 28]. Linezolid and SXT showed susceptibilities of 88.4% and 83.3%, respectively, while CLA was active against 50.6% isolates. *M. fortuitum* infections are usually treated with two drugs, including AMI, LZD, sulfonamides, DOX [1]. Our observations that the fluoroquinolones MXF and CIP were very active *in vitro* may be useful for the management of these infections.

M. chelonae

Clarithromycin, AMI and TOB were the most active drugs against this species (susceptibilities of 94.6%, 72.2% and 61.7%, respectively) but TOB showed high intermediate MIC rates (32.4%). A similar pattern was shown by a large study on RGM [27]. All other drugs had susceptibilities ≤40.9%. Regimens for treatment of *M. chelonae* infections may include CLA, TOB or AMI, LZD, IMI or CLO [1].

CONCLUSIONS

The NTM species distribution in Italy is similar to that reported in other European countries [6]. Furthermore, the MIC values, being similar to those reported in other nationwide studies on SGM [25] and RGM [27], indicate a good quality of the performance of NTM DST in our country. The observation that LZD, despite adverse reactions observed during treatment with this drug in some cases [23], was highly active *in vitro* against *M. xenopi* and *M. kansasii* isolates, may be important to design new therapeutic regimens against these pathogens.

Authors' contributions

FG, AL, AI and LF conceived and wrote the study; the IMS-NTM laboratories collected the data and critically revised the manuscript.

Conflict of interest statement

None.

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Epidemiology of perinatal depression in Italy: systematic review and meta-analysis

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Abstract

Introduction. This review aims to synthesise the studies that have estimated the prevalence of perinatal depression in Italy, summarising the results of the existing literature based on their quality.

Materials and methods. Systematic searches were conducted in four major databases, and a random effect meta-analysis was performed to achieve the pooled variance of perinatal depression.

Results. The pooled prepartum risk of depression prevalence was 20.2% (CI 95% 15.3-24.5) while the postpartum risk of depression prevalence was 27.5% (CI 95% 17.8-37.3) for an Edinburgh Postnatal Depression Scale (EPDS) cut-off score ≥9 and 11.1% (CI 95% 6.0-16.2) for an EPDS cut-off score ≥12. Significant publication bias was found and was determined by the presence of a small study with a low prevalence and a large study with a high prevalence.

Conclusion. The prevalence of perinatal risk of depression is similar to that reported in other countries. The high prevalence of prepartum risk suggests the need to activate specific prevention actions during this period.

Key words

- prepartum depression
- postpartum depression
- prevalence

INTRODUCTION

Depression is one of the most frequent complications for women in the perinatal period, defined as the period from pregnancy to the first year after childbirth [1]. It is a moment characterised by greater vulnerability, often associated with anxiety, and an impoverishment of the quality of personal and family life, which can lead to compromise in the child's emotional, intellectual, and cognitive development. Several reasons may explain women's increased vulnerability to depression during and after pregnancy, including the physical, emotional, and hormonal changes associated with pregnancy and childbirth, as well as the life-changing and family redefinition that having a child brings [2]. Based on current research, the strongest predictors of depression during the perinatal period are maternity blues, previous depression, family psychiatric history, unplanned pregnancy, partner relationship difficulties, stressful life events, and poor social support [3-6].

Recent systematic reviews highlight a prevalence of depressive disorder of 15-20% in the prenatal period and 16-18% in the postpartum period, with higher proportions in low- and middle-income countries [7, 8].

In Italy, several studies have investigated the diffusion of depression in the perinatal period, reporting highly variable prevalence estimates. Most of the studies were conducted locally on small samples, making results difficult to compare because of the period in which the screening was performed (in pregnancy, at delivery, and 1, 3, 6, and 12 months after delivery), the various instruments used, and the chosen cut-off values. The most commonly used screening tools are the Whooley questions [9], the Edinburgh Postnatal Depression Scale (EPDS) [10], the Beck Depression Inventory (BDI) [11, 12], the Center for Epidemiological Studies-Depression Scale (CES-D) [13], the Patient Health Questionnaire-9 (PHQ-9) [14, 15]. Among the tools mentioned, the most communly used for assessing the risk of depression in women during pregnancy and after childbirth [16, 3] is the EPDS. As indicated in the validation study of the Italian version [17], the choice of the cut-off value to use depends on the objectives of the evaluation: a cut-off of 9/10 seems to be the most suitable in screening programmes or population surveys, while a cut-off of 12/13 is usually recommended in clinical assessment and research, particularly in ef-

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fectiveness studies in practise (effectiveness), in which it is intended to treat only people with a higher probability of developing depression in the perinatal period. Different cut-offs result in different values of sensitivity, specificity, and positive and negative predictive values. A recent Italian study showed high internal consistency with a Cronbach's alpha of 0.80 during pregnancy and 0.87 following delivery [18].

The present systematic review aims to revise the studies that have estimated the prevalence of perinatal depression in Italy, summarizing the results of the existing literature based on their quality.

METHOD

This systematic review adheres to the PRISMA guidelines [19-21].

The Web of Science, Pubmed, PsycoInfo and Scopus electronic databases were systematically queried, considering papers published from January 1, 2000, to May 20, 2022. The following MESH terms and free words were combined to construct the search string: "depression" "maternal depression" "postpartum", "perinatal", "prenatal", "postnatal", "pregnancy", "prevalence", "incidence", "mother", "maternal", "Italian study", "Italian women". Finally, the bibliographies of the included studies were evaluated to identify additional relevant studies, including grey literature.

The inclusion criteria were: 1) studies reporting prevalence estimates of depression in the perinatal period; 2) studies using the EPDS as a screening tool for assessing the risk of depression; and 3) studies conducted in Italy.

Studies reporting prevalence estimates of depression in association with anxiety and studies using screening tools other than the EPDS were excluded.

After the exclusion of the duplicates through the titles, the abstracts were analysed to select the studies pertinent to the topic based on the exclusion/inclusion criteria.

The complete text of the studies considered eligible for this review was acquired.

Two reviewers independently assessed the methodological quality of the extracted studies. For the quality assessment, the "checklist for prevalence studies" developed by the working group of the Joanna Briggs Institute, Australia [22] was used (*Figure 1*).

The checklist questionnaire contains 9 items with a four-level response method: "yes/no/unclear/not applicable". The items investigate the representativeness and size of the sample, recruitment methods, setting, validity of the tools used, appropriateness of the statistical methods, reproducibility of the study, and adherence to the study by the people recruited.

Disagreements regarding the qualitative evaluation of the studies were resolved with the help of a third

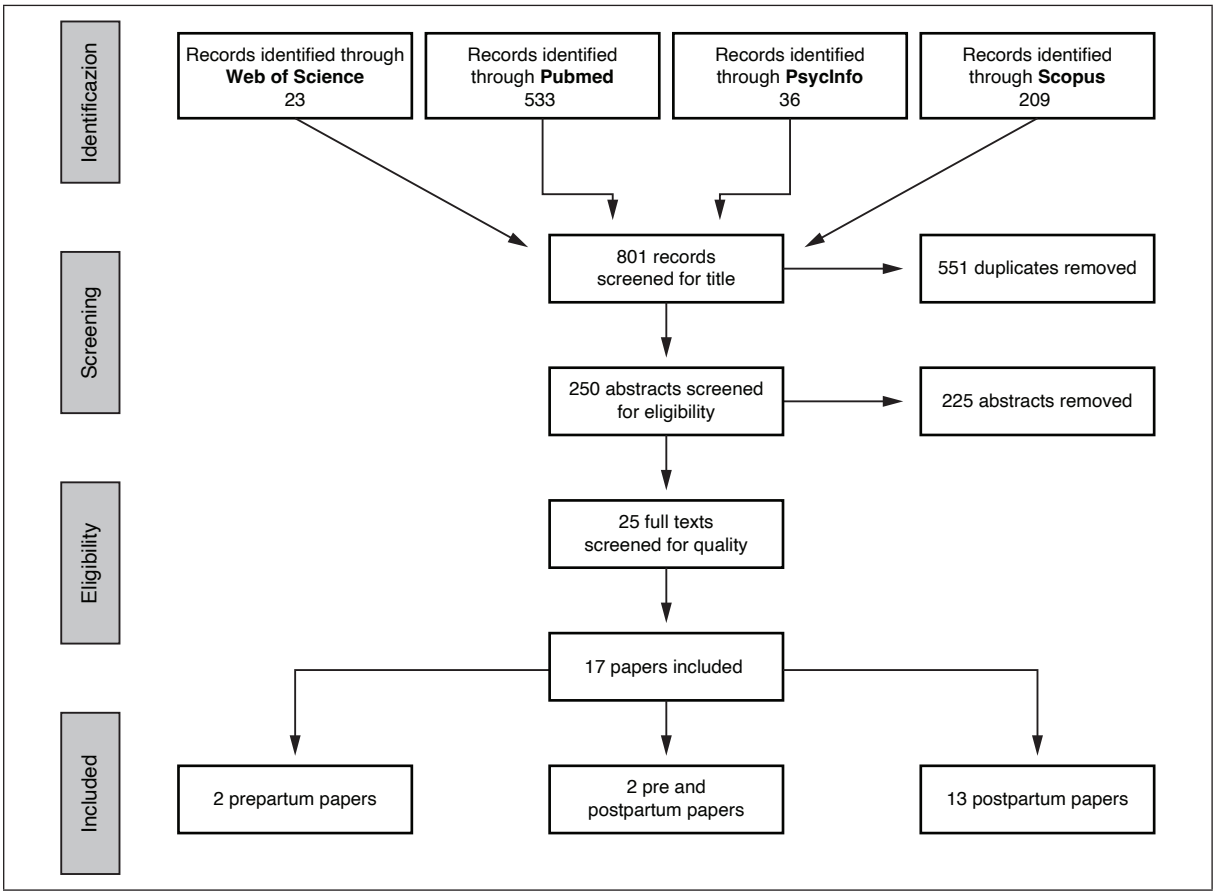

Figure 1
Flowchart of the systematic review literature search illustrating the identification of included studies.

reviewer. Studies reporting a score ≥5 out of a maximum possible score of 9 were considered to be of good quality.

Prevalence estimates of pre- and postpartum depression were extracted from studies rated as having good methodological quality, and 95% confidence intervals were calculated where they were not available.

Three meta-analyses were conducted, one referring to prepartum and two to postpartum, one of which including studies with an EPDS cut-off score ≥9 and the other included studies with an EPDS cut-off score ≥12. Studies that were screened after the first three months of delivery were considered. This last distinction was necessary due to the great heterogeneity of the sample in terms of the cut-off and sample size. Where studies reported prevalence estimates relating to different cut-off scores, the number of events to consider was obtained by summing the relevant data.

The Statistical Package for Social Science (SPSS) version 28 was used for the analyses. Heterogeneity between included studies and overall estimates was calculated with the random effects model, and the test for heterogeneity was applied using the Chi^2 and the I^2 statistics. The I^2 represents the percentage of the total study variation due to heterogeneity rather than chance. An I^2 value below 25% indicates a low degree of heterogeneity, 25-75% indicates moderate heterogeneity, and a value above 75% indicates high heterogeneity [23].

RESULTS

A total of 801 studies were extracted. Of these, 551 were eliminated because they were duplicates, and of the remaining 250, after careful examination of the abstracts, 225 studies were excluded because they did not meet the inclusion criteria. The remaining 25 studies were evaluated for methodological quality, and 17 were found to be of good quality and therefore included in the final evaluation. Of these, 2 studies reported data relating to the antepartum period, 13 to the postpartum period, and 2 studies to both the antepartum and postpartum periods (*Figure 1*).

Most of the included studies were carried out in the Departments of Gynaecology and Obstetrics of various Italian Hospitals and Paediatric Clinics. Two studies were conducted at local Maternal-Child Health Centres and one at vaccination centres (*Table 1*) [24-48].

Most of the studies included in this review were conducted in northern and central Italy. In particular, eight studies recruited participants in northern regions, six in central Italy and only one in southern Italy. Finally,

Table 1
Characteristics of the studies included in the systematic reviews (Italy)

					Before childbirth		After childbirth		
Author (year)	Healthcare centre	Region/city	N. of women participants	N. of women at risk of depression	% prevalence (CI 95%)	Screening time	% prevalence (CI 95%)	Screening time	Cut-off EPDS
§ Monti *et al.* (2008) [24]	6 Obstetrics and Gynaecology Unit	Emilia-Romagna	234	31			13.2±4.7	3 months	≥13
			217	12			5.5±3.2	9 months	
			167	8			4.8±3.3	18 months	
§ Currò *et al.* (2009) [25]	Pediatric Unit. A. Gemelli Hospital	Rome	1,122	298			26.6±2.5	15-20 days	≥10
§ Piacentini *et al.* (2009) [26]	3 Hospitals	Bergamo	509	38			7.5±2.3	8-12 weeks	≥12
De Magistris *et al.* (2010) [27]	Neonatal Intensive Care Unit	Cagliari	113	26			23.0±8.9	>4 weeks	≥10
			100	8			8.0±5.5	4-8 weeks	
Aceti *et al.* (2011) [28]	Obstetrics and Gynaecology Unit Umberto I Hospital	Rome	453	92	20.3±4.2	3° trimester			≥12
§ Gremigni *et al.* (2011) [29]	Obstetrics and Gynaecology Unit	Ancona	70	39			55.7±17.5	3 months	>9
§ Aceti *et al.* (2012) [30]	Obstetrics and Gynaecology Unit Umberto I Hospital	Rome	253	49	19.3±5.1	3° trimester			≥12
§ Balestrieri *et al.* (2012) [31]	4 Obstetrics and Gynaecology Unit	Ascoli, Bari, Verona, Udine	1,608	175	10.9±1.6	12-15 weeks			10-12
				133	8.3±1.4				≥13
				75	4.7±1.1				≥15

Continues

Table 1
Continued

Author (year)	Healthcare centre	Region/city	N. of women participants	N. of women at risk of depression	Before childbirth		After childbirth		Cut-off EPDS
					% prevalence (CI 95%)	Screening time	% prevalence (CI 95%)	Screening time	
§ Giardinelli *et al.* (2012) [32]	Obstetrics and Gynaecology Unit, Careggi Hospitals	Florence	590	129	21.9±3.2	28-32 weeks			≥10
				70	11.9±2.7				10-12
				60	10.2±2.6				≥13
				78			13.2±2.48	12 weeks	≥10
				45			7.6%±2.2		10-12
				33			5.6±1.9		≥13
§ Elisei *et al.* (2013) [33]	Prenatal Clinic, Hospital Santa Maria della Misericordia	Perugia	85	5			5.5±5.1	72 hours	≥12
				5			5.5±5.1		13-14
				26			30±11.7		9-12
				6			7.4±5.6	3 months	≥15
				8			9.3±6.5		13-14
				20			24.1±10.3		9-12
§ Mirabella *et al.* (2014) [34]	Local maternal-child health centres	Bergamo, Treviso	567	42			7.4±1.87	6-12 weeks	≥12
Cattaneo *et al.* (2015) [35]	Maggiore Hospital	Milan	122	29			23.8±8.6	2-5 days	≥10
				19			15.6±7.0	2 months	
				11			9.0±5.3	6 months	
Vismara *et al.* (2016) [36]	Hospitals and local maternal-child health centres	Cagliari. Turin. Cesena, Rome	181	36			19.9±6.5	3 months	9-12
				31			17.1±6.1		>13
				21			11.6±5.0	6 months	9-12
				17			9.4±4.5		>13
§ Clavenna *et al.*(2017) [37]	Local maternal-child health centres	Milan	2,706	126			4.7±0.8	60-90 days	≥12
Lucarini *et al.* (2017) [38]	Prenatal clinic, Hospital Santa Maria della Misericordia	Perugia	54	3			5.5±6.3	1 week	13-14
				3			5.5±6.3		≥15
				16			30±14.5		9-12
				5			9.3±8.1	3 months	13-14
				4			7.4±7.3		≥15
				13			24.1±13.1		9-12
§ Della Vedova *et al.* (2020) [39]	Vaccination centres	Brescia	416	48			11.5±3.3	2-4 months	≥10
§ Ferrari *et al.* (2020) [40]	Local Psychiatry Department Camposampiero	Padova	3,102	454			14.6±1.2	6-8 weeks	≥9
Molgora *et al.* (2020) [41]	Online survey		389	133	34.2±5.8	pregnancy			≥13
			186	49			26.3±7.4	0-6 months	
Spinola *et al.* (2020) [42]	Online survey		243	108			44.4±8.4	1 year	>12
§ Zanardo *et al.* (2020) [43]	Abano Terme Hospital	Padova	192	38			19.79%	2 days	>12

Continues

Table 1
Continued

Author (year)	Healthcare centre	Region/city	N. of women participants	N. of women at risk of depression	Before childbirth		After childbirth		Cut-off EPDS
					% prevalence (CI 95%)	Screening time	% prevalence (CI 95%)	Screening time	
§ Cena *et al.* (2021) [44]	11 centres (local maternal-child health centres, Obstetrics and Gynaecology Unit)	Bergamo, Bologna, Brescia, Enna, Florence, Mantova, Milan, Novara, Rome, Turin	2	0	0	1-13 weeks			≥12
			129	16	12.4±6.1	14-26 weeks			
			1,029	58	5.6±1.5	27-40 weeks			
			1,160	74	6.4±1.4	1-40 weeks			
			220	40			18.2±5.6	1-13 weeks	
			66	14			21.2±11.1	14-26 weeks	
			16	6			37.5±30.0	27-40 weeks	
			1,462	133			9.2±1.5	1-40 weeks	
Della Corte *et al.* (2021) [45]	Local maternal-child health centres	Naples	80	9			11.3±7.3	3 months	>10
§ Luciano *et al.* (2021) [46]	Obstetrics and Gynaecology Unit	Naples	178	31			17.4±6.1	1 months	≥10
			161	31			19.2±6.7	3 months	
			109	18			16.5±7.6	6 months	
			106	19			17.9±8.1	12 months	
§ Molgora *et al.* (2022) [47]	Maggiore Hospital	Milan	137	28			20.3±7.6	3 months	≥12
				29			21.3±7.7	6 months	
				30			21.9±7.8	12 months	
				56			40.9±10.7	3 months	≥9
				49			36.0±10.0	6 months	
				56			40.9±10.7	12 months	
Smorti *et al.* (2022) [48]	Santa Chiara Hospital	Pisa	80	22	27.5±11.5	23-32 weeks			≥10
			75	40	53.3±16.6				

§ Studies included in the metanalysis.
CI: confidence interval. EPDS: Edinburgh Postnatal Depression Scale.

two studies enrolled women from northern, central and southern Italy.

Most of the screenings took place during prenatal checks at the health facilities to which the women regularly belonged and during childbirth preparation courses.

The prevalence values observed in the 4 prenatal studies and the 15 studies relating to the postpartum period are highly variable and depend, as already mentioned, on the type of centre that carried out the screening, and consequently on the women who refer to it, on the cut-off used, and on the sample size (*Tables 2, 3, 4*).

As *Figure 2* shows, the pooled prevalence estimate was 20.2% (95% CI 15.3-24.5) for the 4 prepartum studies with cut-off scores ≥10. Significant heterogeneity was observed between studies (I^2=0.97; p<0.001). Observation of the funnel plot shows the presence of a significant publication bias, determined by the presence of a small study with a low prevalence and a large study with a high prevalence. The small number of studies included in this meta-analysis does not allow for a sensitivity analysis.

Regarding the studies relating to postpartum, after a preliminary analysis that showed significant heterogeneity, a sensitivity analysis was conducted, distinguishing the studies that used a cut-off ≥9 from those with a cut-off ≥12.

Figure 3 of postpartum studies using cut-off scores ≥9 shows an overall prevalence estimate of 27.5% (95% CI 17.8-37.3). However, significant heterogeneity was observed between the studies (I^2=0.98; p<0.001).

Figure 4 of postpartum studies using cut-off scores ≥12 shows an overall prevalence estimate of 11.1% (95% CI 6.0-16.2). In addition, in this case, significant heterogeneity is observed (I^2=0.95; p<0.001).

DISCUSSION

To our knowledge, this is the first systematic review that intends to summarise prevalence estimates of

Table 2
Prevalence studies during the prepartum period included in the meta-analysis

Authors (year)	N. of women participants	N. of women at risk of depression	% prevalence (CI 95%)	Screening time	Cut-off
Aceti *et al.* (2012) [30]	253	49	19.3±5.1	3 months	≥12
Balestrieri *et al.* [31]	1,608	383	23.8±2.4	12-15 weeks	≥10
Giardinelli *et al.* [32]	590	129	21.9±3.8	28-32 weeks	≥10
Cena *et al.* [44]	129	16	12.4±6.1	14-26 weeks	≥12

Table 3
Prevalence studies (with EPDS ≥9) during the post-partum period included in the meta-analysis

Authors (year)	N. of women participants	N. of women at risk of depression	% prevalence (CI 95%)	Screening time	Cut-off
Currò *et al.* (2009) [25]	1,122	298	26.6±2.5	15-20 days	≥10
Gremigni *et al.* (2011) [29]	70	39	55.7±17.5	3 months	≥9
Giardinelli *et al.* (2012) [32]	590	78	13.2±2.48	12 weeks	≥10
Elisei *et al.* (2013) [33]	85	34	40.0±13.4	3 months	≥9
Lucarini *et al.* (2017) [38]	54	22	40.7±17.0	3 months	≥9
Della Vedova *et al.* (2020) [39]	416	48	11.5±3.3	2-4 months	≥10
Ferrari *et al.* (2020) [40]	3,102	454	14.6±1.2	6-8 weeks	≥9
Luciano *et al.* (2021) [46]	161	31	19.2±6.7	3 months	≥10
Molgora *et al.* (2022) [47]	137	56	40.9±10.7	3 months	≥9

EPDS: Edinburgh Postnatal Depression Scale.

Table 4
Prevalence studies (with EPDS ≥12) during the post-partum period included in the meta-analysis

Authors (year)	N. of women participants	N. of women at risk of depression	% prevalence (CI 95%)	Screening time	Cut-off
Monti *et al.* (2008) [24]	234	31	13.2±4.7	3 months	≥13
Piacentini *et al.* (2009) [26]	509	38	7.5±2.3	8-12 weeks	≥12
Mirabella *et al.* (2014) [34]	567	42	7.4±1.87	6-12 weeks	≥12
Clavenna *et al.* (2017) [37]	2,706	126	4.7±0.8	60-90 days	≥12
Cena *et al.* (2021) [44]	66	14	21.2±11.1	14-26 weeks	≥12
Molgora *et al.* (2022) [47]	137	28	20.3±7.6	3 months	≥12

EPDS: Edinburgh Postnatal Depression Scale.

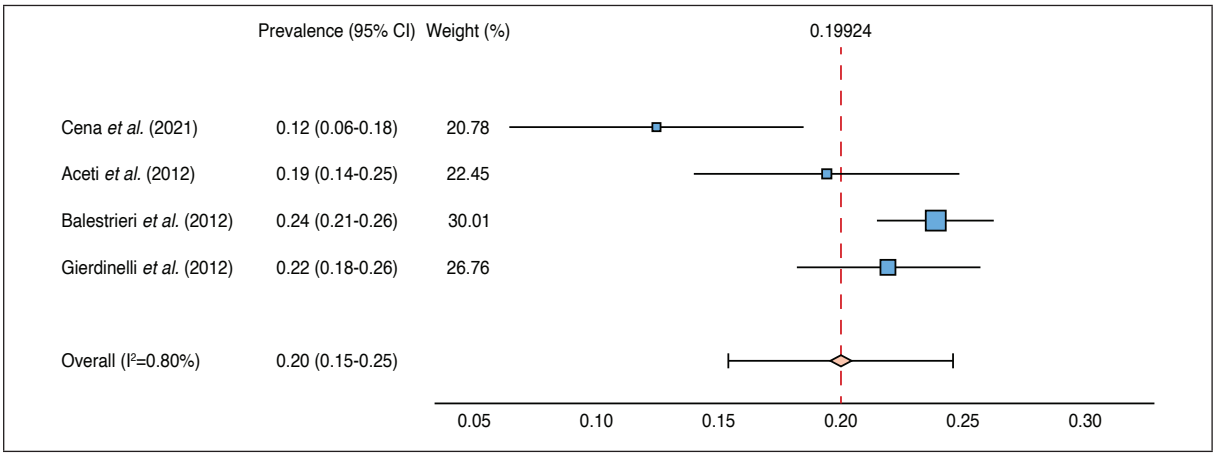

Figure 2
Forest plot of prevalence studies during the prepartum period.

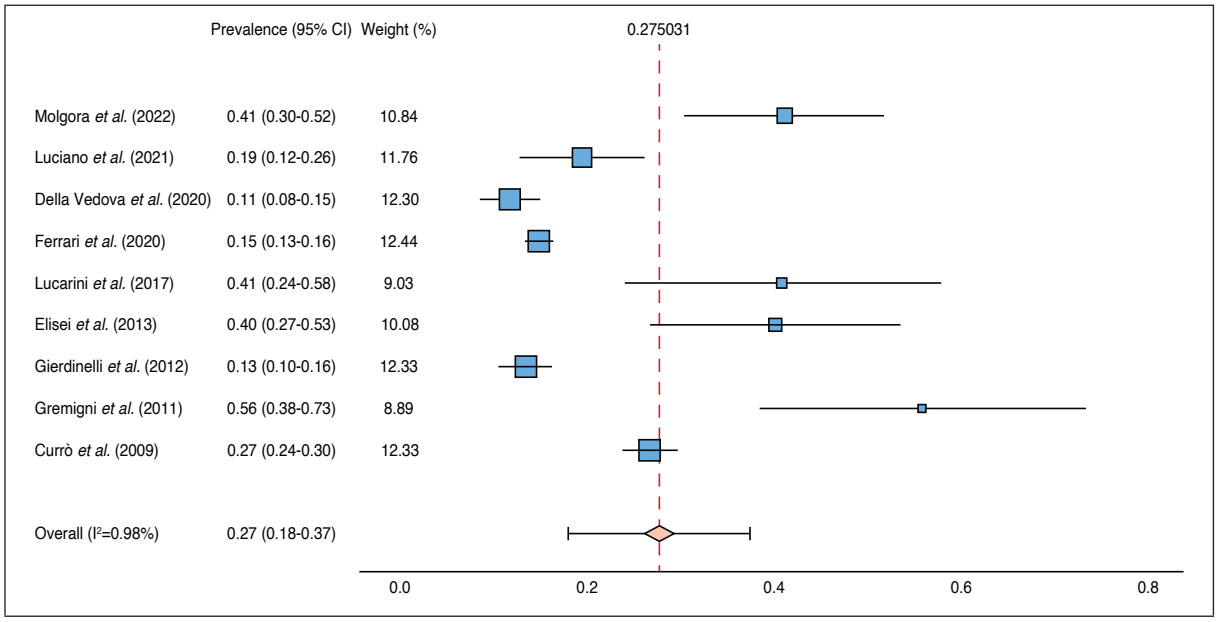

Figure 3
Forest plot of prevalence studies (with EPDS ≥9) during the post-partum period.
EPDS: Edinburgh Postnatal Depression Scale.

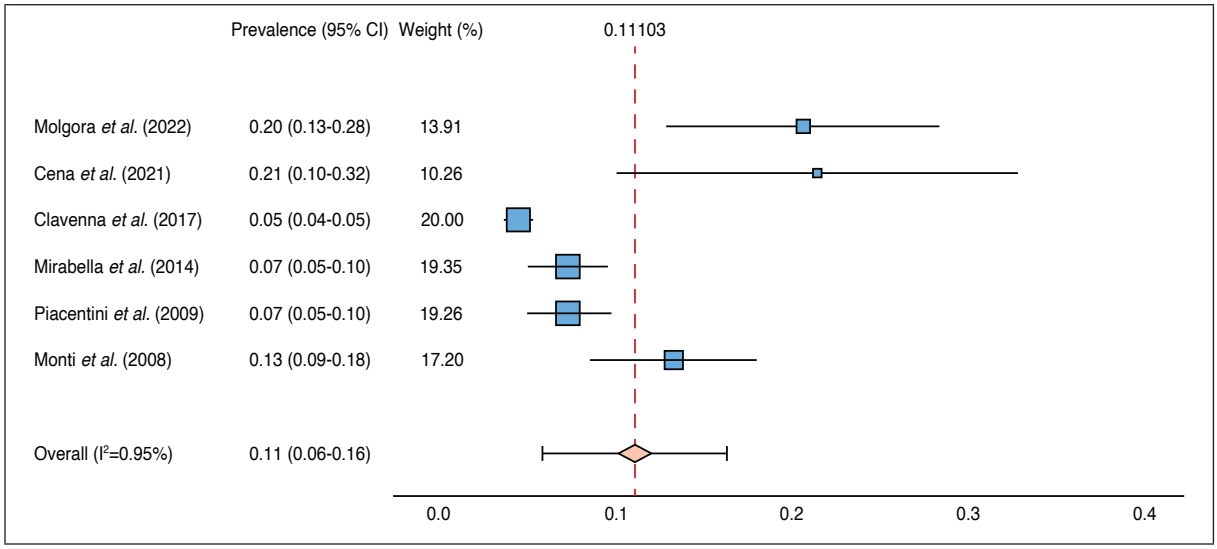

Figure 4
Forest plot of prevalence studies (with EPDS ≥12) during the post-partum period.
EPDS: Edinburgh Postnatal Depression Scale.

depression in the perinatal period in Italy, taking into consideration the studies that used the same screening tool.

The different cut-off scores used help to explain the variability of prevalence estimates: lower cut-off scores correspond to higher prevalence estimates, and vice versa.

The results of the meta-analysis show that in the prepartum period, about one in five women shows a risk of depression, while in the postpartum period, more than one in four women shows a risk of depression if we consider the EPDS with a cut-off ≥9, and about one in ten when a cut-off ≥12 is considered.

Our estimates of the risk of prepartum depression are similar to those observed in other systematic reviews. In particular, the review of Nisar [49] which includes only studies conducted in China, shows prenatal depression values of 19.7%. While the review by Gavin [50] which also included studies conducted in Western countries, reports an estimate of prenatal depression prevalence of 18.4%.

Furthermore, our data are in line with the review by Underwood [51] which found a prevalence of depression of 17.2% during pregnancy for EPDS cut-off values ≥10 and ≥12.

Regarding the postpartum period, other systematic reviews show an overall estimate ranging from 14 to 17% [49, 52, 53]. It should be noted, however, that the studies included in these reviews also used other screening tools (CES-D, BDI, PHQ-9) in addition to the EPDS to calculate overall prevalence. Also, where EPDS was used, no differentiation was made for the cut-off scores used or for the periods in which screening was performed.

The estimates found in our country are consistent with those of another recent Italian study in which the EPDS was used (11-24%) during the perinatal period [54].

Concerning the general population, the only epidemiological study conducted in Italy on the prevalence of common mental disorders in a representative sample of the adult population and performed with a highly reliable diagnostic tool (Composite International Diagnostic Interview, CIDI) is the European Study of the Epidemiology of Mental Disorders (ESEMeD) study [55] which showed estimates of lifetime major depression in the female population equal to 13.4% (95% CI 11.0-15.0). Importantly, the sample of this survey suffers from depression, not the risk of depression that our systematic review refers to. Our overall estimate is therefore consequently higher because it refers to a more vulnerable population and to a probability of depression that, if confirmed with an appropriate diagnostic tool, would probably have lower values.

Finally, this systematic review shows that the risk of depression is also high during pregnancy and underlines the need to monitor women during this period, given that prenatal depression has always been recognised as one of the major risk predictors for depression during pregnancy and the postpartum period [56, 57]. Very often, prenatal depression is not recognised as such, partly due to its insidious onset and partly because many women do not recognise the disorder as such or are afraid to seek help from a specialist. A timely diagnosis is instead essential because it allows effective treatments to be undertaken, not only to reduce women's suffering but also to limit the consequences for children and family relationships in general [58, 59].

CONCLUSION

This review and meta-analysis attempted to summarise the principal screening studies on the risk of depression for women in the perinatal period. The studies analysed are methodologically very different from each other and not always comparable. The reported prevalences are not always clearly referable to a clear cut-off score used, the screening periods are highly variable, and the centres where screening is performed have, by their very nature, a very different reference population as regards the risk of depression.

However, the data appear to tend towards values that are not too far apart when considering cut-off scores and uniform screening periods.

Monitoring the frequency of depression in the perinatal period is essential from a public health point of view to identify early women to be referred to a treatment that is easy to implement and of proven efficacy to reduce major complications for the woman and for the child.

Authors' contributions

LC and FM developed the outline of this review, performed the statistical analysis, and contributed to the writing of the manuscript; GG and EP searched the literature and performed the quality analysis; AG contributed to the final version of the manuscript and supervised the whole study. All the Authors have read and approved the final manuscript.

Conflict of interest statement

We declare no competing interests.

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Architecture of the health system as an enabler of better wellbeing

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Abstract

Introduction. Health systems worldwide have heterogenous capacities and financing characteristics. No clear empirical evidence is available on the possible outcomes of these characteristics for population wellbeing.

Aim. The study aims to provide empirical insight into health policy alternatives to support the development of health system architecture to improve population wellbeing.

Method and results. We developed an unsupervised neural network model to cluster countries and used the Human Development Index to derive a wellbeing model. The results show that no single health system architecture is associated with a higher level of population wellbeing. Strikingly, high levels of health expenditure and physical health capacity do not guarantee a high level of population wellbeing and different health systems correspond to a certain wellbeing level.

Conclusions. Our analysis shows that alternative options exist for some health system characteristics. These can be considered by governments developing health policy priorities.

Key words

- population wellbeing
- health system capacity
- public health system
- health policy
- neural networks

INTRODUCTION

Health systems have an increasingly important role in national economies. Developed countries with higher income levels are willing to spend more on health systems and, because the average age of populations is getting higher, have a greater need for health care for elderly people. Growing populations in developing countries is another significant driver of demand for health care. In response to the increasing role of the healthcare services in national economies, governments have developed a range of different health systems [1, 2].

The current literature highlights the complexity of measuring the quality of health care services and the effectiveness of strategies to improve healthcare practices in developed countries [3, 4], particularly low-income and middle-income countries [5]. The World Health Organization (WHO) has reported heterogeneity in healthcare characteristics and in the effectiveness and implementation of healthcare quality strategies across Europe [6]. In addition, the leadership and governance of population health management and health payment systems varies across countries [7, 8]. For various reasons, including low satisfaction of healthcare service users [9], there is a clear demand to transform healthcare services towards more sustainable health and population wellbeing systems [10]. Furthermore, the COVID-19 pandemic has increased the focus on health system sustainability [11, 12].

Economic wellbeing is often measured by gross domestic product (GDP) per capita, which approximates the level of economic development. However, GDP per capita as a measure of economic development is only one driver of population wellbeing. To overcome this limitation, another measure of population wellbeing could be considered, such as the Human Development Index (HDI). The HDI takes into account that the criteria for assessing a country's development should encompass people and their capabilities and not only economic growth [13]. Wellbeing is a multidimensional condition that encompasses social, material, spatial and other conditions. It can be assesses using asset-based and health capability approaches [14]. Maintaining and contributing to wellbeing requires multidimensional actions with environmental, physical and/or psychological components, for example the use of urban public spaces for relaxation, education or recreation [15]. Overall wellbeing comprises three layers: personal, community and societal wellbeing. These layers are interconnected, but may compete for scarce

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resources [16]. Health and wellbeing are interlinked in quality of life measures that form the basis of public interventions (including for health, public health and social care), and are used as a combined dimension to evaluate health policy interventions [17, 18]. Wellbeing has already been adopted as a development goal to "deliver human and ecological wellbeing" within national development and wellbeing frameworks, including in Finland, Iceland, New Zealand, Scotland and Wales, within the Wellbeing Economy Governments initiative [16].

A wider framework has been introduced to assist in planning and evaluating development policies towards the 2030 Agenda for Sustainable Development [19]. Some studies have investigated different aspects of improvements in health systems and population wellbeing in different countries [20-22] by analysing factors such as the financial characteristics of health systems, as related to the prices of and expenditure on different health inputs such as medical equipment, medicines and health services. Other studies have investigated physical health capacities, efficiencies, and impacts on economic efficiency or reasons for inefficiency. Digitalization of health systems (e.g., electronic health records) can positively impact on healthcare quality [23]. Although both aspects of health systems are subject to health policy, so far there is little or no evidence or analysis linking them to population wellbeing.

This study analysed the architecture of national health systems using aggregated country data to investigate whether health system characteristics are linked to population wellbeing and, if so, in which combination. Health policy-makers are encouraged to promote specific health practices, such as increasing health system capacity and health financing, with the aim of increasing population wellbeing. However, the question remains of whether health systems with similar architecture can achieve similar levels of population wellbeing, and whether there might be a non-linear prerequisite for improving health system architecture. We focused on two specific research questions (RQs):

- RQ1: do specific characteristics of national health systems influence population wellbeing?
- RQ2: can similar levels of population wellbeing be achieved through different health system architectures?

This study addresses trade-offs between health system indicators in policies to enhance population wellbeing. Firstly, existing secondary data on financial characteristics and capacity characteristics of health sectors were analysed over time for a global sample of countries to provide robust results. Secondly, a methodological approach based on neural networks enabled us to determine the impact of input variables on the results. Finally, the study provides empirical evidence to help policy-makers to make decisions on designing health system architecture. The initial development of health systems and targets for population wellbeing can be important for the further evolution of health systems. However, the results show that different policy approaches can achieve similar levels of population wellbeing.

MATERIALS AND METHODS

Data variables

Variables were selected based on theoretical reasoning. Therefore, unlike in a classical econometric approach, a priori elimination of variables resulting from possible multicollinearity or outliers was not needed. Variables were selected to reflect characteristics of health system financing and national healthcare capacities. The final selection of variables was based on the availability of national data.

Available data for years between 1990 and 2019 on the two groups of variables were collected for a global sample of 45 countries *(Table 1)*. The number of years of available data varied from 8 years for Belgium and Canada to 3 years for Mexico and 2 years for Burkina Faso. However, data for 6 or 7 years were available for most countries. *Table 1* lists the annual data included in the analysis by country. A total of 283 observations was included in the final database.

Next, the data were sorted into two groups: those describing population wellbeing and those describing health system architecture. To assess population wellbeing, we considered multiple global measures and indexes to determine the general level of population wellbeing for each country and year. Based on the composition, availability, reliability and consistency of the data, we decided to use the United Nations Development Programme's HDI [13]. The HDI has three dimensions: (1) long and healthy life, (2) knowledge and (3) a decent standard of living. Each dimension has one or more indicators: life expectancy at birth (in years) for the first dimension, expected years of schooling (in years) and mean years of schooling (in years) for the second dimension, and gross national income per capita in 2017 purchasing power parity in US dollars for the third dimension (using the natural logarithm to reflect the diminishing importance of income). For each dimension, an individual dimension index was calculated and the HDI was given as the geometric mean of the indices for all three dimensions [13, 24]. We obtained HDI values from the Data Center of the United Nations Development Programme [25].

In the second group (health system architecture), we used selected variables to describe the financing characteristics and capacity of each country's health system. Health outcome indicators were deliberately omitted because this study assessed health system architecture as related to healthcare policy. To ensure that data were reliable and comparable across countries, all variables were obtained from a single source, the WHO [26]. Within these parameters, data were obtained for 11 variables *(Table 2)*. The possibility of double counting particular characteristics of health sector architecture and population wellbeing or any of its dimensions was minimised by ensuring that the HDI dimensions did not include any of the 11 selected variables of health system architecture. The 12 selected variables describe health system financing (such as different categories of health expenditure) and health sector capacities (such as numbers of different types of medical experts and number of hospital beds).

Table 1
Included countries, showing the years of available data

Country	Code	Year								Number of observations
		1990	2000	2010	2014	2015	2017	2018	2019	
United Arab Emirates	ARE	X	X	X	X	X	X			6
Australia	AUS	X	X	X	X	X				5
Austria	AUT	X	X	X	X	X	X	X		7
Belgium	BEL	X	X	X	X	X	X	X	X	8
Burkina Faso	BFA		X	X						2
Bangladesh	BGD	X	X	X	X	X				5
Canada	CAN	X	X	X	X	X	X	X	X	8
Switzerland	CHE	X	X	X	X	X	X	X		7
Chile	CHL	X	X	X	X	X	X	X		7
Colombia	COL	X	X	X	X	X	X	X		7
Czechia	CZE	X	X	X	X	X	X	X		7
Germany	DEU	X	X	X	X	X	X			6
Dominican Republic	DOM	X	X	X	X	X	X			6
Spain	ESP	X	X	X	X	X	X	X		7
Estonia	EST	X	X	X	X	X	X	X		7
France	FRA	X	X	X	X	X	X	X		7
United Kingdom	GBR	X	X	X	X	X	X	X	X	8
Georgia	GEO		X	X	X					3
Greece	GRC	X	X	X	X	X	X	X		7
Hungary	HUN	X	X	X	X	X	X	X		7
Indonesia	IDN	X	X	X	X	X	X			6
Ireland	IRL	X	X	X	X	X	X	X		7
Iceland	ISL	X	X	X	X	X	X	X	X	8
Israel	ISR	X	X	X	X	X	X	X		7
Italy	ITA	X	X	X	X	X	X	X		7
Jordan	JOR	X	X	X	X	X	X			6
Republic of Korea	KOR	X	X	X	X	X	X	X		7
Sri Lanka	LKA	X	X	X	X	X	X			6
Lithuania	LTU	X	X	X	X	X	X	X		7
Latvia	LVA	X	X	X	X	X	X	X		7
Republic of Moldova	MDA	X	X	X	X					4
Mexico	MEX	X	X	X						3
Myanmar	MMR	X	X	X	X	X	X			6
Montenegro	MNE			X	X	X	X			4
Netherlands	NLD	X	X	X	X	X	X	X		7
Norway	NOR	X	X	X	X	X	X	X		7
New Zealand	NZL	X	X	X	X	X	X	X	X	8
Oman	OMN		X	X	X	X	X			5
Pakistan	PAK	X	X	X	X	X	X			6
Panama	PAN	X	X	X	X	X				5
Saudi Arabia	SAU	X	X	X	X	X	X			6
Slovakia	SVK	X	X	X	X	X	X	X		7
Slovenia	SVN	X	X	X	X	X	X	X		7
Trinidad and Tobago	TTO	X	X	X	X	X	X			6
Türkiye	TUR	X	X	X	X	X	X	X		7
Total number of observations										283

Table 2
Two groups of used variables

	Wellbeing
1	HDI – Human Development Index
	Health system's architecture
1	UHC Service Coverage Index (SDG 3.8.1)
2	Hospital beds (per 10,000 of population)
3	External health expenditure (EXT) as a percentage of current health expenditure (CHE), in %
4	Out-of-pocket expenditure as a percentage of current health expenditure (CHE), in %
5	Current health expenditure (CHE) as a percentage of gross domestic product (GDP), in %
6	Domestic general government health expenditure (GGHE-D) as a percentage of gross domestic product (GDP), in %
7	Domestic general government health expenditure (GGHE-D) as a percentage of general government expenditure (GGE), in %
8	Pharmacists (per 10,000 of population)
9	Dentists (per 10,000 of population)
10	Medical doctors (per 10,000 of population)
11	Nursing and midwifery personnel (per 10,000 of population)

Source: data on HDI were obtained from the United Nations Development Programme (https://hdr.undp.org/data-center/documentation-and-downloads); data on health system architecture were obtained from the World Health Organization (https://www.who.int/data/gho/data/indicators).

Self-organizing map clustering model

For our analysis, we designed a modelling procedure. We first develop a clustering model based on Kohonen's self-organizing map (SOM) method [27], which has been widely used to cluster scientific data in its original or modified form or combined with other methods (for example, see references [28-32]). Kohonen's SOM creates an artificial neural network based on an unsupervised learning algorithm in which the neurons compete with one another to correspond to the data. Data with similar characteristics are ordered to the same or a neighbouring node of the map. The SOM can form a one-, two-, or three-dimensional network of nodes; higher dimensions are also possible but not reasonable. For a further details of three-dimensional models and network topologies, see Jagric and Zunko [33]. The network learns via an iterative procedure in which learning data are presented to the network in a random order in each iteration. Thus, multidimensional input data are transformed into a lower-dimension output map or pattern array, usually (as in our case) a two-dimensional network [27, 29, 30].

In this study we designed a SOM of 20×20 neurons in size. The neurons were positioned on the two-dimensional network via hexagonal ordering, which determined the neighbouring nodes in the network. The SOM size was chosen based on the amount of input data within a testing procedure since no statistical rule exists for optimal size determination. The input data space included 11 variables per country and a total of 283 observations (consisting of available secondary data for individual years for 45 countries). Data were not pooled per year or per country. The SOM model generated data clusters; therefore, the a priori position of an individual country did not influence the position of data for subsequent years for the same country. The SOM model was trained using MATLAB software by MathWorks (Massachusetts, USA) (2022).

In the second step, the addition of a third dimension comprising data on population wellbeing resulted in the three-dimensional positioning of countries (XYZ). The data on population wellbeing were derived from HDI values that had been translated into country rankings from 1 to 185 (best to worst). This ranking was based on the total global sample of countries but, since only 45 countries were included in our dataset, not all rankings are present in the analysis. The XYZ positioning evolved as follows: the SOM's two-dimensional position represents the XY plane, and population wellbeing is the Z dimension.

In the third step, we aimed to resolve the "black box problem" of neural networks by attempting to explain the position of a particular country in the wellbeing model. Therefore, we observed the association of each input variable of the SOM model within the wellbeing model. In this unusual methodological approach, the relationship to population wellbeing as identified in the final step is set independently from the learning process of the initial SOM model, which uses only the characteristics of the health system (categories of healthcare expenditure and healthcare capacity) and not population wellbeing data.

RESULTS

SOM clustering model

A SOM model was trained using the 11 variables of health system architecture as input data. *Figure 1* shows the resulting network, with the number of observations indicated for each winning node. Clustering neighbourhoods are apparent as areas of greater density and clear boundaries called "valleys" between the cluster areas.

The third dimension generates the wellbeing model

We added the third dimension to the SOM clustering model using an estimated polynomial model based on the following general model:

$$z = \sum_{i=1}^{n+1} p_i x^{n+1-i} + \sum_{j=1}^{m+1} q_j y^{n+1-j}$$

where $n+1$ and $m+1$ are the orders (number of coefficients to be fitted), and n and m are the degrees of the polynomial (highest power of the predictor variable). This methodological approach has the advantages of having reasonable flexibility for uncomplicated data and being linear, which simplifies the fitting process. Its disadvantages are that high-degree fits are potentially unstable and that, while such models can provide a good fit within the data range, they can diverge outside that range [34]. Therefore, we decided to limit the orders to three levels in the estimation process. The procedure for fitting polynomials uses the predictor values

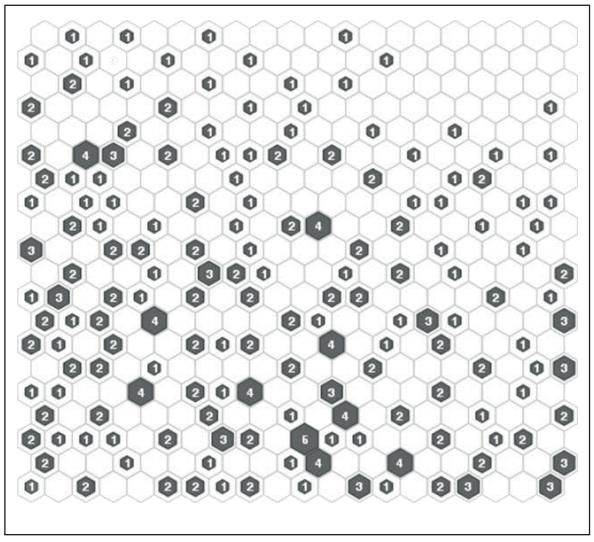
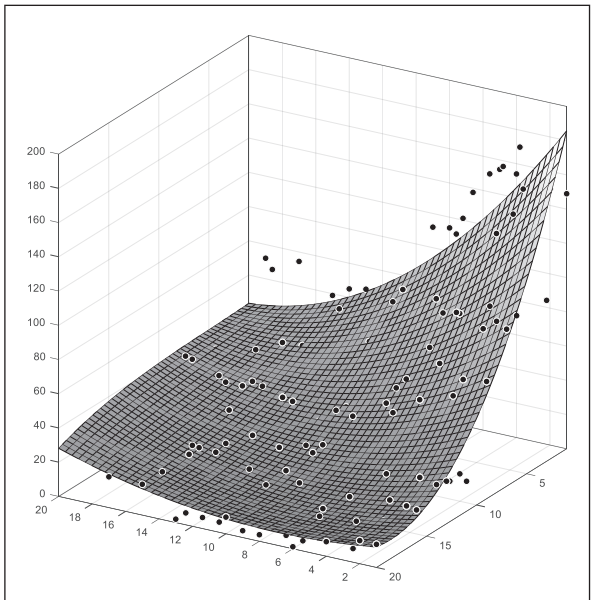


Figure 1
SOM model structure and number of hits.

as the basis for a matrix with very large values, which can result in scaling problems. To overcome this problem, we normalized the data by centring to a zero mean and scaling to unit standard deviation.

Figure 2 shows the SOM wellbeing model with unitless coordinates for the XY plane. These coordinates play a similar role to a principal component analysis. For each of the 283 observations, data on population wellbeing were added as a third dimension and marked by a dot. HDI data is given as the ranking. The best ranks (low values) in the HDI signify countries with higher population wellbeing and the worst ranks (high values) signify countries with lower population wellbeing. Next, a model estimation was designed, in which a planar surface represents the estimated relation between position in the SOM network and the population wellbeing level. The model estimation indicates areas of greater and lower population wellbeing, depending on the SOM positioning.



Note: the X- and Y-axes are unitless coordinates
of the neuron position in the SOM model.
The Z-axis is the HDI ranking that reflects the wellbeing level.

Figure 2
Wellbeing model.

Model decomposition – solving the black box problem

We next explored the association of individual characteristics of health system architecture with the wellbeing model. Henceforth, the SOM clustering model is presented as an XY plane (as in *Figure 2*) and data on population wellbeing are presented in greyscale (rather than a third dimension). Areas with similar levels of population wellbeing form regions. Notably, areas with the highest levels of population wellbeing are darkest and are located in the top left corner. We next analysed the SOM model to determine whether countries with the same level of population wellbeing share similarities in the individual variables. *Figure 3* shows that having a small number of medical doctors, dentists or nurses/midwives is associated with low population wellbeing. However, in countries with a high level of population wellbeing, the number of each category of medical staff vary considerably. In countries with high population wellbeing, current health expenditure as a percentage of GDP is homogenously high, whereas in countries with low population wellbeing expenditure is low. In comparison, out-of-pocket expenditure as a percentage of current health expenditure is higher in countries with low population wellbeing than in those with high population wellbeing.

The model accuracy assessment

To critically evaluate the results, we assessed the accuracy of the wellbeing model. For this, we compared the predicted and true HDI values for each country using a standard ordinary least squares regression model *(Figure 4* and *Table 3)*. The results show that even though we did not model time series data, the adjusted R^2 value is extremely high (0.839), signifying that the model explains 84% of the total variation in HDI.

DISCUSSION

Two sets of findings were obtained. Firstly, the SOM clustering model revealed country clustering based on the characteristics of national health systems. A wellbeing model provided an empirical level of population wellbeing associated with each country cluster. However, the methodological approach did not provide sufficient evidence to indicate a causal relationship. Secondly, some unexpected patterns of association were observed between areas with different levels of population wellbeing and the average values of individual characteristics of health system architecture. For some characteristics, certain values were restricted to countries with specific levels of population wellbeing, whereas for others similar values were obtained for countries with low or high levels of population wellbe-

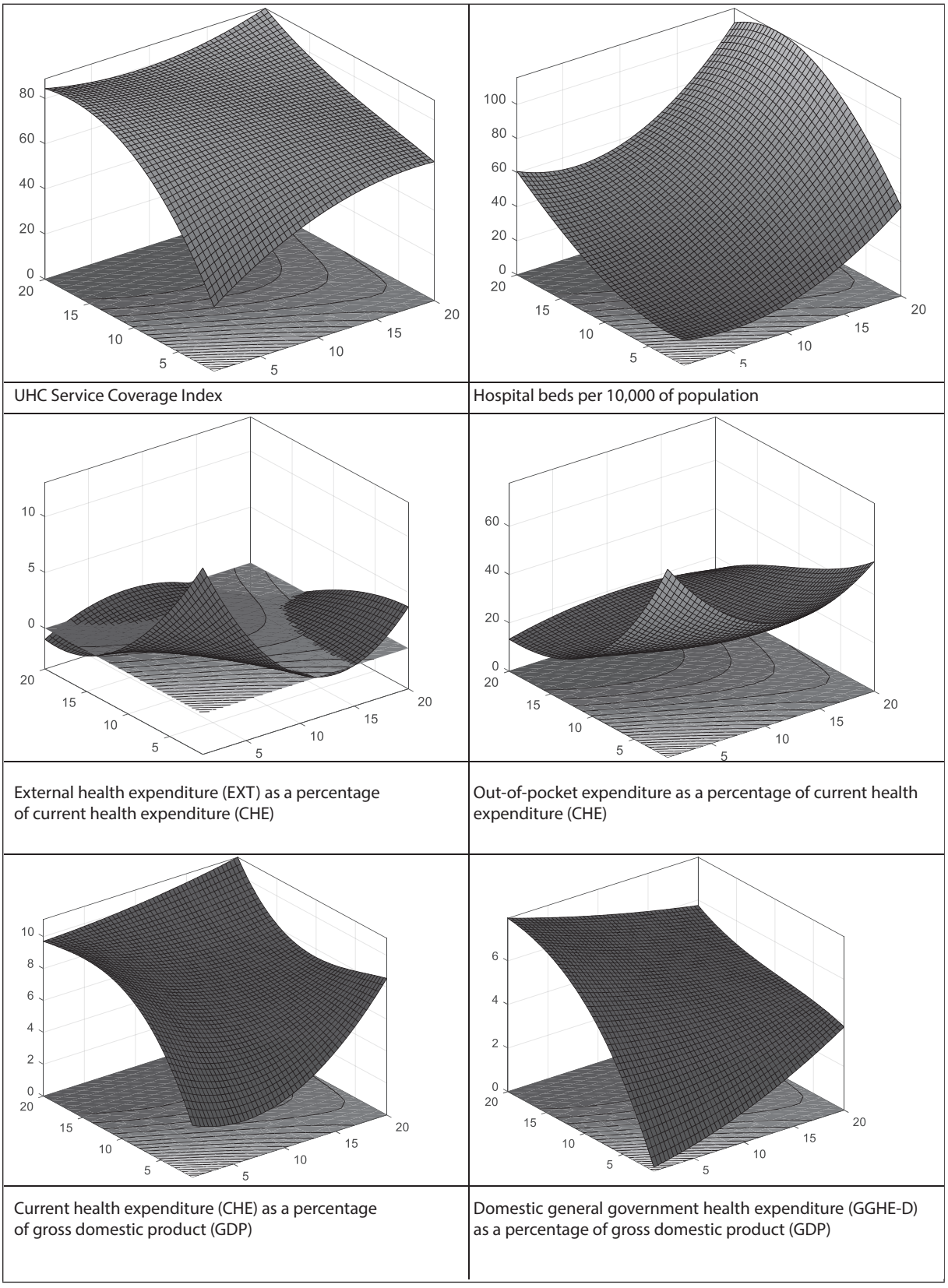
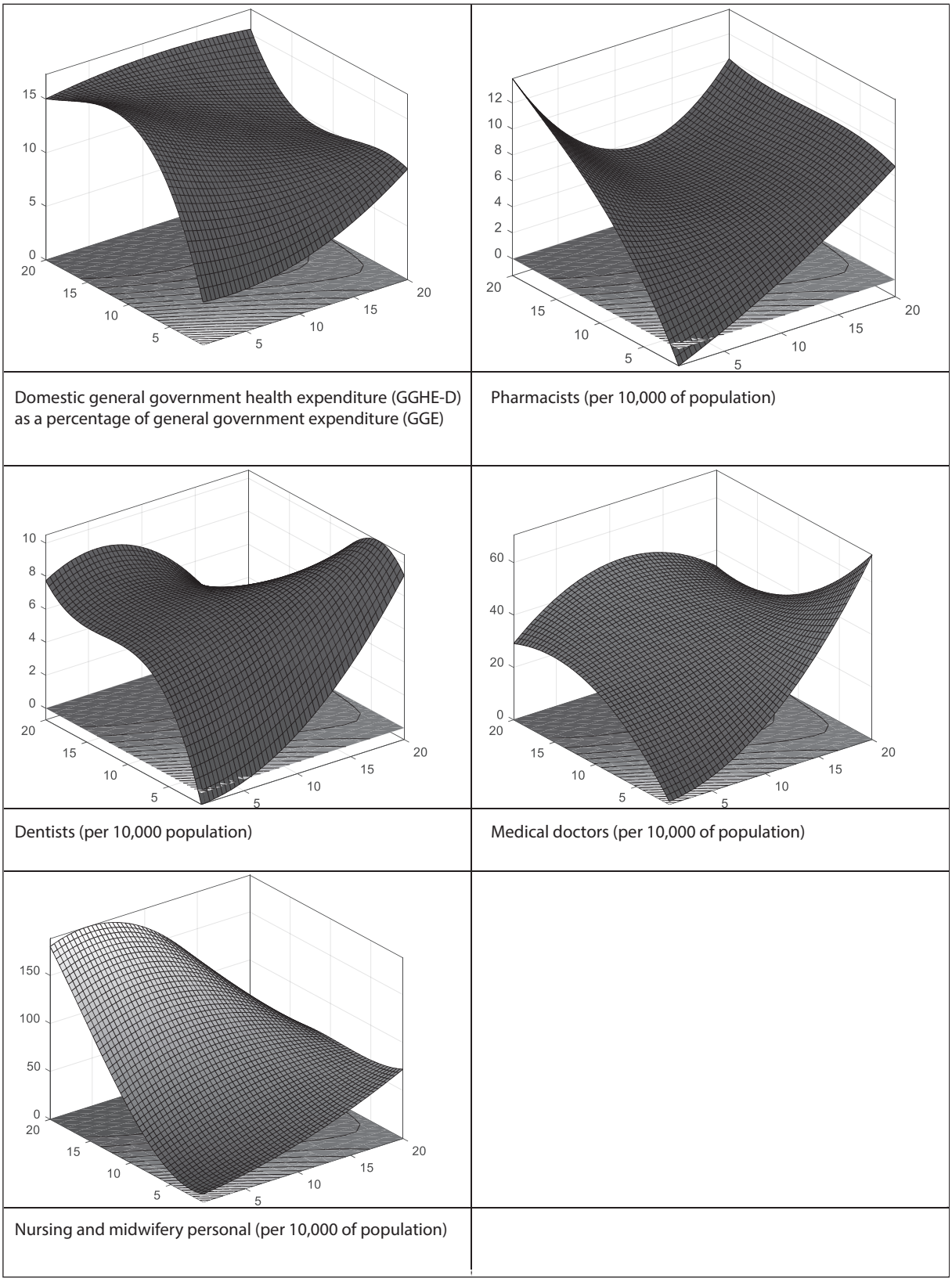


Figure 3
Associations of individual variables of health system architecture with population wellbeing.



Domestic general government health expenditure (GGHE-D) as a percentage of general government expenditure (GGE)

Pharmacists (per 10,000 of population)

Dentists (per 10,000 population)

Medical doctors (per 10,000 of population)

Nursing and midwifery personal (per 10,000 of population)

Figure 3
Note: the X and Y axes are unitless coordinates derived from the SOM model that reflect the position of neurons; the Z axis is the value of the individual variable. On the XY plane, the coloured areas reflect the projection of the forecast HDI value.

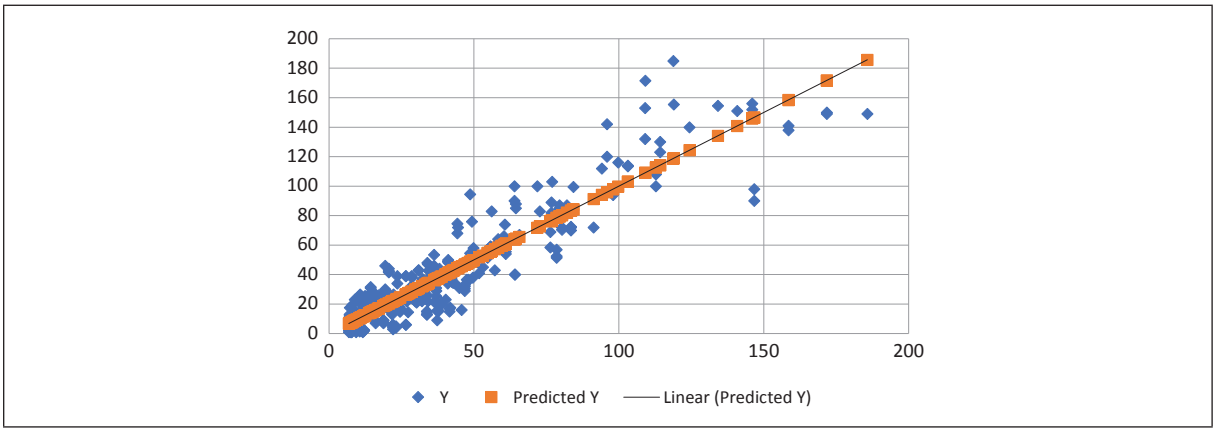


Figure 4
Accuracy assessment of the model.
Note: The X-axis is the model forecast and the Y-axis the country ranking. Wellbeing model.

ing. For example, analysis of the variable "Hospital beds per 10,000 population" *(Figure 3)* revealed that having a medium quantity of hospital beds is associated with both higher and lower levels of wellbeing. Furthermore, having an extremely high quantity of hospital beds is not a prerequisite for high population wellbeing, since the same level of wellbeing was found for countries with a medium quantity of hospital beds. In contrast, having a very low quantity of hospital beds was associated only with a low level of population wellbeing.

The limitations of the study should be considered when interpreting the results. Firstly, we measured wellbeing using the HDI, which simplifies human development by capturing some of its aspects and not others, such as human security and empowerment [13, 24]. However, the main limitation was the size of the database. The inclusion of more countries in the analysis would have resulted in greater robustness. However, the number of countries included in the study was determined by the availability of relevant data. Furthermore, for some countries, data were available for only a few years, resulting in a short time frame that is incompatible with the research aim. Therefore, when we excluded countries with too few years of available data, the number of countries was reduced from 185 to 45. To overcome the limitations of classical econometric methodology, we designed a tailored methodological approach. Firstly, the SOM clustering model benefits from properties of unsupervised learning of a neural network. Next, wellbeing information was strictly separated from other input data for country clustering. Therefore, the level of wellbeing was determined solely by independently assessed features of the healthcare sector.

The results indicate that different healthcare policy choices can achieve similar levels of population wellbeing. Therefore, once social agreement is reached on the desired level of population wellbeing, a broad set of policy options is available for specific health system characteristics. However, for other characteristics, the range of policy alternatives is much narrower. These findings may be useful for choosing national policy on designing health system architecture.

The findings have practical and managerial relevance: although the characteristics of a country's health system did not directly correspond to its development, it was possible to identify some patterns. Health systems were found to have different scopes and levels; however, countries in geographical proximity had similar health systems, suggesting that the countries also had a similar level of population wellbeing. Some countries without a large healthcare capacity could provide a reasonable

Table 3
Regression statistics

Regression statistics						
Multiple R	0.916169					
R Square	0.839365					
Adjusted R Square	0.838793					
Standard Error	15.60306					
Observations	283					
	Coefficients	**Standard Error**	**t Stat**	**P-value**	**Lower 95%**	**Upper 95%**
Intercept	-0.00586	1.467349	-0.00399	0.996818	-2.89425	2.882534
X variable 1	1.000031	0.026098	38.31852	1.4E-113	0.948659	1.051403

or good level of population wellbeing, suggesting a complex scenario in which the policy mix needs to be optimized in some countries. In other words, providing resources to the health system is not guaranteed to increase population wellbeing. Therefore, future research should focus on finding ways to achieve the maximum level of population wellbeing at the minimum cost to the health systems. The findings suggest that two levels of analysis are important: firstly, the analysis and comparison of countries within a certain group or cluster with similar health system characteristics and levels of population wellbeing; and secondly, an in-depth analysis of a country' s strengths, weaknesses, opportunities and threats based on micro- and sectoral-level data.

CONCLUSIONS

This study presents empirical findings that are important for science, health policy, society and health practice. A methodological approach based on neural networks was applied to secondary data from a large sample of countries in order to study the evolution of health systems in terms of country specificity and level of population wellbeing.

It contributes original and novel empirical results obtained from a large sample of country data on health system characteristics for selected years. We measured health system development based on its financial and healthcare capacity characteristics, as well as the level of population wellbeing. We assessed associations between these characteristics in country groupings but did not determine causality. The findings provide empirical evidence that similar levels of population wellbeing can be achieved in health systems with different characteristics based on differing policy options. The investigation confirmed both research questions: RQ1, that the specific characteristics national health system are reflected in population wellbeing; and RQ2, that similar levels of population wellbeing can be achieved with different health system architectures.

Therefore, it is crucial to increase not only expenditure and capacity in the healthcare sector but also the efficiency of the health system. Empirical evidence for a large number of countries suggests that different levels of health system performance can be achieved in different ways. Some countries with fewer resources were able to achieve high levels of population wellbeing, and other with more resources had achieved modest or low levels of population wellbeing. This suggests that resource availability cannot be the main constraint to achieving population wellbeing. If resources are used inefficiently or there is a lack of competition or bottlenecks in the health system, more resources do not necessary improve population wellbeing. It is important to understand how the health system functions and its constraints. This is impossible to achieve without comparisons of health systems in both neighbouring countries and worldwide, which is a crucial contribution of this study.

During the COVID-19 pandemic and associated healthcare crisis, expenditure on health system characteristics and capacities was raised in many countries. However, whether increased healthcare expenditure led to improved population wellbeing is a question for future research. Other suggestions for future research include an in-depth investigation of individual health systems based on an analysis of time series data or of country clusters to identify the drivers of (in)efficiencies over time and between countries.

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Conflict of interest statement

The Authors declare no conflict of interest.

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Sustainability of Italian seaports located near contaminated sites: results of an exploratory analysis

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Abstract

Introduction. Ports are strategic areas of economic importance, but they are also very critical contexts. Many Italian ports are included in contaminated sites of concern for remediation, with the presence of pressure factors that overload the burden capacity of local ecosystems and communities.

Aim. The aim of this study is to characterize Italian seaport areas through a general theoretical path on the theme of ports-sustainability-local communities, identifying the ports located in municipalities included in contaminated sites studied by the SENTIERI Project (Epidemiological Study of Residents in Italian Contaminated Sites). Many of the selected ports, are being part of complex industrial areas, where, in addition to the port area, there are other sources of environmental contamination potentially harmful to health.

Results. Excesses risk were observed for mesothelioma and for respiratory diseases, pathologies for which there is epidemiological evidence of an excess of risk associated with residence in port areas.

Discussion. The strong environmental pressures that characterize these areas make it necessary to adopt adequate environmental and health protection measures.

Key words

- seaports
- port areas
- maritime transport
- contaminated sites
- sustainability

INTRODUCTION

Italy's strategic position in the Mediterranean Sea has always favoured maritime transport and the construction of important ports distributed along its long coasts. Maritime transport is a strategic sector in international trade, and even in Italian ports it plays an extremely important role in both cargo and passenger transport.

At global level, ports are essential nodes of the maritime traffic network and of the links between maritime and land traffic. Each port differs according to dimension, activity and the type of goods handled, such as bulk goods transported directly into the ships holds, into containers, or RO-RO (Roll-on, Roll-off) ships that allow vehicles to enter and exit independently, without the use of cranes or elevators. Ports represent an important source of economic development and employment, but they are also highly anthropized geographical areas that exert considerable pressure on the environment, ecosystems, and local communities.

The different activities carried out in port areas, including maritime transport, may have negative impacts on human health and marine ecosystems, due to several factors, such as: emissions of pollutants in the atmosphere [1-6], noise [7, 8], soil and water pollution [9-11], production of port and naval waste [12], dredging operations, exchange of ballast water and sediments identified as vectors for the transfer of harmful and pathogenic aquatic organisms between different marine ecosystems, handling of goods, internal vehicular traffic, storage of hazardous materials or accidental events such as spills of hazardous substances into the sea [13, 14].

The environmental impact of ports can be associated with three main aspects: i) problems caused by the port activity itself; ii) problems caused to the sea by ships calling into port; iii) emissions from intermodal transport networks serving the port hinterland [15]. The major ports developed in large urban contexts with a high population density and frequently incorporated into the full city context, can have a significant impact on the environmental hazardous exposures and health of local populations. The port-city relationship has changed a lot over time, and today the main ports are real nerve centres, complex logistics and shipbuilding chains with

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large rear-port spaces, passenger terminals and other activities that are strongly interconnected with the surrounding areas.

In these areas, it is therefore important to pay increasing attention to combine the development of the transport system with the protection of the environment and health, implementing suitable policies to ensure sustainable development. At a national and international level, environmental policies have been launched aiming to transform maritime ports into *Green Ports* that are ports committed to a sustainable development, with a continuous improvement of environmental performances. A sustainable port is one in which the port authority, together with port users, proactively and responsibly adopt a green growth strategy and promote stakeholders' participation in mapping the long-term vision in a way that ensures that the port development meets the current needs of the region it serves, without compromising the ability of future generations to meet their own needs [16].

In Italy there are about three hundred and fifty main ports, more than fifty of which are of national importance from an administrative point of view. Many of them are in highly impacting areas on the territory, where other sources of industrial pollution are also present. Numerous Italian contaminated areas are in fact located along the coastal territory and coincide with important port areas. These areas which are currently or were in the past interested by anthropogenic activities that have produced chemical contamination of environmental media, with possible impact on human health. Some of these are contaminated sites of national interest for remediation, identifiable in relation to the characteristics of the site, as well as the quantity and the danger of the pollutants present, the impact on the surrounding environment in terms of health and ecological risk, and to the damage to cultural and environmental heritage [17].

The communities residing in districts close to port areas can suffer an overload of environmental, social and health stress compared to the communities residing in other districts, with the emergence of problems concerning Environmental Justice [18, 19], defined by the US Environmental Protection Agency as the "fair treatment and meaningful involvement of all people regardless of race, color, national origin, or income, with respect to the development, implementation, and enforcement of environmental laws, regulations, and policies" (https://www.epa.gov/environmentaljustice/learn-about-environmental-justice).

It is important to understand the measures that are being adopted in the sustainable management of ports, to improve the living and working conditions of local communities.

The objective of this study is to characterise Italian seaport areas through a general theoretical path on the theme of ports-sustainability-local communities, identifying and geo-referencing the national seaports located in the Italian municipalities included in contaminated sites studied by the SENTIERI Project (Epidemiological Study of Residents in Italian Contaminated Sites). SENTIERI is the epidemiological surveillance system of the populations residing in the municipalities affected by the main Italian contaminated sites of interest for remediation [20]. The presence of port areas in Italy, combined with complex environmental conditions, make it important to further assess these areas in order to monitor and evaluate the environmental qualities necessary to guarantee the protection of public health through sustainable development. Indeed, environmental factors can negatively affect the health and well-being of populations, for this reason some of the main environmental health priorities of ports identified by EcoPorts, the main environmental initiative of the European Port Sector [21], will be examined factors such as the air quality, noise and the relationship with the local community.

METHODS

Selection of seaports

The seaports selected for this study are located in one of the Italian municipalities included in the Fifth Report of the SENTIERI Project. SENTIERI currently covers 46 sites (39 classified as sites of national interest and 7 of regional interest, covering a total of 316 Italian municipalities) [20]. The SENTIERI Project describes the health profiles of the populations residing in these sites, in relation to their sources of environmental contamination which include chemical plants, petrochemical plants and refineries, steel plants, power plants, steel mills, mines or quarries, production and asbestos mining, landfills, incinerators and port areas.

From the 45 sites analysed by the project, a "coastal site" criterion was adopted identifying all coastal sites with contamination extending both on land and in the sea. For many of them the "harbour area" is specifically indicated as one of the sources of contamination, but for the selection made in this work, the "coastal site" criterion was preferred because there are ports that do not fall within the boundaries of the site, but which may contribute to additional impact factors in the surrounding area.

Characteristics of the seaports selected for the study

Information on the SENTIERI contaminated sites of interest for remediation, whose municipalities include seaports selected for the study, were collected and summarised concerning i) the Italian establishing law, ii) the municipalities included in the site, iii) the land/sea extent of the contaminated areas, and iv) the current Italian Ministerial Decree defining the boundary, as retrieved from the Ministry of Ecological Transition (Ministero dell'Ambiente e della Sicurezza Energetica) website (https://bonifichesiticontaminati.mite.gov.it).

Information on the seaports included in this study, in relation to the coordination of ports of national importance in Port System Authorities (PSAs), was retrieved and analysed in order to characterise the activities carried out in the main Italian seaports [22]. The seaports studied were then divided into their respective PSA, by assigning them two main attributes. The first one is the univocal UN / LOCODE (United Nations Code for Trade and Transport Locations), the geographical coding scheme developed and maintained by the United

Nations Economic Commission for Europe (https://unece.org/trade/uncefact/unlocode). The second attribute is the exact geographical location, retrieved with the geographical coordinates from Marine Traffic (https://www.marinetraffic.com), the provider of ship tracking and maritime intelligence. The inclusion of the port in the Trans-European Transport Network (TEN-T) was also verified [23].

Evaluations were also made to verify the presence or absence of the selected seaports on the EcoPorts website (https://www.ecoports.com), the main environmental initiative of the European port sector to raise awareness on environmental protection through cooperation and sharing of knowledge among ports and to improve environmental management. Ecoports is fully integrated into the European Sea Ports Organization (ESPO) (https://www.espo.be), the community-level representative of seaports.

Health profile of seaports populations

This study summarises the main aspect of the health profile of the populations residing in the municipalities of the selected seaports included in the SENTIERI Project. As each site includes one or more municipalities within its boundaries, a geospatial analysis was carried through the Geographical Information System (GIS) software, to identify the national seaports located in one of the SENTIERI municipalities. Main results for each Site including ports documented in the VI SENTIERI Report [20] will be summarized, focusing on the diseases classified in SENTIERI as associable with ports as a source of contamination based on the evidence from the epidemiological scientific literature [24].

Finally, some of the main environmental health priorities related to ports are described, also reported by the ESPO Environmental Report 2022 [21].

RESULTS

Based on the SENTIERI Project, 17 contaminated sites were selected for this investigation. These sites met the criteria outlined in the methods section. 18 seaports located in one of the municipalities included in these sites were identified (*Figure 1*). The ports are more numerous than the sites because the site of Priolo includes two ports (Syracuse and Augusta). The Italian regions with the greatest presence of ports located near contaminated sites are Sicily and Apulia: 4, Tuscany: 3, Sardinia: 2, while Calabria, Friuli Venezia Giulia, Veneto, Marche and Liguria have one seaport. Information on the Italian contaminated sites of interest for remediation establishing law, the municipalities of the site, the land/sea extent of the contamination, and the current Italian Ministerial Decree defining the boundary, are reported in *Table 1*.

In terms of sources of contamination, most of these sites are characterised by the presence of complex industrial settings, 82% (14 out of 17) including chemical plants, 65% (11/17) with petrochemical and/or refinery industry, and 53% (9/17) including both chemical plants and petrochemical/refinery industry. Moreover, 30% of sites have a steel factory together with chemical or petrochemical/refinery plant. 10 sites (59%) already

Figure 1
18 Italian seaports located in one of the municipalities of 17 contaminated sites included in the SENTIERI Project (Epidemiological Study of Residents in Italian Contaminated Sites). The Priolo Site includes two seaports: Syracuse and Augusta.

included, by Ministerial Decree, an arbour area in the site boundaries.

During the economic development of the 1960s these areas were chosen for the construction of major industrial centres precisely because of the presence of infrastructure such as ports, airports or railways, as the case of Gela (Sicily), Porto Torres (Sardinia) and other localities which later became contaminated sites.

Some of the analysed port areas in this study are internal or close to the borders of the sites and in some cases involve both land and sea areas. Many of them have developed in conjunction with important industrial plants, close to urban environment and, at times, with industrial piers that occupy much of the space available in the port. The marine-coastal areas included in these contaminated sites are generally made up of port areas, lagoons, coastal stretches, and river mouths, where there is often the concomitance of various high-impact industrial activities, uncontrolled landfills, military arsenals, shipyards, port areas with high maritime traffic, etc. Thus, the natural conditions of these places have been altered by an input of contaminants into the aquatic environment or as a result of physical changes, such as the modification of the shoreline due to the construction of anthropogenic activities [25].

In Italy in 2016, the port reorganization for the coordination of ports of national importance led to establish sixteen new PSAs, defined as special non-economic public bodies entrusted with the management of some of the 57 main national ports [22]. *Table 2* shows the 18 selected seaports divided into their respective PSA.

Eight of the selected seaports (La Spezia, Livorno, Augusta, Bari, Taranto, Ancona, Venezia-Marghera

Table 1
Description of the 17 main Italian contaminated sites selected in this study of interest for remediation and of the 18 seaports located in one of the municipalities including in the sites

Region	Site name and establishing law	Municipality/ municipalities	Sources of emissions§	Extension (ha)		Current perimeter Italian Decree	Seaport located in one of the municipalities of site
				Land	Sea		
LIGURIA	Pitelli L. 246/98	La Spezia, Lerici	A, AP, C, D, E	4 km²*	1,564*	Decree of the Minister of the Environment and Land and Sea Protection of 11 January 2013	Port of La Spezia
TUSCANY	Massa e Carrara L. 426/1998	Carrara e Massa	A, AP, C, D, I, P&R, S	116		Decree of the Minister of the Environment and Land and Sea Protection of 29 October 2013	Port of Carrara
	Piombino L. 426/1998	Piombino	AP, C, D, E, S	931	2,117	Decree of the Minister of the Environment January 10, 2000	Port of Piombino
	Livorno L. 468/2001	Livorno	AP, P&R	206		Decree of the Minister of Ecological Transition November 17, 2021	Port of Livorno
SARDINIA	Aree industriali di Porto Torres L. 179/2002	Porto Torres e Sassari	AP, C, D, E, P&R	1,874	2,748	Decree of the Minister of the Environment and the Protection of the Territory and the Sea of 21 July 2016	Port of Porto Torres
	Sulcis - Iglesiente - Guspinese D.M. 18/09/2001, n. 468	Portoscuso + 38 other municipalities	C, D, M	19,751	32,416	Decree of the Minister of the Environment and Land and Sea Protection of 28 October 2016	Port of Portovesme (Portoscuso)
CALABRIA	Crotone - Cassano - Cerchiara D.M. 18/09/2001, n. 468	Cassano allo Ionio, Cerchiara di Calabria, Crotone	C, D	874	1,448	Decree of the Minister of the Environment and Land and Sea Protection of 9 November 2017	Port of Crotone
SICILY	Milazzo L. 23 dicembre 2005, n. 266	Milazzo, San Filippo del Mela, Pace del Mela, San Pier Niceto e Monforte San Giorgio	A, D, E, P&R, S	549	2,198	Decree of the Minister of the Environment and Land Protection of 11 August 2006	Port of Milazzo
	Gela L. 426/1998	Gela	C, D, P&R	795	4,583	Decree of the Minister of the Environment January 10, 2000	Port of Gela
	Priolo L. 426/1998	Augusta, Priolo, Melilli and Siracusa	A, AP, C, D, P&R	5,814	10,129	Decree of the Minister of the Environment and Land Protection of 10 March 2006	Port of Siracusa and Port of Augusta
APULIA	Bari - Fibronit D.M. 18/09/2001, n. 468	Bari	A	15		Decree of the Minister of the Environment and Land Protection of 8 July 2002	Port of Bari
	Brindisi L. 426/1998	Brindisi	AP, C, D, E, P&R	5,851	5,597	Decree of the Minister of the Environment January 10, 2000	Port of Brindisi
	Taranto L. 426/1998	Taranto	AP, D, P&R, S	4,383	7,006	Decree of the Minister of the Environment January 10, 2000	Port of Taranto
	Manfredonia L. 426/1998	Manfredonia	C, D	216	855	Decree of the Minister of the Environment January 10, 2000	Port of Manfredonia
MARCHE	Falconara Marittima L. 31 luglio 2002, n. 179	Falconara Marittima	C, E, P&R,	108	1,165	Decree of the Minister of the Environment and Land Protection of 26 February 2003	Port of Falconara/ Port of Ancona
VENETO	Venice (Porto Marghera) L. 9 dicembre 1998, n. 426	Venice	AP, C, D, P&R	1,618		Decree of the Minister of the Environment and the Protection of the Territory and the Sea of 22 December 2016	Port of Venice (Marghera)
FRIULI VENEZIA GIULIA	Trieste D.M. 18/09/2001, n. 468	Trieste	AP, C, P&R, S	435	1,196	Decree of the Minister of Ecological Transition March 16, 2021, n. 95	Port of Trieste

*For sites within the competence of the regions, as the case di Pitelli site, the information was recovered from the official documents of the Region (http://www.comune.laspezia.it/export/sites/SPEZIAnet/Aree_tematiche/Ambiente/Focus/bonifiche/doc/Microsoft-Word-descrizione-pitelli.pdf).
§Legend of acronyms of environmental sources of contaminations (20): A: asbestos/other mineral fibres; AP: harbour area; C: production of chemical substance/s; D: landfill; E: electric power plant; I: incinerator; M: mine/quarry; P&R: petrochemical plant and/or refinery; S: steel industry.

Table 2
Geographical characteristics and other information of the seaports located in the municipalities of the contaminate sites of the SENTIERI Project (Epidemiological Study of Residents in Italian Contaminated Sites)

Port located in one of the municipalities of the contaminated site	The Italian Port System Authorities (PSAs)	UN/ LOCODE	Latitude/ Longitude	Trans-European Transport Network (TEN-T)	EcoPorts*
Port of La Spezia	PSA of the Eastern Ligurian Sea	ITSPE	N 44° 06′ 16.98″ E 009° 50′ 15.01″	Core network	
Port of Carrara	PSA of the Eastern Ligurian Sea	ITMDC	N 44° 01′ 55.63″ E 010° 02′ 26.21″	Comprehensive network	
Port of Piombino	PSA of the North Tyrrhenian Sea	ITLIV	N 43° 33′ 46.12″ E 010° 18′ 22.18″		Ecoports network: ISO14001Certified EMAS Certified
Port of Livorno	PSA of the North Tyrrhenian Sea	ITPIO	N 42° 55′ 57.50″ E 010° 32′ 56.25″	Core network	Ecoports network: ISO14001 Certified EMAS Certified
Port of Porto Torres	PSA of the Sardinian Sea	ITPTO	N 40° 50′ 31.62″ E 008° 23′ 57.17″	Comprehensive network	
Port of Portovesme	PSA of the Sardinian Sea	ITPVE	N 39° 11′ 42.12″ E 008° 23′ 42.93″	Comprehensive network	
Port of Crotone	Southern Tyrrhenian and Ionian Sea	ITCRV	N 39° 04′ 48.33″ E 017° 08′ 14.00″		
Port of Milazzo	PSA of the Strait	ITMLZ	N 38° 13′ 04.83″ E 015° 15′ 33.46″	Comprehensive network	
Port of Gela		ITGEA	N 37° 02′ 53.24″ E 014° 14′ 56.36″	Comprehensive network	
Port of Augusta	PSA of the Eastern Sicily Sea	ITAUG	N 37° 11′ 57.10″ E 015° 12′ 51.02″	Core network	
Port of Siracusa		ITSIR	N 37° 03′ 41.91″ E 015° 17′ 04.94″	Comprehensive network	
Port of Bari	PSA of the Southern Adriatic Sea	ITBRI	N 41° 08′ 11.63″ E 016° 51′ 29.19″	Core network	Ecoports network
Port of Brindisi	PSA of the Southern Adriatic Sea	ITBDS	N 40° 38′ 53.22″ E 017° 57′ 34.30″	Comprehensive network	Ecoports network
Port of Taranto	PSA of the Ionian Sea	ITTAR	N 40° 29′ 20.00″ E 017° 11′ 16.33″	Core network	
Port of Manfredonia	PSA of the Southern Adriatic Sea	ITMFR	N 41° 37′ 31.13″ E 015° 55′ 07.89″		Ecoports network
Port of Falconara/ Port of Ancona	PSA of the Central Adriatic Sea	ITFAL	N 43° 38′ 24.84″ E 013° 23′ 08.91		
		ITAOI	N 43° 37′ 10.33″ E 013° 30′ 08.69″	Core network	
Port of Venice/ Marghera	PSA of the Northern Adriatic Sea	ITVCE	N 45° 26′ 11.31″ E 012° 17′ 19.17″	Core network	
Port of Trieste	PSA of the Eastern Adriatic Sea	ITTRS	N 45° 38′ 16.37″ E 013° 45′ 50.74″	Core network	

*For some ports, ISO14001 and EMAS (Eco-Management and Audit Scheme) Environmental Management Standards are indicated.

and Trieste) are part of the Core network of the TEN-T based on a "corridor approach". The remaining seven ports (Carrara, Porto Torres, Portovesme, Milazzo, Gela, Siracusa and Brindisi) are part of the comprehensive network, a global network that ensure full coverage of the EU territory and accessibility to all regions. The TEN-T is divided into these two levels for the development of the international network. The most handled goods in Italy are energy products (coal, coke, crude oil, refined petroleum products, natural gas) [26].

As for the Ecoports European port sector environmental initiative, the network currently includes 108 member ports. The Italian ports included are the Port of Genoa, North Tyrrhenian Ports Sea, and Southern Adriatic Sea Port Authority. An environmental certification recognized at a European level, is issued to ports that comply with stringent eco-sustainability parameters. Among the ports included in the contaminated sites that are part of the Ecoports network, Livorno and Piombino are certified with the Environmental Management System (EMS) ISO14001 and Eco-Manage-

ment and Audit Scheme (EMAS). The port of Brindisi, while part of the network, is currently working to obtain environmental certifications (https://www.adspmam.it/i-porti/network-ecoports).

Italian Port System Authorities have dedicated a section of their websites to Environmental Policy and Protection and a series of initiatives and publications, which will be considered in the discussion section, aimed at developing a green port policy with particular special attention to the port-city relationship.

Health profile of the Italian seaports included in SENTIERI Project

SENTIERI identified the following diseases with "Limited Evidence" of health risk for the populations living in the neighbourhood of port areas as sources of contamination: pleural mesothelioma/pleural malignant tumors, respiratory system diseases and asthma [24]. *Table 3* shows results of the VI SENTIERI report for mortality and hospitalization for such diseases.

Almost all sites (10 out of 12, 83%) with the inclusion of ports as sources of contamination show an excess of risk for mesothelioma in men for both the mortality and hospitalization outcomes. In the same sites, many excesses of risk of mesothelioma are present in women, albeit based on a lower number of cases. The picture is different for the group of respiratory diseases for which higher than expected risk in both outcomes and genders concern 4 sites: Pitelli, Trieste, Porto Torres, and Bari; in other sites, this pattern is not consistent across genders and/or outcomes, while in the sites of Livorno and Piombino, the risk is prevalently lower than expected. Results for asthma are not shown in the *Table 3* since they are often below the privacy threshold of three observed cases.

As to the five SENTIERI coastal sites with ports (*Table 3*), an excess mortality risk for mesothelioma in the Manfredonia site, and an excess risk of hospitalization in the Gela site were observed among males, while no excess of risk was observed in women. An excess of risk related to respiratory diseases in both health outcomes and genders was observed in the site of Sulcis Iglesiente Guspinese, In the other four sites mesothelioma and respiratory diseases were in excess for both mortality and hospitalization but only in males.

Sustainability and environmental health priorities for ports

The increasing attention to the issue of sustainable development in the port area has led the recent reform of port legislation to introduce significant innovations in

Table 3

Summary table of results of SENTIERI Project (Epidemiological Study of Residents in Italian Contaminated Sites) for mortality (2013-2017) and hospitalization (2014-2018) for mesothelioma and respiratory system diseases

A - PLEURAL MESOTHELIOMA / PLEURAL MALIGNANT TUMORS§

Site	Mortality males*		Hospitalization males**		Mortality females*		Hospitalization females**	
	OSS	SMR (CI 90%)	OSS	SHR (CI 90%)	OSS	SMR (CI 90%)	OSS	SHR (CI 90%)
SENTIERI - Sites with port area as source of contamination								
Pitelli+	74	263 (217-318)	72	219 (180-266)	11	148 (91-243)	16	160 (106-241)
Venice - Porto Marghera+	42	189 (147-244)	66	197 (161-241)	11	133 (81-217)	19	137 (94-199)
Trieste+	45	133 (104-169)	99	349 (296-411)	7	121 (66-223)	17	145 (97-215)
Massa e Carrara+	18	225 (153-331)	30	251 (186-338)	7	386 (209-712)	7	138 (75-254)
Livorno+	45	411 (322-525)	50	306 (242-386)	14	580 (375-897)	14	206 (133-318)
Piombino	6	240 (124-464)	9	244 (142-419)	<3		3	201 (80-503)
Bari+	34	195 (148-259)	51	187 (148-235)	13	299 (190-471)	18	176 (120-259)
Brindisi+	9	204 (118-350)	19	271 (186-395)	<3		<3	
Taranto+	40	366 (282-474)	50	286 (227-361)	10	359 (214-600)	25	377 (271-523)
Aree industriali di Porto Torres+	8	119 (67-211)	14	98 (63-152)	<3		11	270 (165-441)
Milazzo+	<3		<3		<3		<3	
Priolo+	20	208 (144-300)	35	218 (165-287)	8	386 (218-685)	11	235 (144-384)
SENTIERI - Coastal sites with ports								
Falconara Marittima+	5	352 (171-723)	4	137 (62-306)	<3		<3	
Sulcis Inglesiente - Guspinese	13	103 (66-162)	30	113 (84-152)	<3		5	71 (35-146)
Manfredonia	<3		5	89 (43-184)	<3		<3	
Crotone+	3	146 (58-365)	4	84 (38-187)	<3		3	195 (78-488)
Gela	6	170 (88-329)	10	170 (101-284)	<3		<3	

Continues

Table 3
Continued

B - RESPIRATORY SYSTEM DISEASES§

Site	Mortality males*		Hospitalization males**		Mortality females*		Hospitalization females**	
	OSS	SMR (CI 90%)	OSS	SHR (CI 90%)	OSS	SMR (CI 90%)	OSS	SHR (CI 90%)
SENTIERI - Sites with port area as source of contamination								
Pitelli+	318	109 (99-120)	2,994	123 (119-127)	287	105 (95-115)	2,794	124 (120-127)
Venice - Porto Marghera+	531	87 (81-94)	5,990	99 (97-101)	638	102 (95-108)	5,632	103 (101-105)
Trieste+	641	118 (111-126)	5,867	116 (113-118)	687	111 (104-118)	5,716	122 (119-125)
Massa e Carrara+	338	124 (114-136)	3,008	103 (100-106)	285	101 (92-112)	2,710	99 (96-102)
Livorno+	337	82 (75-90)	3,415	84 (82-86)	343	90 (82-99)	3,068	83 (81-86)
Piombino	97	101 (86-120)	742	87 (82-92)	62	74 (60-91)	606	79 (74-85)
Bari+	34	195 (148-259)	51	187 (148-235)	13	299 (190-471)	18	176 (120-259)
Brindisi+	158	97 (85-111)	1,763	99 (95-103)	152	117 (103-134)	1,635	116 (112-121)
Taranto+	422	103 (95-112)	4,690	107 (104-110)	338	104 (95-113)	3,766	107 (104-110)
Aree industriali di Porto Torres+	273	121 (109-133)	3,469	112 (109-115)	261	142 (128-157)	3,092	121 (117-125)
Milazzo+	88	91 (76-108)	920	99 (93-104)	65	101 (82-124)	679	94 (88-100)
Priolo+	297	86 (78-94)	4,570	122 (119-125)	215	95 (85-106)	3,514	123 (120-127)
SENTIERI - Coastal sites with ports								
Falconara Marittima+	50	74 (59-93)	601	97 (90-103)	37	67 (51-88)	520	100 (93-108)
Sulcis Inglesiente - Guspinese	652	147 (138-157)	6,228	111 (108-113)	420	123 (114-134)	4,840	109 (107-112)
Manfredonia	111	75 (64-87)	1,689	113 (109-118)	81	75 (63-90)	1,307	118 (113-123)
Crotone+	79	94 (78-113)	1,191	110 (104-115)	55	99 (79-123)	883	108 (102-114)
Gela	125	102 (88-118)	1,679	113 (109-118)	72	106 (87-128)	1,382	(120-131)

*Number of observed cases (OSS), standardized mortality ratio (SMR), 90% confidence intervals (CI 90%) (ratio * 100).
**Number of observed cases (OSS), standardized hospitalization ratio (SHR), 90% confidence intervals (CI 90%) (ratio * 100).
+Presence of asbestos or presence of shipbuilding activities in which the presence of asbestos is recognized.
§Estimates are not reported for privacy reasons under <3 cases.

terms of sustainability. The Legislative Decree 169/2016 provides that the Port System Authorities promote an Energy and Environmental Planning Document of the Port System to define the strategic guidelines for an environmental energy planning with the aim of improving the environmental quality of the port area, to safeguard health and the well-being of local communities and workers and increase the competitiveness of port systems. Art. 5 introduces article 4-bis to law No. 84/1994 ("Reorganization of port legislation": https://www.assoporti.it/media/11132/testo-legge-84_94-vigente-versione-2022.pdf) for promote the drafting of the energy and environmental planning document of the Port System with the aim of pursuing adequate objectives, with reference to the reduction of CO2 emissions (https://www.assoporti.it/it/autoritasistemaportuale/atti-adsp-italiane/documento-di-pianificazione-energetico-ambientale-del-sistema-portuale-dpeasp). Below is a description of the main environmental priorities of the ports among the 10 reported by the European Port Sector [21].

Climate change

Climate change has become the top environmental concern for the port sector in 2022, overtaking air quality. Attention to climate change in recent years has in fact grown a lot, becoming a fundamental objective for the port industry. Ship traffic emissions contribute to global climate impacts and degrade local air quality. More stringent environmental regulations are adopted by the authorities to limit emissions of pollutants and greenhouse gases (GHG) resulting from energy consumption.

Air quality

Air quality move down on the second place of environmental concern of the port sector. Maritime transport is a significant source of emissions of sulfur dioxide (SO_2), nitrogen oxide (NO_x), particulate matter (PM) and volatile organic compounds (VOCs), and reduction policies have been introduced for these emissions, starting with the MARPOL Convention (MARine POLlution) 73/78 [27]. Air pollution in port areas can come from vessels navigating in the port or at berth, port operations, and relating land traffic in the area. Most of these ports are near urban areas and then air quality is very important to safeguard the health of the local community and the port bat also the port workers. Furthermore, the ports selected for this study are close to sites of industrial activity often polluting the air, and for this reason the ports could add further

emission contributions to an already critical environmental situation.

Noise

There are many potential sources of noise in the port area, which can be ambient and/or, underwater. It is also very important in the port-city relationship because, like air pollution, exposure to noise can also have serious health effects. Noise can come from machinery and cranes used for loading and unloading goods, but also from the use of ship's auxiliary engines in ports. Noise can disturb people living near ports, harbour wildlife and surrounding habitats. In addition, the industrial activities often present in ports (oil, shipbuilding, etc.) contribute to the already complex port situation, by adding additional sources of noise.

Relationship with the local community

The relationship with the local community is the sixth environmental priority. It is extremely important from both the health point of view and the quality of life of the populations living or working near these areas. Many great Italian ports are incorporated into the urban context and many neighbourhoods border the port area which often causes problems and concerns to the local community, as atmospheric pollution, noise, road traffic.

The need to identify and mitigate environmental inequalities in ports has been addressed by the Environmental Protection Agency which has developed a guidance document "Environmental Justice Primer for Ports. The Good Neighbour Guide to Building Partnerships and Social Equity with Communities" [28] with the aim of helping port authorities and decision makers to identify and respond to the needs of resident communities, and to build trusted relationships with the local context during planning activities. In Europe the ESPO Award for social integration has been established instead, and a Code of good practices has also been published to strengthen the relationship between port and city.

Other environmental priorities of the ports are energy efficiency, water quality, ship waste, port waste, port development (land related) and dredging operations.

DISCUSSION

This paper presents, for the first time to our knowledge, an overall picture of the Italian seaports located in complex areas characterised by the presence of multiple environmental pressures. The attention has been focused on ports located in the municipalities included in the contaminated sites of concern for remediation, given that these areas are more critical than others due to the additional impact of the surrounding industrial activities, which may further increase the health risks for the local communities and workers, as well as for the ecosystems. Industrial activities have left a legacy of thousands of areas contaminated by toxic chemicals that represent a current or future potential threat to the health [29]. In the Italian marine-coastal and transitional areas included in National Priority Contaminated Sites (NPCSs), the extent of the contamination is directly related not only to type of activity and the amount of the released contaminants but also to the geomorphological, bathymetric, and sedimentological characteristics of the area [25].

The results of the SENTIERI Project report excess risk for pathologies for which there is *a priori* epidemiological evidence of a causal association with ports as sources of contamination, in most of the sites for mesothelioma, and in some sites for the group of respiratory diseases [20].

It is probable that the criticalities observed in the health profile of population living in seaports are related to the complex environmental contamination, and in particular are linked to air pollution, deriving from the presence of multiple anthropic and industrial activities in most of the sites that include harbours. Furthermore, an excess risk of malignant tumors of the pleura/mesotheliomas was also observed in these sites, highlighting the presence of asbestos, classified as a human carcinogen by IARC [30]. The results highlighted that 13 sites examined show an excess risk of pleural mesothelioma (hospitalization and mortality), for example in sites where asbestos is present such as in Pitelli, Massa Carrara, Milazzo, Priolo, etc. In the site of Pitelli for example, considering data on asbestos exposure [31] methods show that in 84% of cases asbestos exposure occurred in the workplace, including in the shipbuilding sectors. Though asbestos as environmental exposure is explicitly mentioned in the Decrees for only some of these sites, all areas include port or shipyards, where the presence of asbestos is well recognized. In the excesses for asbestos-related pathologies, an important role of exposure to asbestos in the workplace can be conceivable. The presence of asbestos or shipbuilding activities (where the use of asbestos is recognised) is documented in 11 of the sites examined. In addition to industrial sites, the impact on health from exposure to asbestos affects a wide range of activities and work and living environments characterized by the "in place" presence of this material [32].

Excesses of risks in both genders, particularly for mesothelioma, would lead to hypothesize a non-negligible role of environmental exposures, as occupational activities involving asbestos use were mainly carried out by men.

However, regarding the respiratory diseases, a possible synergistic effect between the various factors analysed, such as the lifestyle of the population, the environmental emission sources and occupational factors should also be considered.

The ports always affect, as a source of contamination, only a sub-area of the sites' territory, and usually a municipality, while the health results in SENTIERI concerns a set of municipalities. In a few cases a site corresponds to a single municipality, and those examined include Piombino, Falconara Marittima, Bari, Brindisi, Gela and Venice. Furthermore, even within the same municipality, some neighbourhoods may be, or may have been, potentially exposed to pollutants, as some areas are closer to port activities. In addition, port areas can be located inside or outside the contaminated site area and the boundaries can vary over time with

increases or decreases in the affected surfaces. A port area, even if formally not internal to the site, can still potentially represent an additional source of impact for the territory and the local community.

This limitation of SENTIERI underlines the need to have an accurate monitoring of the impact of port emissions, especially in the areas adjacent to the ports and the need for analytical epidemiological studies to verify if the presumed causal factor(s) is/are associated to the pathology under study.

There are different sources of emissions in these areas, and it is not easy to identify the precise apportionment of the sources in order to evaluate the contribution of each one. Moreover, factors related to the conformation of the territory and the influences of local meteorology must also be examined: meteorology, ship positioning and engine type influence the port role on nearby cities air quality [33]. Geographically, many seaports on the peninsula have coastal hills that limit the widespread dispersion of emissions and therefore regularly increase the level of local pollutants [34]. It would be important, especially for these areas, to create targeted studies on sources apportionment to obtain a complete chemical characterization. Several studies have highlighted the difficulty of identifying the impact of ship emissions in situations where there is the joint presence of industrial, port and urban emissions, while also considering the weather conditions and the territorial morphology; all factors that can also affect the exposure of the population [2, 35]. For example, Gobbi *et al.* [33] distinguishes emissions originated in the port area from the ones pertaining to the city of Civitavecchia, the mayor port of Rome. This is a critical area due to the simultaneous presence of many industrial agglomerations. The study identified main points of emission and their contribution to the measured loads of regulated pollutants as NO_2, PM_{10}, and SO_2, representing a reasonable estimate of the ports area contribution to the air pollution at the port-city border and a good quantification of sources of unregulated pollutants.

As described by Merico *et al.* [36], port logistics also play an important role in determining the total impact of maritime transport on the air quality of nearby coastal areas, since the dimensional distributions of maritime contributions are different for the manoeuvring and hotelling phases.

Just as difficult is the accurate field measurements of port noise, given the complexity of the port area. Port noise prevention and management are also rendered difficult by the quite limited knowledge of specific sources in scientific literature, as reported in the study carried out by Fredianelli *et al.* [37], which reports field measurements as difficult to perform and interpret when multiple types of sound emitters are mixed and confused with each other.

Each port examined is characterized by its own peculiarities due to its geographical morphology or its type of productivity, which makes the comparison among different realities it is very difficult. Brewer's study [34] notes that, although there are a variety of sources regarding data on ship activity and emissions in Italian ports, there are notable differences in the lists of indicators, and for this reason it is not currently possible to carry out a complete comparison of port indicators but only a summary of the overall systems and data concerning each port.

However, the ESPO report finds that ports are demonstrably improving their environmental management [21] and major Italian ports, including those examined in this study, have undertaken major environmental initiatives to become green ports. Some of them are part of the Ecoports network and have achieved specific environmental certifications, while others are still working on it. Fifteen ports examined are part of the TEN-T, and this allows for a better use of infrastructures, a reduction of the environmental impact of transport, greater energy efficiency and greater safety.

Many of the port authorities consulted have already published, or are about to do so, sustainability reports to measure their contribution to achieving sustainable development. For example, in the sustainability report of La Spezia and Carrara ports, the concrete contribution to achieve 12 of the 17 Sustainable Development Goals (SDGs) of the UN 2030 Agency was assessed, which concern energy efficiency, air quality monitoring, and sustainable cities and communities, the fight against noise pollution and the protection of life underwater, with particular attention to marine protected areas [38]. Many of them, as described on their websites, have undertaken actions of urban regeneration and improvement of the quality of the city communities, with urban and environmental enhancement projects of the port waterfronts (the urban strip overlooking the sea), buffer zones located on the border between the port and the city, and sound absorbing barriers.

CONCLUSIONS

Seaports are strategic areas of economic importance but the strong environmental pressures that characterize them make it necessary to have adequate environmental and health protection measures. The environmental performance of ports represents an element of competitiveness in the panorama of international traffic, and for this reason it is necessary to harmonize the relationship between port and city, promoting knowledge on environmental issues and involving all interested parties in decision-making processes, to encourage concrete actions for the benefit of the entire local community and to ensure sustainable development for all activities to be implemented.

It is crucial to encourage the use of standardized and homogeneous methods and approaches in the European Community for monitoring pollutants generated by port activities and to make the data comparable and shareable. It would be also advisable to launch specific epidemiological surveillance plans in port areas to investigate criticalities in the health profile of the populations residing in these complex areas.

The environmental health issues in complex seaports areas are therefore best addressed with a strong sustainability perspective, considering both the human and ecosystem health, and the social context. These aspects require an intersectoral approach leading to a social ne-

gotiation, where the legitimate needs and aspirations of residents, workers, and investors, are considered in a balanced cost-benefit analysis process.

In Italy a focus on Environmental Justice has been launched for contaminated sites, since usually the communities living in or close to contaminated areas have socioeconomic fragilities, in addition to being affected by the exposure to pollutants [39, 40]. Seaports are indeed frequently represented in Italian contaminated sites assessed by the SENTIERI Project (about 40% based on our study). It is therefore important to extend attention on Environmental Justice also to the communities living in the neighbourhoods close to the ports, even more so when it comes to critical areas such as those of contaminated sites. It is also important to carry out adequate analytical epidemiological studies on the communities living in Italian seaport, trying to address also the mobility of local populations and to account for residential and occupational exposure to key contaminants. To this aim, a polycentric cohort mortality study performed in five Italian harbours, including active and retired workers (longshoremen) employed between 1960 and 1981, found an excess of lung cancer in four out of five harbours [41].

Studies on the impacts that directly affect the daily lives of these local populations, who often bear a disproportionate burden of port activities, are also desirable. Residents' concern can be reduced by improving direct access to technical and scientific information in lay language and by developing specific risk reduction strategies to improve the conditions and quality of life in the neighbourhood, thus enhancing the cultural and identity heritage of the Italian port cities.

A comprehensive analysis of different environmental health scenarios can support the identification of policies for climate change mitigation and adaptation, at global and local levels. Public health actions in some areas, like those represented by seaports in industrially contaminated sites, can help to achieve multiple health benefits while reducing emissions.

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Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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Book Reviews, Notes and Comments

Edited by
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GLI INTERFERONI NEI TUMORI E NELLE MALATTIE AUTOIMMUNI
Il loro ruolo nella cura e nella ricerca per la salute globale
Filippo Belardelli
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[Interferons in cancer and autoimmune diseases. Their role in global health care and research]

It is a privilege and a pleasure for me to comment on this book written by Filippo Belardelli, past director of the Department of Hematology, Oncology and Molecular Medicine at the Istituto Superiore di Sanità (Italian National Institute of Health, ISS) who represented a valuable landmark person for my scientific activity. The Author is one of the most reliable scientists among those who have studied the mechanisms of innate immunity and the biology of the interferon (IFN) system. In this book, he exploits a lay language to tackle the complex history of the IFN research and provides the reader with a simple and comprehensive overview on the role of IFN in cancer and autoimmune and infectious diseases and on perspectives to exploit this system to face global health challenges in today's society.

In 1957 IFN was discovered by Alick Isaacs and Jean Lindenmann at the World Influenza Centre of the National Institute for Medical Research in London. The discovery followed a path of intense investigation of many years of research by several virologists working in different countries on the identification of the mechanisms responsible for the phenomenon of viral interference (i.e., the observation that the infection with a given virus generally results in protection against a secondary infection).

This path never ends and is still exploited to provide us new cues on the host response to microbial invasion. By means of well-designed experiments, Isaacs and Lindenmann were able to show that the viral interference was indeed caused by a soluble factor released by the infected cells, named IFN. We now know that the IFN system is not represented by a single factor, but by many different proteins belonging to 3 major IFN types: type I (including multiple IFN-α subtypes and the IFN-β), type II (IFN-γ) and type III (IFN-λ), endowed with many biological functions in addition to their antiviral activity. Of note, the history of IFN research has been defined as "aiming at a moving target" since a variety of new biological activities have been ascribed to these pleiotropic cytokines over the years, thus changing our concepts on their role and mechanisms of action.

The importance of the IFN research and its impact on the progress of our knowledge on the biology of the living systems is well known and Filippo provides in his book a picture of the contribution provided to this field by the Italian scientific community. It is worth noting that the IFN research has been fully instrumental to the development of our knowledge on the molecular mechanisms of action of many other cytokines, which have been subsequently identified.

IFN are the cytokines with the longest record of clinical use. IFN-α and IFN-β were the first cytokines cloned in the year 1980 and extensively used as biological recombinant drugs in patients with cancer (IFN-α), viral diseases (especially hepatitis B and C) and multiple sclerosis (IFN-β).

Today, many clinicians may consider IFN as "dead drugs", replaced by new tools and protocols, although the clinical use of type I IFN was back in fashion during COVID19 pandemics and pegylated IFN is currently used as first-therapy in the early treatment of Multiple sclerosis patients.

It should be also noted that in the past type I IFN were used in patients when their mechanisms of action were largely unknown, as either conventional cytostatic drugs or non-specific biological response modifiers. They were generally utilized at high dosages and administered continuously. Biological activities subsequently ascribed to these cytokines were barely considered for clinical use. Even today, many data in humans and mice underline the importance of endogenous IFN-I, produced by both immune and tumor cells, in the control of tumor growth and in the response to antitumor therapies. In many cases, the presence of an IFN-I signature in the tumor microenvironment is a marker of the so-called "hot tumors" (i.e., tumors exhibiting specific immune cell infiltrates predicting a potential therapeutic response). In contrast, the suppression of IFN-I system, at the transcriptional level or by effect of receptor downregulation, is often associated with worse clinical outcome and increased tumor progression.

Notably, in other pathologic scenarios such as some autoimmune diseases, IFN signatures have acquired the value of biomarkers of the disease and represent the so-called Janus Face of these cytokines. In line with these evidences, a pathogenic role of autoantibodies against type I IFN for worsened outcome of SARS-CoV-2 infections after age 65 years has been proposed

on the data showing that the autoantibodies were found in about 20% of deceased COVID19 patients.

Today, the reference to the IFN system has become a constant feature in the books of microbiology, cell biology, oncology, pathology and immunology. However, the history of the different phases of the IFN research is still largely unknown to young investigators. It represents a fascinating journey through many obstacles, hopes, difficulties, different discoveries, contrasts, mythization and media pressures affected by industrial interests, and subsequent evolution of the knowledge based on the most recent research progress.

With a clear and calm gaze, the book has the merit to carefully describe this complex historical journey, from the first discoveries to the evolution of the IFN research up to now. The book is structured in 4 main parts. The first one represents a reference text for young researchers and students for learning the complex history of IFN research.

The second part is focused on the state of art of our current knowledge on the IFN system in viral infections and neoplastic and autoimmune diseases. In the third part, the author describes the most recent advances in specific research fields of great health relevance, including those of cancer immunology and immunotherapy, predictive and personalized medicine and immune prevention and therapy of pandemic viral infections, such as that caused by SARS-CoV-2. In this regard, the potential importance for the impact on public health of strategies aimed at exploiting mechanisms of the innate and trained immunity by modulation of the IFN system is discussed.

Notably, through all this part it remains constant the reference to the emerging role of the IFN system, which turns out to be important and can be modulated by selective up-dated treatments according to the medical needs. In approaching the last part of his book, the Author cannot forget his long-lasting experience in the coordination of international research projects, which calls for messages to convey to young investigators regarding the complexity of the relationships between research, science and health issues in the today's society.

The book ends with the author's hope of a new society aimed at structurally solving the problems of poverty, inequality and environment, in which scientific research should be based on the imagination of young investigators and increasingly oriented towards global health and development of knowledge and education.

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ISBN 978-88-1528-672-7
€ 12,00

[Beware of dogs. A history of 40,000 years]

The history of dog domestication represented a fundamental cultural step in the long history of humankind progression. Beyond that (therefore a booklet dealing with this issue is worth reading) the reciprocal relationship between *Homo sapiens sapiens* and *Canis familiaris* – derived likely through different domestication episodes from ancestral wolves during centuries of close ecological proximity with humans – in the last decades also represented a socio-sanitary issue of increasing relevance. Such a peculiar discipline is presently labelled as zooanthropology and is becoming a first-line, hot topic in applied biomedicine, particularly veterinarian and biobehavioural sciences.

The likely most historical step, at least for our "Western" scientific communities, occurred between 1979 and 1998 when deaths caused by dogs – for which the breed was known – amounted to 238 [1]. In 2001, 368.245 patients were treated for injuries sustained as a result of assaults in the US, when the highly recognized Centers for Disease Control and Prevention (US-CDCs) witnessed a kind of subtle epidemics of intraspecific aggression, monitoring both fatal human events and cases causing wounds of various degree. Such a formal CDCs reflection on the state-of-the-art of dangerous dog-humans intraspecific relationship initiated similar monitoring efforts activities at the global level.

It is worth mentioning that in Italy, in our Italian National Institute of Health (Istituto Superiore di Sanità, ISS), the late veterinarian Prof. Adriano Mantovani, also director of the Parasitology Laboratory at ISS, formerly full professor at Bononia "*Alma Mater*" University, formed a rather innovative, initially informal Veterinary Urban Hygiene Group in which the not rarely conflictual relationships between human urbanized communities and their synantropic vertebrates species (pigeons, rats, feral dogs, feral cats, etc.) were thoroughly discussed by a multi-disciplinary group composed of both intramural ISS experts (EA and Luigi De Acetis among others) and extramural experts of highly recognized scientific status. Such an initiative remains a vivid landmark at the Italian level.

More importantly, such an informal group was after a while transformed in a joint WHO/FAO Center again headed by the then retired Prof. Mantovani, a cultural and operative unit which also edited a series of original

issues dealing with such an emerging scientific, biomedical and socio-sanitary field.

A couple of years after the CDCs initiative, around 2003, the problem of dog-caused human wounds or deaths somehow exploded also in Italy, mainly because of a media campaign stressing for a few months the problem. Any major wound or especially human death caused by dogs immediately raised mediatic attention at a national level often being released as a top story in the news. This trend became viral on the various media.

The then Ministry of Health Girolamo Sirchia reacted releasing a list of "dangerous dog breeds". However, in the following weeks and months this list lost its main legal significance, and the Consiglio Superiore di Sanità itself stated that more often individual dogs, more than particularly risky breeds, were responsible for most of the reported dangerous interactions. Single problematic dog biographies were attentively examined. In the following few years, a debate raged involving veterinarians, ethologists, experts of canine training, lawyers, etc. Presently some dog breeds (see also the website of the Italian Ministry of Health) are enlisted as deserving special attention: and single animals were, in the case of single individual animals causing human deaths or repeated biting or attacks, addressed to special re-training or re-habilitation paths. The debate about these rules and/recommendations and their efficacy is still a matter of discussion. More in general, the academic and experience qualifications of those involved in dog education or behavioral "recovery" remains a hot issue also in our days.

Very special cases, such as the ones of homicidal dogs, were addressed experimentally toward fostering practice by sensitive "zoophilic associations" and in general the culls became less and less frequent. Some attempts to establish specific guidelines also occurred.

Therefore, an essay as the one few are reviewing here, fluidly written, elegantly illustrated, yet scientifically solid and exhaustive, as the one by recognized pet carnivore expert Paola Valsecchi (professor of applied ethology and vertebrate evolution at Parma University) and a long-time fellow of the very high-level international school of behavioral sciences established by the late Prof. Danilo Mainardi, a pioneer of the subject in the early '70s, in Parma.

Among the most relevant topics of this vivacious book, the recent recognition of dog personalities (*sure, insecure-avoiding, insecure-ambivalent*, page 94), an emerging field in animal behavior an individual character are well presented and discussed, as well as the very relevant role of "early critical periods" in dog education, instruction and training. A very vivid and well-depicted part regards the repercussions of the successive domestication and breed/strain production on the contemporary problems caused by dogs, particularly those entrapped in the melanchonic condition of urban areas or even spending their lives in central zones of rapidly enlarging cities or metropolis. Genetic components, local practices of training and maintenance, anthropological elements in both urban and rural (or peri-urban) areas, all contribute to shape the various problematic trends that territorial public health system units have to cope. Valsecchi clearly disentangle them, while producing a clear and convincing array of weighted recommendations.

Chapter 2 is really an enlightening reading for anyone within the public health system dealing with dog-triggered zoo-anthropological problems. Intelligent reflections on watchdog management are another useful topic here illustrated. Last but not least, the final, elegantly reasoned list of further suggested readings is particularly worth for those in need of more specialized information on the matter.

In conclusion, this agile booklet, well written by an expert author who dedicated a long period of her scientific interests toward dogs (and cats) in urban areas, to their behavioural patterns when living in home, feral or feralized social units, is therefore a highly recommended cultural aid, whose translation is highly auspicate. Her ethological expertise will well complement the most current university or post-university manuals of Behavioral Medicine adopted by a number of Italian veterinary schools.

1. Centers for Disease Control and Prevention (CDC). Nonfatal dog bite-related injuries treated in hospital emergency departments – United States, 2001. MMWR. 2003;52:605-10.

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IL COSTO DELLA VIRILITÀ
Quello che l'Italia risparmierebbe se gli uomini si comportassero come le donne
Ginevra Bersani Franceschetti, Lucile Peytavin
Roma: Il Pensiero Scientifico Editore; 2023.
192 p.
ISBN 978-88-4900-743-5
€ 22,00

[The cost of manhood. What Italy would save if men behaved like women]

How many euros does male behaviour cost to the Italian society?

Which are the risky behaviours (deadly behaviours) such as balconing, railroad planking, car surfing, fire challenge etc. all typical highly risky patterns of young / adolescent human males? Which is the role of social behaviour during the adolescent age? Is that more (a rather reductionistic explanation indeed) caused by circulating testosterones levels or early educational factors?

This somehow due, yet provocative evaluation, actually originates from an analogous estimate of economic costs due to typical male behavioural patterns performed by Lucile Peytavin, a recognized expert of history of economics. Such an evaluation, a very good and vivid example of interaction between physical and cultural anthropology, triggered an analogous estimate for the Italian context. The co-author Ginevra Bersani Franceschetti got a degree in financial sciences at the Institut d'Études Politiques de Paris.

This well-arranged book, especially chapter 12 "the cost of virility in the principle public policies" is worth reading by anyone, in the biomedical field looking for planning both short-and long term strategies to cope with human violence, both from an economic, but also a bioethical perspective.

Finally, the paragraph on "male ancestry" (*The Palaeolithic, an immense prejudice*, page 13) remains an only apparently hilarious narrative about current interpretations of the different, or even divergent, ways to cope with societal challenges according to cultural and "hormonal" driving factors.

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Publications from International Organizations on Public Health

Edited by
Annarita Barbaro

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS (FAO)

Metwally S, Viljoen G, El Idrissi A (Eds). **Veterinary vaccines: principles and applications**. Rome: Food and Agriculture Organization of the United Nations and John Wiley & Sons Limited 2022; 442 p. ISBN 9781119506270 (epub). This work is a concise and authoritative reference featuring easily readable reviews of the latest research in vaccinology and vaccine immune response to pathogens of major economic impact to livestock. It covers advice and recommendations for vaccine production, quality control, and effective vaccination schemes including vaccine selection, specifications, vaccination programs, vaccine handling in the field, application, failures, and assessment of herd protection. In addition, the book presents discussions on the current status and potential future developments of vaccines and vaccination against selected transboundary animal diseases. Veterinary Vaccines: Principles and Applications is an important resource for veterinary practitioners, animal health department officials, vaccine scientists, and veterinary students. It will also be of interest to professional associations and NGO active in livestock industry.

Wildcheck – Assessing the risks and opportunities of trade in wild plant ingredients. Rome: Food and Agriculture Organization of the United Nations 2022; 140 p. ISBN: 978-92-5-135965-5. Thousands of consumer products around the world contain ingredients obtained from wild plants. Wild harvest accounts for some or all of the harvest of the majority of plant species in trade. This report aims to address the challenges associated with wild harvesting by making information on a selection of 'flagship' wild plant ingredients, the Wild Dozen, readily available and easy to understand. FAO offers this information without obligation to a specific prescription for follow-up action (e.g. through certification or policy change), hoping that a wide range of users will access the report as a first step towards responsible sourcing. Along with a broader update on the state of wild plants trade, the report provides a "profile" on each of the Wild Dozen species, summarising key facts on production and trade. Each profile contains a traffic-light risk rating on biological and social factors, along with an overview of opportunities for responsible sourcing. The information is aimed at industry, consumers, policy-makers, investors, and practitioners, concluding with a summary of what these various stakeholders can do to contribute to a sectoral shift towards responsible sourcing of wild plant ingredients.

INTERNATIONAL SCIENCE COUNCIL (ISC)

Unprecedented & Unfinished: COVID-19 and Implications for National and Global Policy. Paris: International Science Council 2022; 110 p. The object of this report is, firstly, to inform policy-makers and the public about the wide-ranging, long-term impacts on the entire global community from COVID-19, and to help elucidate the key decisions and actions that could shift the evolution of the pandemic towards more positive and equitable outcomes across societies. Secondly, it should inform planning and responses to other existential crises, whether pandemics, natural disasters, or the impacts of climate change. This report therefore provides an entry point to addressing the wide-ranging impacts of COVID-19 in two parts. Part 1 sets the scene by outlining three plausible scenarios over a five year time horizon that could conceivably emerge from the pandemic's cascading impacts, taking into account policy interactions and uncertainties that may affect outcomes. These scenarios are intended as simply as illustrations to help the global community plan for the future, by seeking to assess the broader impact of decisions taken today and the costs of inaction. Part 2 provides recommendations on how the global community can prepare for the future to mitigate the impacts of COVID-19 and address other existential crises that we will inevitably face.

UNITED NATIONS ENVIRONMENTAL PROGRAMME (UNEP)

Bracing for Superbugs: Strengthening environmental action in the One Health response to antimicrobial resistance. Geneva: United Nations Environmental Programme 2023; 100 p. ISBN 978-92-807-4006-6. This report provides evidence that the environment plays a key role in the development, transmission and spread of antimicrobial resistance (AMR). Prevention is at the core of the action and environment is a key part of the solution. It aims to demystify and unpack the different, while interconnected, aspects of the environmental dimensions of AMR, offering a comprehensive overview of scientific findings on the subject. It provides actionable evidence of the importance of the environment in the development, transmission and spread of AMR, and it shows that environmental dimensions of AMR are multifaceted and the response rests on collaboration between sectors. A concerted systems approach such as "One Health," which recog-

nizes that the health of people, animals, plants and the environment are closely linked and interdependent, is the approach needed to tackle it. This report analyses the three economic sectors and their value chains that are key drivers of AMR development and spread in the environment: pharmaceuticals and other chemicals, agriculture and food, and healthcare, together with pollutants from poor sanitation, sewage and waste effluent in municipal systems. The report synthesizes current knowledge gaps, and it shows that while several actions are ongoing, more needs to be done and offers solutions to prevent and respond to AMR. A One Health response to AMR will not only help reduce the risk and burden of AMR on societies but will also help address the triple planetary crisis.

Emissions Gap Report 2022: The Closing Window — Climate crisis calls for rapid transformation of societies. Nairobi: United Nations Environment Programme 2022; 132 p. ISBN 978-92-807-3979-4. The Emission Gas Report 2022 is the 13th edition of an annual series that provides an overview of the difference between where greenhouse emissions are predicted to be in 2030 and where they should be to avert the worst impacts of climate change. This report shows that updated national pledges since COP26 – held in 2021 in Glasgow, UK – make a negligible difference to predicted 2030 emissions and that we are far from the Paris Agreement goal of limiting global warming to well below 2°C, preferably 1.5°C. Policies currently in place point to a 2.8°C temperature rise by the end of the century. Implementation of the current pledges will only reduce this to a 2.4-2.6°C temperature rise by the end of the century, for conditional and unconditional pledges respectively. The report finds that only an urgent system-wide transformation can deliver the enormous cuts needed to limit greenhouse gas emissions by 2030: 45 per cent compared with projections based on policies currently in place to get on track to 1.5°C and 30 per cent for 2°C. This report provides an in-depth exploration of how to deliver this transformation, looking at the required actions in the electricity supply, industry, transport and buildings sectors, and the food and financial systems.

EUROPEAN FOOD SAFETY AUTHORITY (EFSA)

EFSA (European Food Safety Authority), Dujardin B, Ferreira de Sousa R, Gómez Ruiz JA. **Scientific Report on the dietary exposure to heavy metals and iodine intake via consumption of seaweeds and halophytes in the European population**. EFSA Journal 2023;21(1):7798, 47 pp. EFSA assessed the relevance of seaweed and halophyte consumption to the dietary exposure to heavy metals (arsenic, cadmium, lead and mercury) and the iodine intake in the European population. Based on sampling years 2011-2021, there were 2,093 analytical data available on cadmium, 1,988 on lead, 1,934 on total arsenic, 920 on inorganic arsenic (iAs), 1,499 on total mercury and 1,002 on iodine. A total of 697 eating occasions on halophytes, seaweeds and seaweed-related products were identified in the EFSA Comprehensive European Food Consumption Database (468 subjects, 19 European countries). The impact of a future increase in seaweed consumption ("per capita") on the dietary exposure to heavy metals and on iodine intake will strongly depend on the seaweeds consumed. These results underline the relevance of the current consumption of seaweeds in the overall exposure to different heavy metals and in the intake of iodine. Recommendations are provided for further work needed on different areas to better understand the relationship between seaweed consumption and exposure to heavy metals and iodine intake.

EFSA (European Food Safety Authority) and ECDC (European Centre for Disease Prevention and Control). **The European Union Summary Report on Antimicrobial Resistance in zoonotic and indicator bacteria from humans, animals and food in 2020/2021**. EFSA Journal 2023;21(3):7867, 232 p. Antimicrobial resistance (AMR) data on zoonotic and indicator bacteria from humans, animals and food are collected annually by the EU Member States (MSs) and reporting countries, jointly analysed by EFSA and ECDC and presented in a yearly EU Summary Report. This report provides an overview of the main findings of the 2020-2021 harmonised AMR monitoring in Salmonella spp., Campylobacter jejuni and C. coli in humans and food-producing animals (broilers, laying hens and turkeys, fattening pigs and bovines under 1 year of age) and relevant meat thereof. Where available, monitoring data from humans, food-producing animals and meat thereof were combined and compared at the EU level, with emphasis on multidrug resistance, complete susceptibility and combined resistance patterns to selected and critically important antimicrobials, as well as Salmonella and E. coli isolates exhibiting ESBL-/AmpC-/carbapenemase phenotypes. The temporal trend analyses in both key outcome indicators (rate of complete susceptibility and prevalence of ESBL-/AmpC- producers) showed that encouraging progress have been registered in reducing AMR in food-producing animals in several EU MSs over the last years.

WORLD HEALTH ORGANIZATION (WHO)

Food safety aspects of cell-based food. Geneva: World Health Organization and Food and Agriculture Organization of the United Nations 2023; 145 p. ISBN (FAO) 978-92-5-137723-9 (print) ISBN (WHO) 978-92-4-007094-3 (electronic version) ISBN (WHO) 978-92-4-007095-0 (print version). The Food and Agriculture Organization of the United Nations (FAO), in collaboration with the World Health Organization (WHO), has developed the present document to engage with respective Members and relevant stakeholders by proactively sharing the current knowledge to identify concrete ways to inform consumers and all

other stakeholders about the food safety considerations for cell-based food products. The primary objective of this document is to provide readers with up-to-date technical knowledge on the multidisciplinary topic of cell-based food production, with a focus on the food safety aspects, through the process of literature synthesis and expert elicitation. This document includes a literature synthesis of relevant terminology issues, principles of cell-based food production processes and the global landscape of regulatory frameworks for cell-based food production. Case studies from Israel, Qatar and Singapore have been included to highlight different scopes, structures and contexts surrounding their regulatory frameworks for cell-based food. While the primary target audience of this document was set for national food safety competent authorities, the global community of scientists, developers, the cell-based food industry as well as academics doing research in the area of cell-based food production may benefit from reading this document.

Report 2022: pesticide residues in food: Joint FAO/WHO Meeting on Pesticide Residues. Geneva: World Health Organization and Agriculture Organization of the United Nations 2023; 1000 p. ISBN (FAO) 978-92-5-137585-3 (print) ISBN (WHO) 978-92-4-006960-2 (electronic version) ISBN (WHO) 978-92-4-006961-9 (print version). A Joint Meeting of the Food and Agriculture Organization of the United Nations (FAO) Panel of Experts on Pesticide Residues in Food and the Environment and the World Health Organization (WHO) Core Assessment Group on Pesticide Residues (JMPR) was held at FAO Headquarters, Rome (Italy), from 13 to 22 September 2022. The Meeting evaluated 34 pesticides, including seven new compounds and four compounds that were re-evaluated within the periodic review programme of the CCPR, for toxicity or residues, or both. The Meeting also estimated the dietary exposures (both short-term and long-term) of the pesticides reviewed and, on this basis, performed a dietary risk assessment in relation to the relevant acceptable daily intakes (ADIs) and where necessary acute reference doses (ARfDs).

WHO global report on sodium intake reduction. Geneva: World Health Organization 2023; 99 p. ISBN 978-92-4-006998-5 (electronic version) ISBN 978-92-4-006999-2 (print version). Reducing sodium intake is one of the most cost-effective ways to improve health and reduce the burden of noncommunicable diseases, as it can avert a large number of cardiovascular events and deaths at very low total programme costs. The World Health Organization (WHO) has developed this report to monitor progress and identify areas for action in the implementation of sodium reduction policies and other measures within Member States and across WHO regions and World Bank income groups. For the first time, a Sodium Country Score from 1 (the lowest level) to 4 (the highest level) is allocated to each Member State based on the level of implementation of sodium reduction policies and other measures. The Sodium Country Score is used to estimate the impact of policy progress on population dietary sodium intake and cardiovascular disease. WHO recommends several sodium-related best buys policies as practical actions that should be undertaken immediately, to prevent cardiovascular disease and its associated costs. These include lowering sodium content in food products; implementing front-of-pack labelling to help consumers select food products with lower sodium content; conducting mass media campaigns to alter consumer behaviour around sodium; and implementing public food procurement and service policies to reduce sodium content in food served or sold.

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Articles in journal

Bozzuto G, Ruggieri P, Molinari A. Molecular aspects of tumor cell migration and invasion. Ann Ist Super Sanità. 2010;46(1):66-80. doi: 10.4415/ANN_10_01_09

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Godlee F, Jefferson T. Peer review in health sciences. London: BMJ Books; 1999.

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Fadda A, Giacomozzi C, Macellari V. Comparative measurements to validate a new telemetric pressure insoles system. In: 2. International Symposium on measurement, analysis and modelling of human functions. 1. Mediterranean Conference on measurement. Workshop on evaluation check of traceability. Proceedings. Genova: June 14-16, 2004. p. 425-7.

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US Social Security Administration. Evidentiary requirements for making findings about medical equivalence. Final rules. Fed Reg. 2006 Mar 1;71(40):10419-33.

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